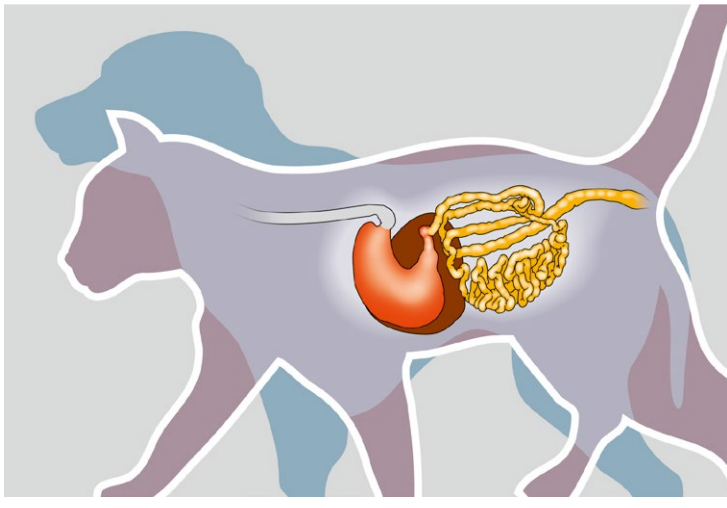
Romy M. Heilmann | Jonathan A. Lidbury |
Jörg M. Steiner (eds.)

# Small Animal Gastroenterology

Second, revised and expanded edition







VET EXPERTISE

schlütersche

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Second, revised and expanded edition

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# Abbreviations

| | |
|---|---|
| **3-BrY** | 3-bromotyrosine |
| **5-ASA** | 5-aminosalicylic acid |
| **5HT** | 5-hydroxytryptamine |
| **$\alpha_1$-PI** | alpha1-proteinase inhibitor |
| **AAFCO** | Association of American Feed Control Officials |
| **AC** | ameroid constrictors |
| **ACA** | adenocarcinoma |
| **ACTH** | adrenocorticotrophic hormone |
| **AFR** | adverse food reactions |
| **AGASACA** | apocrine gland anal sac adenocarcinoma |
| **AH** | acute hepatitis |
| **AHD** | acute hemorrhagic diarrhea |
| **AHDS** | acute hemorrhagic diarrhea syndrome |
| **AIEC** | adherent-invasive *Escherichia coli* |
| **AKI** | acute kidney injury |
| **AL** | alimentary lymphoma |
| **ALKP** | alkaline phosphatase |
| **ALT** | alanine aminotransferase |
| **ARD** | antibiotic-responsive diarrhea |
| **ARE** | antibiotic-responsive enteropathy |
| **ARG** | arginase |
| **ASL** | argininosuccinate lyase |
| **ASS** | arginosuccinate synthetase |
| **AST** | aspartate aminotransferase |
| **ATPase** | adenosine triphosphatase |
| **AUS** | abdominal ultrasonography |
| **APACHE II** | acute physiology and chronic health evaluation II score |
| **APC** | antigen-presenting cell |
| **APP** | acute-phase protein |
| **aPPT** | activated partial thromboplastin time |
| **BA** | bile acids |
| **BARF** | bones and raw food |
| **BCS** | body condition score |
| **BFI** | body fat index |
| **BIPS** | barium impregnated polyethylene spheres |
| **BMI** | body mass index |
| **BUN** | blood urea nitrogen |
| **CAFR** | cutaneous adverse food reaction |
| **CAH** | copper-associated hepatopathy |
| **cAMP** | cyclic adenosine monophosphate |
| **CAPS** | canine acute pancreatitis severity score |
| **CAV-1** | canine adenovirus type-1 |
| **CBC** | complete blood cell count |
| **CBD** | cannabidiol |
| **CCECAI** | Canine Chronic Enteropathy Clinical Activity Index |
| **CCK** | cholecystokinin |
| **CCNU** | lomustine (chlorethyl-cyclohexyl-nitroso-urea) |
| **CD** | Crohn's disease |
| **CDI** | *Clostridium difficile* infection |
| **CE** | chronic enteropathy |
| **CEUS** | contrast-enhanced ultrasonography |
| **CH** | chronic hepatitis |
| **CHF** | congenital hepatic fibrosis |
| **CHOP** | cyclophosphamide, hydroxyldaunorubicin (doxorubicin), vincristine, predniso(lo)ne |
| **CIBDAI** | Canine Inflammatory Bowel Disease Activity Index |
| **CIE** | chronic inflammatory enteropathy |
| **CIRMD** | critical-illness related motility disorder |
| **CK** | creatine kinase |
| **CKD** | chronic kidney disease |
| **CLO** | Campylobacter-like organism |
| **CNS** | central nervous system |
| **COP** | cyclophosphamide, vincristine, predniso(lo)ne |
| **CPA** | cricopharyngeus achalasia |
| **CPD** | cricopharyngeus dyssynchrony |
| **CPE** | *Clostridium perfringens* enterotoxin |
| **cPLI** | canine pancreatic lipase immunoreactivity |
| **CPMD** | cricopharyngeus muscle dysfunction |
| **CPSI** | carbamoyl phosphatase synthetase I |
| **CPSS** | congenital portosystemic shunt |

| | |
|---|---|
| **CPV** | canine parvovirus |
| **CRC** | colorectal cancer |
| **CRI** | continuous rate infusion |
| **CRP** | C-reactive protein |
| **CRT** | capillary refill time |
| **CsA** | cyclosporine A |
| **CSF** | cerebrospinal fluid |
| **CT** | computed tomography |
| **CT angiography** | computed tomography angiography |
| **CTA** | contrast-enhanced abdominal computed tomography |
| **cTLI** | canine trypsin-like immunoreactivity |
| **CVC** | caudal vena cava |
| **CYP** | cytochrome P450 enzyme |
| **DAMP** | damage-associated molecular pattern |
| **DF** | dietary fiber |
| **DGAT** | a-diacylglycerol O-acyltransferase |
| **DGGR** | 1,2-o-dilauryl-rac-glycero-3-glutaric acid-(6′-methylresorufin) ester |
| **DI** | dysbiosis index |
| **DIC** | disseminated intravascular coagulation |
| **DM** | dry matter |
| **DNA** | desoxyribonucleic acid |
| **EAEC** | enteroaggregative *Escherichia coli* |
| **ECG** | electrocardiogram |
| **ECM** | extracellular matrix |
| **EDTA** | ethylenediaminetetraacetic acid |
| **EE** | eosinophilic enteritis |
| **EFA** | essential fatty acid |
| **EGC** | eosinophilic granuloma complex |
| **EGE** | eosinophilic gastroenteritis |
| **EHBO** | extrahepatic bile duct obstruction |
| **EHEC** | enterohemorrhagic *Escherichia coli* |
| **EHS** | enterohepatic *Helicobacter* spp. |
| **EIA** | enzyme immunoassay |
| **EIEC** | enteroinvasive *Escherichia coli* |
| **ELISA** | enzyme-linked immunosorbent assay |
| **EMG** | electromyography |
| **ENS** | enteric nervous system |
| **EPEC** | enteropathogenic *Escherichia coli* |
| **EPI** | exocrine pancreatic insufficiency |
| **Epx** | eosinophil peroxidase |
| **ERCP** | endoscopic retrograde cholangio-pancreatography |
| **ESBL** | extended-spectrum β-lactamase-producing *Escherichia coli* |
| **ESM-1** | endothelial cell-specific molecule-1 |
| **ETEC** | enterotoxigenic *Escherichia coli* |
| **FASS** | feline atopic skin syndrome |
| **FAST** | focused assessment with sonography for trauma |
| **FB** | foreign body |
| **FCEAI** | Feline Chronic Enteropathy Activity Index |
| **FCGS** | feline chronic gingivostomatitis |
| **FCV** | feline calicivirus |
| **FeCoV** | feline coronavirus |
| **FeLV** | feline leukemia virus |
| **FFP** | fresh frozen plasma |
| **FFPE** | formalin-fixed and paraffin-embedded sample |
| **FGESF** | feline gastrointestinal eosinophilic sclerosing fibroplasia |
| **FHV-1** | feline herpesvirus-1 |
| **FHL** | feline hepatic lipidosis |
| **FIM** | feline idiopathic megacolon |
| **FIP** | feline infectious peritonitis |
| **FISH** | fluorescence in situ hybridization |
| **FIV** | feline immunodeficiency virus |
| **FLL** | focal lipogranulomatous lymphangitis |
| **FLR** | functional liver remnant |
| **FLUTD** | feline lower urinary tract disease |
| **FMT** | fecal microbial transplantation |
| **FNA** | fine-needle aspiration |
| **FOS** | fructooligosaccharides |
| **FPA** | fecal proteolytic activity |
| **fPLI** | feline pancreatic lipase immunoreactivity |
| **FPV** | feline parvovirus |
| **FQ** | fluoroquinolone |
| **Fr** | French |
| **FRD** | food-responsive diarrhea |
| **FRE** | food-responsive enteropathy |
| **FRLBD** | fiber-responsive large bowel diarrhea |
| **FSA** | fibosarcoma |
| **fTLI** | feline trypsin-like immunoreactivity |
| **GALT** | gut-associated lymphoid tissue |
| **GB** | gall bladder |
| **GC** | granulomatous colitis |
| **G-CSF** | granulocyte-colony stimulating factor |
| **GDV** | gastric dilatation-volvulus |
| **GE** | gastric emptying |
| **GER** | gastroesophageal reflux |
| **GERD** | gastroesophageal reflux disease |

**GES** gastroesophageal sphincter
**γGT** gamma glutamyltransferase
**GI** gastrointestinal
**GIP** gastric inhibitory peptide
**GIST** gastrointestinal stromal tumor
**GLP** glucagon-like peptide
**GMS** Gomori methenamine silver
**GhRH** growth-hormone-releasing hormone
**GRF** growth hormone-releasing factor
**GRP** gastrin-related peptide
**GSD** German shepherd dog

**HARD** heartworm-associated respiratory disease
**HAVM** hepatic arteriovenous malformation
**HCC** hepatocellular carcinoma
**HDL** high-density lipoprotein
**H&E** hematoxylin eosin stain
**HE** hepatic encephalopathy
**HGE** hemorrhagic gastroenteritis
**HGMS** histology-guided mass spectrometry
**HL** hepatic lipidosis
**HLO** *Helicobacter*-like organism
**HMWK** high-molecular-weight kininogen
**HOC** hypoadrenocorticism
**HTG** hypertriglyceridemia
**HUC** histiocytic ulcerative colitis

**IBD** inflammatory bowel disease
**IBS** irritable bowel syndrome
**IBW** ideal body weight
**ICU** intensive care unit
**IFA** immunofluorescence assay
**Ig** immunoglobulin
**IGH** immunoglobulin heavy chain
**IHC** immunohistochemistry
**IL** interleukin
**IOMP** intra-operative mesenteric portovenography
**IP** intraperitoneal fluid
**IPMD** inflammatory polyp of miniature dachshunds
**IPSID** immunoproliferative small intestinal disease
**IRD** immunosuppressant-responsive diarrhea
**ISH** in situ hybridization
**IU** international unit
**IV** intravenous

**KCS** keratoconjunctivitis sicca

**L-CHOP** L-asparaginase, vincristine, cyclophosphamide, doxorubicin, predniso(lo)ne
**LDH** lobular dissecting hepatitis
**LDL** low-density lipoprotein
**LES** lower esophageal sphincter
**LFA** lymphocyte function associated factor
**LGAL** low-grade alimentary lymphoma
**LGL** large granular lymphocyte
**LI** large intestine
**LP** lymphoplasmacytic
**LPC** lymphoplasmacytic colitis
**LPE** lymphoplasmacytic enteritis
**LPL** lipoprotein lipase
**LV** left ventricular

**MAMP** microbe-associated molecular pattern
**MAT** microscopic agglutination test
**MCAI** modified canine activity index
**MCP** monocyte chemoattractant protein
**MCS** muscle condition score
**MCT** medium-chain triglyceride
**MC tumor** mast cell tumor
**MDR** multiple drug resistance
**ME** metabolizable energy
**MEN** multiple endocrine neoplasia
**MER** maintenance energy requirement
**MI** motility index
**MIF** merthiolate, iodine, formaldehyde
**miR** micro-ribonucleic acid
**MLV** modified live virus
**MMC** migrating motor complex
**MOS** mannan oligosaccharides
**MRI** magnetic resonance imaging
**mRNA** messenger ribonucleic acid
**MSC** mesenchymal stem cell
**MST** median survival time
**MTP** microsomal triglyceride transfer protein
**MVD** microvascular dysplasia

**NAPQI** N-acetyl-p-quinone imine
**NCV** nerve conduction velocity
**NE** nasoesophageal
**NEFA** non-esterified fatty acid
**NET** neutrophilic extravascular trap
**NetF** novel, pore-forming toxin
**NE tumor** neuroendocrine tumor

**NF-κB** nuclear factor-kappa B
**NG** nasogastric
**NK** neurokinin
**NK cell** natural killer cell
**NME** necrolytic migratory erythema
**NMH** N-methylhistamine
**NOD** nucleotide-binding oligomerization domain
**NPO** nil per os (nothing per os)
**NSAID** non-steroidal anti-inflammatory drug
**NTEC** necrotoxigenic *Escherichia coli*

**OCTT** orocecal transit time
**OS** overall survival
**OSA** osteosarcoma
**OTC** ornithine transcarbamoylase

**PAA** pancreatic acinar atrophy
**PAFANT** platelet-activating factor antagonist
**PAMP** pathogen-associated molecular pattern
**pANCA** perinuclear anti-neutrophil cytoplasmic antibody
**PANS** post-attenuation neurological signs
**PARR** polymerase chain reaction for antigen receptor rearrangement
**PAS** Periodic acid-Schiff
**PAS-OD** polyacrylic acid-silicone gradual occlusion devices
**PCR** polymerase chain reaction
**PCV** packed cell volume
**PD** polydipsia
**PDAC** pancreatic ductal adenocarzinoma
**PEG** percutaneous endoscopic gastrostomy
**PERT** pancreatic enzyme replacement therapy
**PFS** progression-free survival
**PIND-ORF** paramunity inducers derived from poxviruses
**PLE** protein-losing enteropathy
**PLN** protein-losing nephropathy
**PLRP** pancreatic lipase related proteins
**PO** per os
**POMC** pro-opiomelanocortin C
**PPI** proton pump inhibitor
**PRAA** persistent right aortic arch
**pRBC** packed red blood cell
**PRE** probiotic responisve enteropathy
**PRR** pattern recognition receptor
**PSS** portosystemic shunt
**PSTI** pancreatic secretory trypsin inhibitor
**PT** prothrombin time
**PTHrP** parathormone-related peptide
**PU** polyuria
**PUC** percutaneous ultrasound-guided cholecystocentesis
**PV** portal vein
**PVH** primary portal vein hypoplasia

**QOL** quality of life

**RAGE** receptor for advanced glycation end products
**RECIST** response evaluation criteria in solid tumors
**rFeIFN-omega** recombinant feline interferon-omega
**RER** resting energy requirement
**rER** rough endoplasmatic reticulum
**RILD** radiation-induced liver disease
**RMBD** raw meat-based diets
**RNA** ribonucleic acid
**ROS** reactive oxygen species
**RT-PCR** real-time polymerase chain reaction

**SAF** sodium acetate/acetic acid/formaldehyde
**SAMe** s-adenosylmethionine
**SBS** short bowel syndrome
**SBRT** stereotactic body radiation therapy
**SBW** starting body weight
**SC** subcutaneous
**SCC** squamous cell carcinoma
**SCF** stem cell factor
**SCFA** short-chain fatty acids
**SCL** small-cell T-cell lymphoma
**SCWT** soft-coated wheaten terrier
**SDMA** symmetric dimethylarginine
**SI** small intestine
**SIBO** small intestinal bacterial overgrowth
**SID** small intestinal dysbiosis
**sIgA** secretory immunoglobulin A
**SIRS** systemic inflammatory response syndrome
**SND** superficial necrolytic dermatitis
**SNP** single nucleotide polymorphism
**SOFA** sequential organ failure assessment
**Spec cPL** specific canine pancreatic lipase
**Spec fPL** specific feline pancreatic lipase
**SPECT** single photon emission computed tomography
**SREBF** sterol regulatory element-binding factor
**SRS** somatostatin receptor scintigraphy
**SSR2** somatostatin receptor subtype 2

| | |
|---|---|
| **TACE** | transarterial chemoembolization |
| **TAP** | trypsinogen activation peptide |
| **TCRG** | T-cell receptor γ |
| **TFF** | Trefoil factor |
| **TLR** | Toll-like receptor |
| **TPMT** | thiopurine methyltransferase |
| **Treg** | regulatory T cells |
| **TSH** | thyroid-stimulating hormone |
| **UC** | ulcerative colitis |
| **UCED** | urea cycle enzyme deficiency |
| **UDCA** | ursodeoxycholic acid |
| **UES** | upper esophageal sphincter |
| **UICC** | Union for International Cancer Control |
| **UPC** | urine protein:creatinine ratio |
| **USMI** | urethral sphincter mechanism incompetence |
| **VFSS** | videofluoroscopic swallowing study |
| **VIP** | vasoactive intestinal polypeptide |
| **VLDL** | very-low density lipoprotein |
| **VMDB** | Veterinary Medical Database |
| **VTEC** | verocytotoxin producing *Escherichia coli* |
| **WBC** | white blood cell count |
| **WHO** | World Health Organization |
| **WMC** | wireless motility capsule |
| **WSAVA** | World Small Animal Veterinary Association |
| **XCIP** | X-chromosome inactivation pattern |
| **ZSFC** | zinc sulfate flotation-centrifugation |

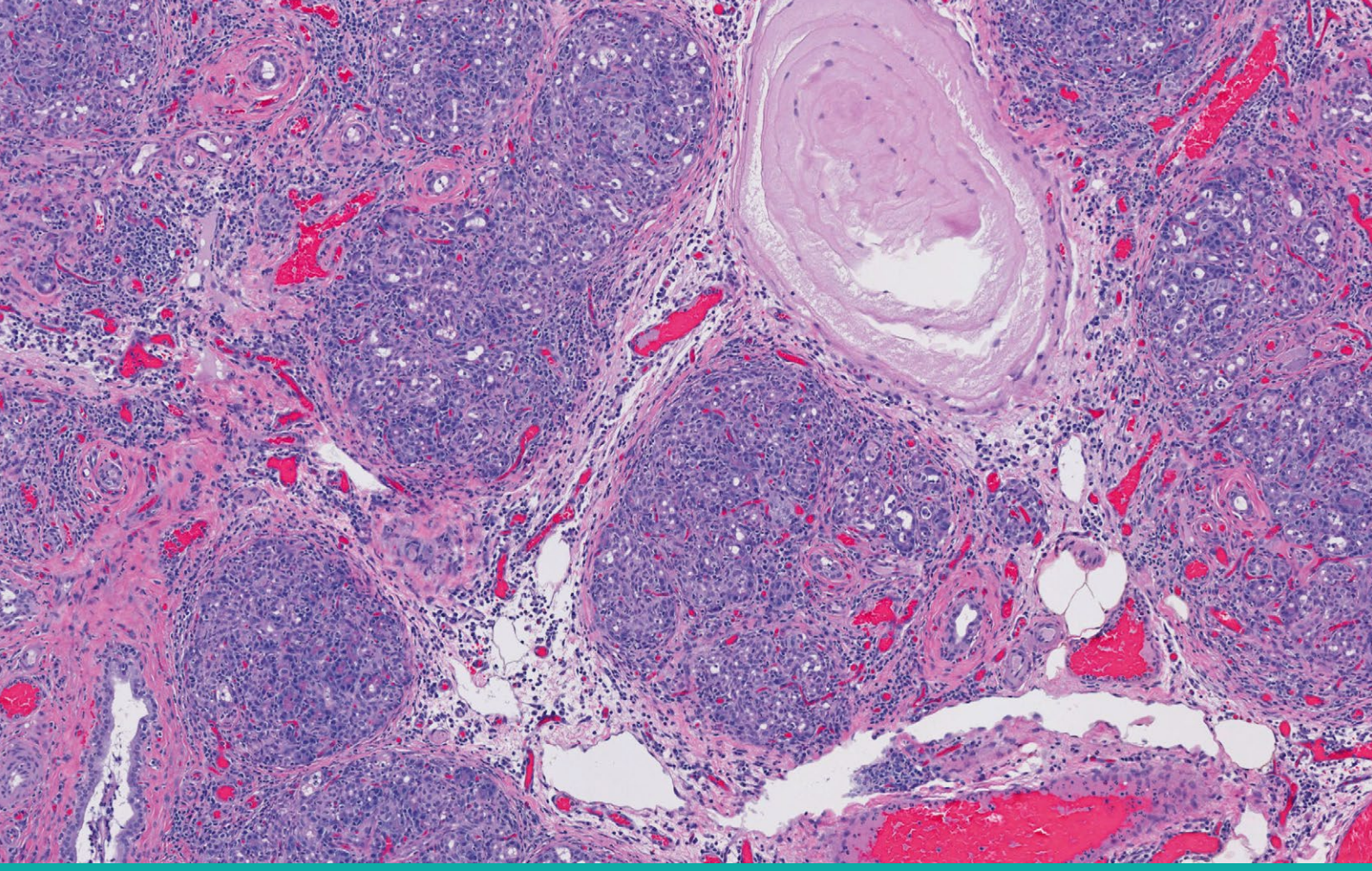
# Preface

Herakles is quoted as stating that "Change is the only constant in life", and indeed, wherever we cast our glance, the world around us is changing. Some change may be challenging or even threatening, while other changes make our lives easier. A lot has changed over the last 15 years in the field of small animal gastroenterology, and in fact, the field has expanded and many more veterinarians have become interested in this field. The second edition of this book is a testament to this change. The list of authors has grown, and the three editors of this edition feel a sense of gratitude and humility to have had the chance to work with such a formidable group of authors – they have made this project what it is – a comprehensive and up-to-date practical reference text for small animal gastroenterology.

As was the case for the first edition, the first part of this edition is again dedicated to diagnostic modalities that are crucial for working up patients with gastrointestinal signs. We hope the reader will find useful tips for everyday practice in this section. The second section is dedicated to the systemic work-up of the most commonly encountered gastrointestinal signs in dogs and cats. The third section of the book is dedicated to a systematic review of specific diseases categorized by the segment of the gastrointestinal tract that it affects. All sections of the book are carefully referenced so that the reader can quickly find the primary literature on which the information provided is based.

We hope that you find this book useful in your everyday practice. It has been a privilege to edit the second edition of this text!

Texas and Leipzig, Spring 2024
*Jörg M. Steiner, Romy M. Heilmann, Jonathan A. Lidbury*



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# I Diagnosis of gastrointestinal disorders

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# 1 Diagnostic tools

## 1.1 Clinical history

Olivier Dossin

### 1.1.1 Introduction

For most clinical problems, acquiring an accurate history can be as important as the clinical findings on physical examination. This is especially true for gastrointestinal disorders since they are usually expressed by clinical signs that cannot be observed during the clinical examination but are instead reported by the owner. Therefore, the clinician must be skilled in obtaining the most accurate information by questioning the owner, which needs to be adapted for each case.

The steps and general guidelines for collecting a good history are shown in ▶Tab. 1-1 and ▶Tab. 1-2. The observations of the owner, which are valuable, must be differentiated from his or her interpretation, which may be misleading. For example, the terms vomiting and regurgitation may be used synonymously by the owner. To avoid confusion, it is essential to ask the owner to describe the patient's clinical signs in his or her own words. The clinician may ask the owner for a smartphone video recording of the clinical signs at home, which may prove to be a very useful tool in interpreting historical clinical signs.

The signalment can be helpful as some age or breed predispositions (▶Tab. 1-3 and ▶Tab. 1-4) have been proposed for various gastrointestinal disorders. Also, a complete vaccination and drug history are important. Many drugs can induce gastrointestinal disturbances (e.g., non-steroidal anti-inflammatory drugs [NSAIDs]) can cause gastric ulcers, and some antibiotic agents can be associated with diarrhea). Intolerance to anesthetic agents has been reported in patients with hepatic disorders, especially in those with portosystemic vascular anomalies (▶Chap. 9.5.3).[6]

**Tab. 1-1** Steps for taking a history in patients with gastrointestinal signs[1–3]

| Parameters addressed |
|---|
| • Signalment |
| • Chief complaint |
| • Present medical history (including chronology and treatments) |
| • Past medical history (including chronology and current treatments, if any) |
| • Systems review |
| • Current health status (including environment and dietary history) |

**Tab. 1-2** Guidelines for history acquisition in patients with gastrointestinal signs[4,5]

| Guidelines for history acquisition |
|---|
| • Always begin with the chief complaint |
| • Start by asking broad questions |
| • Ask narrow questions (questions that can be answered with few words such as "yes," "no," or "I do not know") to confirm previous answers |
| • Try to use the owner's words to avoid confusion about what the owner means |
| • Do not bombard the owner with questions |
| • Avoid combining questions |
| • Try to be reassuring when necessary |
| • Try to focus the owner on the main points of the history |
| • Avoid categorical answers or judgments at the time of history collection |
| • Avoid external interruptions |
| • Ask for video recordings (ideally before the visit) |

**Tab. 1-3** Suspected or confirmed breed predispositions for gastrointestinal diseases in dogs[7,8]

| Breed | Disease predisposition |
|---|---|
| Australian cattle dog | Portosystemic vascular anomalies |
| Basenji | Hypertrophic gastritis, immunoproliferative lymphoplasmacytic enteritis, lymphangiectasia |
| Beagle | Intestinal dysbiosis, cobalamin deficiency |
| Bedlington terrier | Copper-associated chronic hepatitis |
| Belgian shepherd dog | Gastric carcinoma |
| Border collie | Selective cobalamin malabsorption, portosystemic vascular anomalies |
| Boston terrier | Pyloric muscular stenosis, vascular ring anomalies |
| Bouvier des Flandres | Muscular dystrophy-associated dysphagia |
| Boxer | Granulomatous colitis, eosinophilic enteritis, lymphoplasmacytic colitis, pyloric muscular stenosis, vascular ring anomalies, constipation |
| Brachycephalic breeds | Hiatal hernia, esophageal dysmotility, hypertrophic gastropathy, pyloric stenosis, granulomatous colitis |
| Cairn terrier | Portosystemic vascular anomalies |
| Cavalier King Charles spaniel | Chronic pancreatitis, exocrine pancreatic insufficiency |
| Chow chow | Exocrine pancreatic insufficiency, gastric neoplasia |
| Cocker spaniel | Anal sac adenocarcinoma, chronic hepatitis and cirrhosis, portal vein hypoplasia, gall bladder mucocele, pancreatitis |
| Dalmatian | Copper-associated chronic hepatitis |
| Doberman pinscher | Parvoviral enteritis, eosinophilic enteritis, chronic hepatitis, copper-associated chronic hepatitis, portal vein hypoplasia |
| English bulldog | Vascular ring anomaly, constipation, fecal incontinence |
| English springer spaniel | Chronic hepatitis |
| German shepherd dog | Exocrine pancreatic insufficiency, megaesophagus, vascular ring anomaly, lymphoplasmacytic enteritis, eosinophilic enteritis, intestinal dysbiosis, perianal fistula, idiopathic hepatic fibrosis |
| Giant schnauzer | Selective cobalamin malabsorption |
| Golden retriever | Cricopharyngeal dysphagia, megaesophagus |
| Great dane | Gastric dilatation-volvulus |
| Irish setter | Megaesophagus, gastric dilatation-volvulus, gluten-sensitive enteropathy, vascular ring anomaly |
| Irish wolfhound | Portosystemic vascular anomalies (intrahepatic shunt) |
| Jack Russel terrier | Salivary gland necrosis |
| Labrador retriever | Megaesophagus, portosystemic vascular anomalies, chronic hepatitis, copper-associated chronic hepatitis |
| Lhasa apso | Hypertrophic pyloric gastropathy |
| Maltese | Hypertrophic pyloric gastropathy, microvascular dysplasia, portosystemic vascular anomalies |
| Miniature schnauzer | Pancreatitis, portosystemic vascular anomalies, gallbladder mucocele |
| Norwegian lundehund | Protein-losing enteropathy, lymphangiectasia, gastric neoplasia |
| Pekinese | Hypertrophic pyloric gastropathy |
| Pembroke Welsh corgi | Exocrine pancreatic insufficiency |
| Rottweiler | Parvoviral enteritis, eosinophilic enteritis, protein-losing enteropathy |
| Rough collie | Exocrine pancreatic insufficiency, gastric carcinoma |

**Tab. 1-3** Suspected or confirmed breed predispositions for gastrointestinal diseases in dogs[7,8] (Continuation)

| Breed | Disease predisposition |
|---|---|
| Scottish terrier | Vacuolar hepatopathy, hepatocellular carcinoma |
| Chinese shar-pei | Hiatal hernia, protein-losing enteropathy, lymphoplasmacytic enteritis, eosinophilic enteritis, cobalamin deficiency, hepatic amyloidosis |
| Shetland sheepdog | Gallbladder mucocele |
| Shih tzu | Hypertrophic pyloric gastropathy |
| Skye terrier | Copper-associated chronic hepatitis |
| Soft-coated wheaten terrier | Protein-losing enteropathy and/or nephropathy |
| Standard poodle | Gastric dilatation-volvulus, lobular dissecting hepatitis |
| West Highland white terrier | Chronic hepatitis, copper-associated chronic hepatitis, portosystemic vascular anomalies |
| Yorkshire terrier | Acute pancreatitis, portosystemic vascular anomalies, intestinal lymphangiectasia, hypertrophic pyloric gastropathy |

**Tab. 1-4** Suspected or confirmed breed predispositions for gastrointestinal diseases in cats[7,8]

| Breed | Disease predisposition |
|---|---|
| Abyssinian | Megaesophagus, hepatic amyloidosis |
| Manx | Fecal incontinence, constipation |
| Oriental shorthair | Hepatic amyloidosis |
| Persian | Portosystemic vascular anomalies, polycystic liver disease |
| Siamese | Megaesophagus, hepatic amyloidosis, gastroparesis, pyloric stenosis, intestinal tumors |

### 1.1.2 History of specific gastrointestinal signs

This section focuses on the main specific gastrointestinal signs, but other, less specific signs, such as anorexia, weight loss, jaundice, or polyuria/polydipsia, should not be overlooked.

#### 1.1.2.1 Dysphagia and regurgitation

Dysphagia, which is defined as difficult or painful swallowing, can be classified as oral, pharyngeal, or esophageal. A good history can help the clinician to characterize the type of dysphagia, but a video recording at home should be recommended to better characterize the problem. An owner questionnaire has been evaluated for the characterization of dysphagia and was shown to be useful for the exclusion of oral dysphagia and the detection of pharyngeal dysphagia; however, it was less sensitive and specific for the assessment of esophageal dysphagia.[1]

**Oral dysphagia** is characterized by the dropping of food, leaking of water, or abnormally interrupted chewing followed by rejection of food during the meal. Oral dysphagia is associated with disorders of the oral cavity (▶Chap. 4.2) or with neuromuscular or osteoarticular disorders that impair normal chewing.

Abnormal, repeated swallowing efforts followed by periprandial regurgitation of an alimentary bolus mixed with saliva are the hallmarks of **pharyngeal dysphagia**. Swallowing efforts are frequently associated with coughing or choking and with gagging at rest.

**Esophageal dysphagia** is associated with regurgitation,[9] which is a passive process during which an undigested food bolus is thrown up. Sometimes, the food bolus has a cylindrical shape and is covered with mucus (▶Fig. 1-1). The time elapsed between swallowing the food and regurgitating the bolus is variable but can be quite long, especially when severe esophageal dilation is present. However, the time period is usually shorter in patients with esophagitis, esophageal stricture, or esophageal obstruction (▶Chap. 5.3). In contrast to pharyngeal dysphagia, esophageal dysphagia is usually not associated with swallowing attempts. The history may also reveal respiratory signs, such as coughing or nasal discharge, which may even be the primary complaint. The main task of history taking is to differentiate regurgitation from vomiting (▶Tab. 1-5).

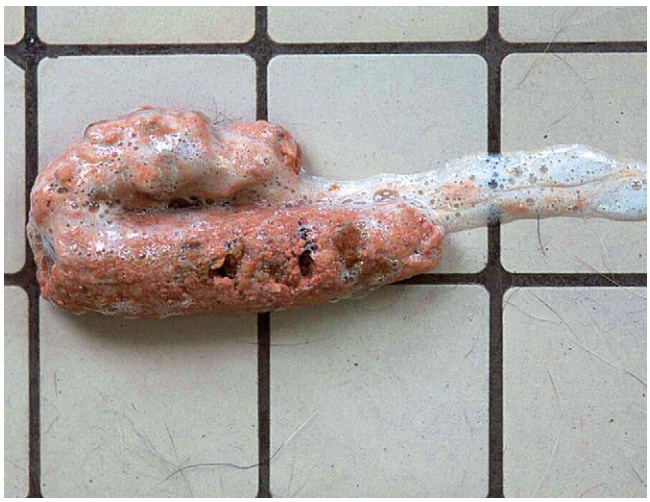


**Fig. 1-1** Regurgitated food

This figure shows regurgitated food from a dog with esophageal stenosis following general anesthesia for spaying. Note the mucus surrounding a cylindrical bolus of food.

**Tab. 1-5** Differentiation of regurgitation and vomiting[11]

| Clinic sign | Regurgitation | Vomiting |
|---|---|---|
| **Abdominal effort** | Absent | Present |
| **Cervical esophageal distension** | Possible | Absent |
| **Prodromal signs** (nausea, retching) | Absent (except rare salivation) | Present |
| **Character of ejected material** | Undigested | Can be partially digested (depending on the time between ingestion and vomiting) |
| | Bile is rare | Bile can be present |
| | pH variable | pH variable, but usually <5 |
| | Typically, cylindrical shape | Variable shape |
| **Time of ejection** | Variable | Variable |
| **Pain on swallowing** | Can be present | Absent |

### 1.1.2.2 Gagging

Gagging is clinically characterized by ejection of pharyngeal material after the elevation of the soft palate and forceful contraction of the pharyngeal muscles. It is a normal defense mechanism to protect the pharynx and upper respiratory tract.[10] Sometimes, gagging is associated with swallowing attempts without the presence of an alimentary bolus. Gagging can be part of the clinical manifestation of dysphagia, especially in patients with pharyngeal disease,[11] but it can also be associated with certain respiratory disorders of the nasal passages, larynx, trachea, or bronchi.[10] Gagging can be associated with ptyalism or retching (defined as non-productive vomiting, ▶Chap. 1.1.2.4) due to activation of the pharyngeal vomiting receptors.

### 1.1.2.3 Vomiting

Vomiting is not always linked to a primary gastrointestinal (GI) tract disorder. It must be differentiated from regurgitation and coughing, as discussed above (▶Tab. 1-5). Vomiting is an active process with prodromal clinical signs and has three phases:

- The first phase, nausea, is frequently associated with hypersalivation, agitation or depression, yawning, lip licking, or repeated swallowing attempts.
- The second phase, retching, appears as a vomiting effort with abdominal wall contractions but without ejection of vomitus and can be associated with belching.
- The last phase, vomiting, is the forceful ejection of gastric contents, which is associated with very repetitive strong abdominal wall contractions.

Vomiting can be classified as acute or chronic, with chronic being defined as lasting for >3 weeks. Also, the content of the vomitus should be characterized, especially concerning the presence of food, parasites, or foreign bodies. Hematemesis is blood-tinged vomitus, containing either fresh or digested blood, resembling coffee grounds (▶Fig. 1-2). Hematemesis is associated with gastric or duodenal erosions and should always be considered a sign of severe disease.[9,12] However, small amounts of fresh blood are sometimes related to capillary rupture, linked to the rise in venous pressure during vomition.[12]



**Fig. 1-2** Hematemesis dog

This figure shows the coffee-ground appearance of vomitus in a dog with gastric bleeding.

Gastritis (▶Chap. 6.3.1) may be associated with vomiting of bile on an empty stomach or vomiting of food, usually shortly (30 minutes to a few hours) after a meal.[9,13] Vomitus consisting of large volumes of fluid can be associated with ileus, small intestinal obstruction, or hypersecretory states such as gastrinoma.[13] Vomitus that smells like fecal material can sometimes be observed in patients with intestinal obstruction (▶Chap. 7.3.6) or small intestinal dysbiosis (▶Chap. 7.3.4). Vomiting associated with bile that occurs in the morning can be due to duodenal reflux gastritis in small breeds. Vomitus, containing food that is produced >8–12 hours after a meal, is highly suggestive of a gastric emptying disorder (▶Chap. 6.3.2).[9,13] Projectile vomiting can be observed in patients with a gastric outflow obstruction but may also simply reflect violent vomiting due to any cause.

Whenever possible, the number of vomiting episodes should be quantified. This is helpful to plan fluid therapy in patients with acute vomiting and also for the assessment of disease severity (e.g., canine inflammatory bowel disease activity index [CIBDAI]; ▶Tab. 1-6) or another clinical scoring system, such as the canine chronic enteropathy activity index ([CCECAI]; ▶Tab. 1-7) or the modified canine activity index ([MCA]I; ▶Tab. 1-8) in patients with chronic vomiting due to a chronic enteropathy.[2,14,15]

### 1.1.2.4 Retching

Retching is characterized by repetitive efforts to vomit without any expulsion of vomitus. Diagnostically, retching should be approached the same as vomiting. However, in some instances, even a good history can not differentiate retching or the regurgitation of saliva or mucus from coughing and/or expectorations.[9,11] In patients that present with acute retching and abdominal distension, gastric dilatation-volvulus (GDV, ▶Chap. 6.3.3) must be ruled out immediately.[9]

### 1.1.2.5 Diarrhea

Diarrhea is defined as the passage of feces that contain more water than normal, which increases daily fecal weight. As for vomiting, the first step is to classify whether the diarrhea is acute or chronic.[16] The next step is to characterize the feces by asking questions about blood, foreign material, undigested food particles, or mucus in the feces (▶Fig. 1-3). The color, volume, odor, and consistency of the feces might also be helpful, narrowing the list of differential diagnoses. For example, rancid-smelling, large volume, grayish brown, and cow-patty stools may suggest exocrine pancreatic insufficiency (EPI, ▶Chap. 10.3.2) or another condition associated with maldigestion (▶Fig. 1-4). The number of bowel movements per day should also be quantified. The main concern is to localize the origin of the diarrhea either to the small or to the large intestine. The characteristics that may be helpful for localizing the cause of the diarrheal disease are shown in ▶Tab. 1-9. However, these characteristics are not absolute, and patients with clinical signs of large bowel disease may have more diffuse disease with more significant small bowel disease. Using a photographic fecal scoring chart may be helpful in characterizing the diarrhea (▶Fig. 1-5).

**Tab. 1-6** Canine inflammatory bowel disease activity index (CIBDAI)

The CIBDAI was one of the first scoring systems proposed for monitoring dogs with chronic inflammatory enteropathies. The table shows six parameters that are being scored for the purpose of this index.[2]

| Parameter | Score | Note |
|---|---|---|
| **Attitude/Activity** | 0: Normal | - |
| | 1: Slightly decreased | - |
| | 2: Moderately decreased | - |
| | 3: Severely decreased | - |
| **Appetite** (voluntary intake) * during the latest meal before the visit | 0: Normal | The animal ate >3/4 of the food |
| | 1: Slightly decreased | The animal ate about 1/2 of the food |
| | 2: Moderately decreased | The animal ate about 1/4 of the food |
| | 3: Severely decreased | The animal did not eat much of the food or at all |
| **Vomiting** * during the 24 hours before the visit | 0: No vomiting | No vomiting |
| | 1: Occasional vomiting | One time per week |
| | 2: Frequent vomiting | 2–3 times per week |
| | 3: Consistent vomiting | >3 times per week |
| **Stool consistency** * stool observed immediately before the visit | 0: Normal | Well formed |
| | 1: Soft | Slightly watery and poorly formed |
| | 2: Diarrhea | No form and runny |
| | 3: Watery diarrhea | Watery with no solids and pale |
| **Stool frequency** | 0: Normal | - |
| | 1: Slightly increased | 2–3 defecations per day or blood, mucous, or both |
| | 2: Moderately increased | 4–5 defecations per day |
| | 3: Severely increased | >5 defecations per day |
| **Weight loss** | 0: None | - |
| | 1: Mild | <5% of body weight |
| | 2: Moderate | 5–10% of body weight |
| | 3: Severe | >10% of body weight |

**Tab. 1-7** Canine chronic enteropathy clinical activity index (CCECAI)

The CCECAI is based on the CIBDAI (▶Tab. 1-6), but adds three additional parameters. The table shows nine parameters that are being scored for the purpose of this index.[14]

| Parameter | Score | Note |
|---|---|---|
| **Attitude/Activity** | 0: Normal | - |
| | 1: Slightly decreased | - |
| | 2: Moderately decreased | - |
| | 3: Severely decreased | - |
| **Appetite** (voluntary intake) **Food Intake** * during the latest meal before the visit | 0: Normal | The animal ate >3/4 of the food |
| | 1: Slightly decreased | The animal ate about 1/2 of the food |
| | 2: Moderately decreased | The animal ate about 1/4 of the food |
| | 3: Severely decreased | The animal did not eat much of the food or at all |
| **Vomiting** * during the 24 hours before the visit | 0: No vomiting | - |
| | 1: Occasional vomiting | One time per week |
| | 2: Frequent vomiting | 2–3 times per week |
| | 3: Consistent vomiting | >3 times per week |
| **Stool consistency** * stool immediately before the visit | 0: Normal | Well formed |
| | 1: Soft | Slightly watery and poorly formed |
| | 2: Diarrhea | No form and runny |
| | 3: Watery diarrhea | Watery with no solids and pale |
| **Stool frequency** | 0: Normal | - |
| | 1: Slightly increased | 2–3 defecations per day or blood, mucous, or both |
| | 2: Moderately increased | 4–5 defecations per day |
| | 3: Severely increased | >5 defecations per day |
| **Weight loss** | 0: None | - |
| | 1: Mild | <5% of body weight |
| | 2: Moderate | 5–10% of body weight |
| | 3: Severe | >10% of body weight |
| **Serum/plasma albumin concentration** | 0: Normal | ≥ 2.0 g/dL |
| | 1: Mildly decreased | 1.5–1.9 g/dL |
| | 2: Moderately decreased | 1.2–1.4 g/dL |
| | 3: Severely decreased | <1.2 g/dL |
| **Ascites and peripheral edema** | 0: None | - |
| | 1: Mild | Mild ascites or peripheral edema |
| | 2: Moderate | Moderate ascites or peripheral edema |
| | 3: Severe | Severe ascites, pleural effusion, and/or peripheral edema |
| **Pruritus** | 0: None | - |
| | 1: Mild | Occasional episodes of itching |
| | 2: Moderate | Regular episodes of itching, but stops when asleep |
| | 3: Severe | Dog regularly wakes up because of itching |

**Tab. 1-8** Modified canine activity index (MCAI)

The MCAI is also based on the CIBDAI (▶Tab. 1-6) and scores seven areas of clinical relevance to dogs with pancreatitis, including activity, appetite (voluntary food intake), vomiting, cranial abdominal pain, dehydration, stool consistency, and blood in the stool.

| Parameter | Score | Note |
|---|---|---|
| **Activity** | 0: Normal | As usual |
| | 1: Slightly decreased | The animal stands less than usual |
| | 2: Moderately decreased | The animal is reluctant to stand up |
| | 3: Severely decreased | The animal does not stand up |
| **Appetite** (voluntary food intake) | 0: Normal | The animal ate >3/4 of the food |
| | 1: Slightly decreased | The animal ate about 1/2 of the food |
| | 2: Moderately decreased | The animal ate about 1/4 of the food |
| | 3: Severely decreased | The animal did not eat much of the food or at all |
| **Vomiting** | 0: None | - |
| | 1: Mild | 1–2 times/day |
| | 2: Moderate | 3–4 times/day |
| | 3: Severe | ≥5 times/day |
| **Cranial abdominal pain** | 0: None | No signs of pain |
| | 1: Mild | Abdominal wall resistance or other signs of pain are elicited upon palpation of the abdomen; the animal moves slowly or is less responsive. |
| | 2: Moderate | The animal resists palpation, is reluctant to move when encouraged, and does not lie on its side. |
| | 3: Severe | Persistent vocalization, howling, and/or insomnia |
| **Dehydration** | 0: None | <5%, no signs of dehydration |
| | 1: Mild | 5%, slight loss of skin elasticity |
| | 2: Moderate | 6–8%, decreased skin turgor, slightly delayed capillary refill time, dry mucous membranes, sunken eyes |
| | 3: Severe | ≥10%, severely decreased skin turgor, delayed capillary refill time, deeply sunken eyes, severely dry mucous membranes |
| **Stool consistency** | 0: None | Well formed |
| | 1: Mild | Slightly watery and poorly formed |
| | 2: Moderate | No form and runny |
| | 3: Severe | Watery with no solids and pale |
| **Blood in the stool** | 0: Absent | - |
| | 1: Present | - |



**Fig. 1-3** Mucoid stool

This figure shows mucoid stools from a dog with severe colitis due to whipworm infestation. Note that the stool is almost exclusively composed of mucus and blood.



**Fig. 1-4** Exocrine pancreatic insufficiency (EPI)

Cow-patty yellowish stools from a dog with EPI.

**Tab. 1-9** Characterization of small and large bowel diarrhea[5,16]

Please note that none of these parameters are absolute.

| Parameter | Small intestine | Large intestine |
|---|---|---|
| Volume per defecation | Normal to increased | Decreased or normal |
| Mucus | Absent (except in patients with ileitis) | Frequently present |
| Melena | May be present | Rarely present |
| Hematochezia | Absent (except in patients with acute hemorrhagic diarrhea) | Frequently present |
| Steatorrhea | May be present | Absent |
| Frequency of defecation | Usually slightly increased up to four times per day but can be severely increased in patients with severe acute enteritis | Increased (many defecations with small volume) |
| Dyschezia | Absent | Often present |
| Tenesmus | Absent | Frequently present |
| Urgency | Absent, except in severe cases | Usually present; sometimes with indoor soiling |
| Flatulence/borborygmus | May be present | May be present |
| Weight loss | May be present | Rare |
| Anal pruritus | Absent | May be present |
| Vomiting | May be present | May be present in patients with acute colitis |

## Fecal Scoring System

### Score 1: Liquid

Liquid stool may not contain any particulate matter. Liquid stools are often deposited in multiple spots instead of a single stool. Liquid stool can also contain mucus or blood. A liquid stool sample is very difficult to collect and a residue is always left on surfaces and gloves.

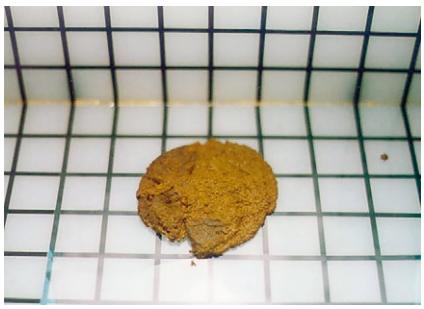




**Fecal Score "1".** Notice splattered appearance indicative of a liquid consistency. Also, note the large surface area of defecation.

### Score 2: Soft, without shape

This stool is soft and does not show any cylindrical shape. Soft stool without shape is also often referred to as cow-patty stool. This stool will lose its original shape when collected and will leave a residue on surfaces and gloves. This stool score is often present with stool of another score, but can comprise the whole stool sample.

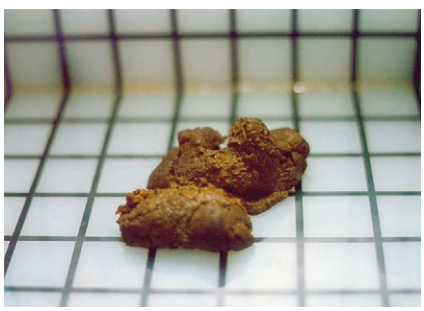




**Fecal Score "2".** This stool sample clearly appears soft and does not show any cylindrical shape. Notice the increased surface area of the sample, which is commonly referred to as a "cow-patty" appearance.

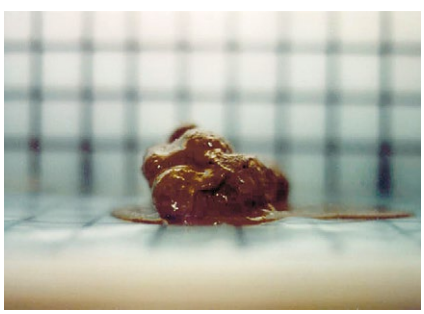
### Score 3: Soft, with shape

This stool is soft, but still has a shape to it. This stool will break apart easily and will leave a residue on surfaces and gloves. The stool often loses the original shape after collection. Soft stool with shape is often present with stool of another score, but can comprise the whole stool sample.





**Fecal Score "3".** This stool sample exhibits a soft appearance but still has shape to it.



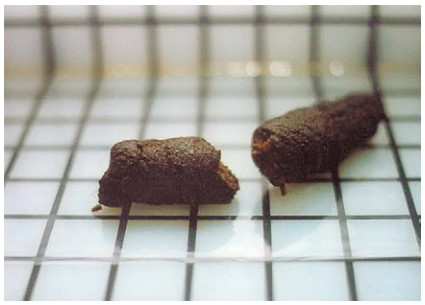
**Fecal Score "3/1".** Soft, shaped fecal material with a liquid portion.



**Fecal Score "3/2".** Portions of this stool sample are soft, but shaped, while other portions do not have any shape to it.

**Fig. 1-5** Fecal scoring system (based on a scoring system used by the former Iams Company, Dayton, OH, USA)
This figure shows an example of a scoring system that can be used by dog owners to evaluate fecal consistency.

## Fecal Scoring System

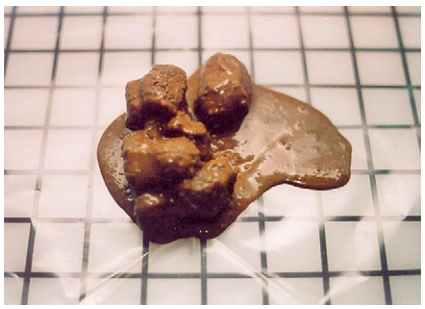




**Fecal Score "4".** This sample exhibits the standard cylindrical shape. Also, notice the equal height of the whole stool sample.

**Score 4: Firm (ideal stool)**

Firm stool is well shaped and cylindrical. This stool does not break apart easily when picked up, but may leave a residue on surfaces and gloves. Firm stool is often defecated as a single stool and maintains its original shape after collection.



**Fecal Score "4/1".** This stool sample has portions with a cylindrical shape (score 4), but also contains a liquid portion (score 1).



**Fecal Score "4/2".** This stool sample shows a clear distinction between some dark cylindrical feces and some lighter and shapeless fecal material.



**Fecal Score "4/3".** This stool sample contains both cylindrical portions and areas that are softer and less well shaped.





**Fecal Score "5".** Please note multiple fecal balls as opposed to a single fecal log.

**Score 5: Extremely dry**

Extremely dry stool is hard and does not stick to surfaces. The stool will roll when pushed. No indentations are made when the stool is picked up and it maintains its original shape after collection. Extremely dry stool is often defecated as multiple fecal balls as opposed to a single stool.



**Fecal Score "Mucous".** Stool of any score can be accompanied by mucus that can be clear or bloody. The mucus may cover the entire stool sample or only a small portion of it.

**Additional Fecal Observation Codes**

11- Blood in stool

15- Foreign object in stool

40- Mucus in stool



**Fig. 1-6** Melena
This figure shows melena in a dog with severe gastric bleeding.



**Fig. 1-7** Perineal herniation
Round stools that resemble the appearance of "horse manure" from a dog with perineal herniation

### 1.1.2.6 Other stool abnormalities

**Melena** is characterized by black and tarry stools and is sometimes associated with diarrhea (▶Fig. 1-6). Melena is a sign of the presence of blood in the gastrointestinal tract. The blood usually comes from the GI tract itself but can also be swallowed in patients that are bleeding into the respiratory tract. Melena is mainly associated with bleeding of the upper GI tract; the black color and tarry consistency are due to the transit of blood through the intestinal tract.[12] Therefore, blood from the upper parts of the large intestine can also be black and tarry, and blood coming from the small intestine can be fresh if the transit time does not allow for the digestion of the blood. Some medications, such as metronidazole, ferrous sulfate, bismuth, or some food ingredients (e.g., liver, spinach), can also produce dark stools that are sometimes confused with melena. Asking about ulcerogenic medications, especially NSAIDs, anticoagulant exposure (e.g., rodenticide), or recent trauma is also important.[12]

**Fresh blood** that is adherent to the feces is called hematochezia and is consistent with large bowel or recto-anal bleeding.[12] Hematochezia can be associated with disorders of the large bowel (e.g., colitis, proctitis, foreign body, or neoplasia) or coagulopathy. It is not always associated with dyschezia or straining to defecate and is, therefore, sometimes not observed by the owner.

**Ribbon-like stools** are observed in conditions associated with narrowing of the colonic, rectal, or anal passage and frequently lead to dyschezia or constipation.
Sometimes, round or ball-like feces resembling horse manure (▶Fig. 1-7) are observed with perineal herniation or anal diverticula (▶Chap. 8.4).

**Acholic feces** are clay-colored feces that can be observed in patients with extrahepatic bile duct obstruction (▶Chap. 9.6.1) or destructive cholangitis (▶Chap. 9.6.3).

### 1.1.2.7 Flatulence and borborygmus

Flatulence and borborygmus (rumbling in the GI tract) are ultimately due to the presence of large amounts of intestinal gas that can occur in association with many digestive disorders. Excessive gas can also be associated with abdominal discomfort. A dietary history is important in these patients since certain types of foods commonly lead to the formation of excessive gas in the intestinal lumen (e.g., legumes, soybeans, or excess fat).

### 1.1.2.8 Dyschezia

Dyschezia is defined as difficult or painful defecation, characterized by straining to defecate with or without producing feces. Dyschezia can be observed in association with large bowel diarrhea but more frequently with constipation, rectal disease, anal disorders such as anal furunculosis or anal gland sacculitis, or prostatic diseases in male dogs. Dyschezia is most commonly a sign of very distal GI disease.[17]

Intestinal tenesmus is straining to defecate and is a clinical manifestation of either dyschezia or colonic and recto-anal disease.[17] However, tenesmus can also be a clinical manifestation of lower urinary or genital tract disease that should be differentiated from intestinal tenesmus.

#### 1.1.2.9 Constipation

Constipation is defined by the passage of dry, hard feces and is associated with a decreased number of bowel movements and straining to defecate.[17] In cases of suspected constipation, it is important to ask about urination behavior, as urinary straining can be confused with straining to defecate in some patients, especially in cats with lower urinary tract obstruction. Straining before defecation is usually associated with obstructive or functional disorders inducing constipation. In contrast, straining throughout defecation or persisting after defecation has been completed is frequently associated with diarrhea due to inflammatory disorders of the colon and/or rectum.[17]

Sometimes, the constipated patient is presented for diarrhea. The diarrhea perceived by the owner is due to a small quantity of liquid fecal material passing around the fecal bolus lodged in the colon and/or rectum.

#### 1.1.2.10 Fecal incontinence

Fecal incontinence is characterized by uncontrolled loss of feces without crouching to defecate.[17] It must be differentiated from urgency to defecate by carefully questioning the owner, as these two causes of fecal soiling are frequently confused. In patients with true fecal incontinence, the stools are usually normal, and the loss of feces frequently occurs during excitation or coughing. The owner should be questioned about the presence of controlled and normal defecation to assess whether the neuro-muscular control of defecation is functional. A history of trauma (especially tail trauma in cats), as well as medical or surgical conditions of the perianal area, are frequently associated with fecal incontinence.

#### 1.1.2.11 Anal pruritus

Anal pruritus is manifested by perineal licking or biting, anal scratching, or scooting. It is usually associated with recto-anal diseases such as anal furunculosis, anal sac disorders (▶Chap. 8.4), or *Dipylidium caninum* infestation, but can also be a manifestation of food allergy (▶Chap. 11.1), constipation, or inflammatory bowel disease (IBD; ▶Chap. 11.2).

#### 1.1.2.12 Abdominal pain

The owner may report certain behaviors, such as a saw horse stance or prayer position (stretching out the forelimbs with the sternum in contact with the floor while standing on the hindlimbs; ▶Fig. 1-9), which are strongly suggestive of cranial abdominal pain.[18] Bruxism (teeth grinding) or restlessness can also sometimes be associated with severe abdominal pain in dogs and cats. Restlessness can sometimes be observed during the first stages of gastric dilatation-volvulus.[3] In cases of extreme abdominal pain, the pet may be severely depressed or even aggressive.

### 1.1.3 Dietary history

A complete dietary history is very important for the diagnosis of gastrointestinal disease and should include specific commercial foods that are being fed, commercial snacks or treats, supplements, and chewable medications, chewable toys, human food (especially leftover food from human meals), access to other sources of food (ask about other pets in the household or about people who may give extra food to the pet).[19] Many medical supplements or certain drugs contain proteins or additives that may elicit allergic or other adverse reactions (especially vitamins, fatty acids, or dermatological supplements). It is also important to try to identify any possible correlation between clinical signs and certain types of food, supplements, or medications.

**Abnormal feeding patterns** should be documented. **Coprophagia** can be observed in any disorders causing polyphagia, such as EPI or high-dose corticosteroid treatment. Also, coprophagia or pica can be observed in patients with severe maldigestion or malabsorption, nutritional deficiencies, or behavioral problems. **Eating grass** is frequently reported in dogs and cats and is of concern when it is followed by nausea and/or vomiting. Eating grass could either be the cause or, more commonly, a consequence of a gastrointestinal problem.

**KEY FACTS**

- Acquiring a detailed history is essential to further characterize the clinical signs related to digestive disease.
- Differentiation between regurgitation and vomiting is necessary to determine an optimal workup for each patient.
- In cats, constipation must not be mistaken for urinary straining.
- A dietary history is a cornerstone in the diagnosis and management of digestive diseases.

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
svg.to/9842-01-01

## 1.2 Physical examination

Andrea Boari, Paolo Emidio Crisi

### 1.2.1 Introduction

By far, the most important diagnostic tool that veterinarians can use is their ability to obtain a complete history and conduct a thorough physical examination. The objective of the physical examination is to recognize and describe gross deviations in the patient's physical appearance and behavior from those recognized as normal for the animal's species, breed, age, sex, and sexual status.

The trend toward increased use of laboratory tests and instrumentation has added diagnostic capabilities, but such techniques are useful adjuncts for diagnosis only when a careful physical examination has been carried out. Thus, information gathered from the laboratory and diagnostic imaging procedures must be considered as a supplement to, not a substitute for, hands-on examination. Traditionally, inspection and observation of the patient, palpation, percussion, and auscultation are all important for every physical examination.

Presentation of a patient that is severely ill or in critical condition only requires a brief initial examination, and the clinician must make every effort to stabilize the animal. In fact, if the patient is in shock or bleeding or is suspected of having gastric dilatation-volvulus (GDV; ▶Chap. 6.3.3) or another critical condition, it is essential to initiate supportive care immediately and obtain a complete history with careful physical examination afterward.

The physical examination of the GI tract, as described in this chapter, is part of the methodical and standardized physical examination. However, the discussion is mainly limited to parameters of the physical examination that are specific and directly related to the gastrointestinal system. However, it is important that the clinician examine all body systems when presented with a patient that shows signs of gastrointestinal disease. Ophthalmic and neurological examinations can sometimes provide invaluable clues as to the cause of gastrointestinal dysfunction.

### 1.2.2 General physical examination

#### 1.2.2.1 Skeletal growth and development

Stunted growth in dogs and cats is often seen with congenital endocrinopathies, such as hyposomatotropism, exocrine pancreatic insufficiency (EPI; ▶Fig. 1-8), or hypothyroidism, but can also result from vascular ring or other esophageal abnormalities (▶Chap. 5.3), malabsorption, or portosystemic shunts (▶Chap. 9.5.3.2).



**Fig. 1-8** Exocrine pancreatic insufficiency (EPI)
This picture illustrates the failure to grow in two puppies with EPI compared with a healthy littermate (these dogs were described in detail in Boari et al. 1994[1]).

#### 1.2.2.2 Body condition

Evaluation of body weight is inexpensive, easy, and very useful. Weight loss can be caused by inadequate nutrient assimilation (i.e., anorexia, regurgitation, vomiting, maldigestion, or malabsorption), increased loss of nutrients (i.e., protein-losing nephropathy and/or protein-losing enteropathy [PLE; ▶Chap. 7.3.8]), and/or increased energy demand, as it occurs in hyperthyroid cats, febrile patients, or patients with neoplastic conditions. Cachexia associated with fever can be due to infectious (e.g., feline infectious peritonitis [FIP], feline leukemia virus [FeLV]), inflammatory (e.g., pancreatitis and others), or neoplastic (e.g., gastrointestinal neoplasia, lymphoma) causes.

Weight loss rarely occurs in dogs and cats with intestinal disorders that are limited to the large bowel but can occasionally be observed in patients with severe, long-standing colitis such as histiocytic ulcerative colitis (HUC), cecocolic intussusception or diffuse colorectal neoplasia (▶Chap. 8.3).[2] However, it can also be due to a tendency of owners to feed their pets with diarrhea less food.

**NOTE**
It is very important to remember that an acute decrease in body weight can be due to water loss (i.e., vomiting and/or diarrhea) and that measurement of body weight will allow for an accurate assessment of the level of dehydration.

### 1.2.2.3 Mental status

**Depression or stupor** can be related to abnormal brain function caused by metabolic (e.g., hepatic encephalopathy, acid-base and osmolality imbalances, or hypoglycemia), inflammatory (e.g., canine distemper, FIP, sepsis), vascular (e.g., hypertension), or coagulation disorders.

The term **"star gazing"** refers to the upward raising of the head and neck extension with subsequent staring at the ceiling or sky and is usually related to a hallucinatory behavior in dogs. However, this behavior may also be a manifestation of esophageal pain secondary to erosive gastritis with reflux esophagitis.

**"Fly snapping"** (also known as "fly biting," "air biting," or "jaw snapping") is a behavior in which dogs appear to watch or see something that is not visible to humans and then snap. This condition has been associated with gastric and/or duodenal eosinophilic or lymphoplasmacytic infiltration, delayed gastric emptying, gastroesophageal reflux, or Chiari malformation.[3]

### 1.2.2.4 Abnormalities in posture and locomotion

Abnormal posture, such as arching of the back or adoption of the "prayer" position (▶Fig. 1-9), are characteristic signs of abdominal pain, which needs to be differentiated from back pain.[4]

Although rare, hind limb weakness or paraplegia secondary to a vascular clot can be observed in dogs that are in a hypercoagulability state secondary to PLE.[5]



In the cat, neck ventroflexion can be a sign of hypokalemia that can be caused by gastrointestinal loss of potassium due to severe vomiting and/or diarrhea, third space losses/sequestration secondary to accumulation of fluid in body cavities (e.g., peritonitis), or a distended gastrointestinal tract (e.g., due to volvulus or ileus).

### 1.2.2.5 Body temperature

At the time the temperature is taken the clinician should also note if the rectal area is clean or soiled from diarrhea or matted and whether the anal sacs are distended. The perineum is also observed for the presence of tapeworm proglottids. At the end of the examination, the thermometer should be examined for any sign of blood, melena, or mucous. The



**Fig. 1-9** "Prayer" position

This picture shows a dog with acute abdominal pain due to acute pancreatitis. This dog has assumed the "prayer" position with his front legs and sternum on the floor and his hind legs standing.

appearance of blood in the feces can vary according to the site of bleeding, the transit time through the GI tract, and the volume of blood lost.[6]

Hematochezia (i.e., fresh blood in the stool, ▶Chap. 1.1.2.6) is strongly suggestive of large bowel disease, in particular, colitis (▶Chap. 8.3.1). However, enterocolic and cecocolic intussusception, colorectal neoplasia, and coagulopathies, especially platelet disorders, must also be considered, even though these are uncommon. Melena describes tar, coal, or asphalt-colored stool, resulting from digested blood and can be observed due to bleeding into the pharynx, esophagus, stomach, or upper small bowel (▶Fig. 1-6). When melena is present, a complete physical examination should include careful inspection of the nares, oropharynx, and lungs for evidence of the source of bleeding. It is important to remember that a life-threatening volume of blood can accumulate within the GI tract with little or no visible signs of external blood loss. If gastrointestinal blood loss is associated with acute diarrhea, regardless of its cause, this signals a loss of normal intestinal mucosal integrity. With the loss of this barrier, the physiologic enteric microbiota can cross into the bloodstream, leading to septicemia. In this case, the clinician needs to address the complications of diarrhea while determining its cause. In young adult small dogs with an acute onset of bloody diarrhea, idiopathic acute hemorrhagic diarrhea syndrome (AHDS, ▶Chap. 7.3.3) should be suspected. In these cases, the clinician must make note of the presence of signs of a potentially life-threatening severe inflammatory response syndrome and/or sepsis to establish prompt and appropriate supportive treatment.

**NOTE**

Dogs with acute diarrhea, and idiopathic acute hemorrhagic diarrhea syndrome (AHDS) in particular, are frequently dehydrated due to the massive loss of fluid into the gut lumen, potentially leading to hypovolemic shock. Hypothermia, tachycardia, and tachypnea are common findings in these patients, and thus, these criteria are not useful in diagnosing severe inflammatory response syndrome in dogs with idiopathic AHDS. Indeed, clinical signs of sepsis were observed in approximately half of the dogs with AHDS, even in the absence of bacteremia.[7]

There are many causes of fever in patients with gastrointestinal disease, ranging from infectious causes (e.g., FeLV, FIP, feline immunodeficiency virus [FIV], canine distemper, feline panleukopenia, canine parvovirus, leptospirosis, salmonellosis, toxoplasmosis, leishmaniosis, histoplasmosis, blastomycosis, cryptococcosis, coccidioidomycosis, or rickettsial infections) to disorders involving the liver, exocrine pancreas, and the peritoneum, or neoplasia such as lymphoma or carcinoma. In patients with a tense abdomen and hyperthermia, the presence of peritonitis secondary to the lesions generated by the migration of a foreign body should be excluded, especially if the patient is young.

In contrast, severely uremic patients, patients with sepsis and shock, or patients in their final stages of several severe systemic diseases can be hypothermic.

### 1.2.2.6 Pulse rate

The effects of many systemic and metabolic diseases on cardiac structure and function are well recognized. In some cases, these changes may constitute the major clinical concern, while in others, these effects may be subtle or of minimal importance. Common causes of tachycardia are excitement, fever, anemia, hemorrhage, shock, hypotension, significant alterations in the concentration of electrolytes or acid-base balance, congestive heart failure, and some infections.

Patients with **gastric dilatation-volvulus (GDV,** ▶Chap. 6.3.3) often show cardiac dysfunction, especially after surgical decompression. This is often times associated with a tachyarrhythmia or, less commonly, a bradyarrhythmia.

**Septic shock**, often caused by gram-negative bacteria, can result in brick-red mucus membranes with a strong pulse during the initial stages or pale mucus membranes and a weak pulse during the latter stages.

**Electrolyte and acid-base abnormalities** can lead to significant alterations in cardiac function. These can often be documented while examining the pulse (e.g., weak, irregular, bradysphygmic) but are better recorded using an ECG. Bradycardia in a collapsed or shocky dog should heighten the index of suspicion for hyperkalemia and its causes, most importantly hypoadrenocorticism, in addition to cardiac conduction abnormalities that can cause bradycardia. Severe hyperkalemia (usually >8 mEq/L) causes severe cardiac dysfunction.

In addition to hypoadrenocorticism, hyperkalemia with hyponatremia (Na/K ratio <27:1) may also be found in dogs with gastrointestinal disease due to trichuriasis, salmonellosis, or a perforated duodenal ulcer.[8]

Decreased Na/K ratios frequently occur in cats with diseases other than hypoadrenocorticism, including gastrointestinal disease, and cats with effusions.[9] Hyperkalemia without hyponatremia is almost always associated with impaired renal excretion due to oliguric or anuric renal failure.

Arrhythmias can also be observed in patients with hypokalemia. Hypokalemia is sometimes associated with alkalemia but more often is due to gastrointestinal loss of potassium or renal loss in patients with polyuric renal failure.

### 1.2.2.7 Respiratory rate

Respiratory rate and quality should be recorded at the beginning of the examination of the respiratory tract.

**NOTE**

It is important to differentiate between an increased respiratory rate that is due to a physiological response to exercise, hyperthermia, pain, or anxiety and one that is due to respiratory disease.

Inspiratory dyspnea can be observed in patients with an elongated or edematous soft palate or in cats with a pharyngeal polyp.

Animals with esophageal disease or vomiting can be presented to a veterinarian for respiratory distress due to aspiration pneumonia. Suspicion of megaesophagus (▶Chap. 5.3.8) or other esophageal diseases should be high if the owner

reports that recurrent regurgitation or vomiting took place before the respiratory signs developed.

Severe life-threatening dyspnea is often present in patients with pleural effusion associated with ascites due to hypoproteinemia or non-septic inflammation (i.e., FIP in cats).

Rapid breathing can also be attributed to cranial displacement of the diaphragm by abdominal masses, fluid, or gas (e.g., due to gastric torsion) and/or acid-base imbalances. Compensatory hyperventilation is frequently seen in animals with metabolic acidosis, which can be caused by severe diarrhea, chronic renal disease, diabetic ketoacidosis, or hypoadrenocorticism.

#### 1.2.2.8 Mucous membranes

Mucous membrane color and capillary refill time (CRT) are used to assess peripheral perfusion. A **slower CRT** suggests either dehydration or high peripheral sympathetic tone and vasoconstriction. Both are associated with a low cardiac output. In a patient presented for vomiting, diarrhea, and/or anorexia, it is very important to address the patient's overall hydration status. To that end, the clinician should assess body weight, skin turgor, or pliability, moistness and color of the mucous membranes, CRT, the position of the eyes in their orbits, and pulse and respiratory rates and their characteristics.

**Pale mucous membranes** are a manifestation of either decreased red blood cell mass or decreased peripheral perfusion. In the latter case, shock (i.e., hypovolemic, cardiogenic, or vasomotor shock) can cause hypovolemia, cardiac insufficiency, and vasoconstriction. In patients with endotoxemic shock, the mucous membranes may become cool to the touch.

Pale mucous membranes can also be associated with hepatobiliary disease due to blood loss secondary to upper gastrointestinal bleeding or impaired coagulation and/or as a result of non-regenerative anemia due to chronic disease. Peptic and neoplastic gastric ulceration may also lead to anemia. Acute blood loss into the abdomen due to the rupture of visceral hemangiosarcoma, which occurs much more frequently in dogs than in cats, can also cause pale mucous membranes, weakness, abdominal distension, and increased pulse and/or respiratory rates. The CRT is normal for anemic patients unless hypoperfusion co-exists.

**Bilirubin** (▶Chap. 1.3.3.5) has a high affinity for elastic tissue, and the oral and conjunctival mucous membranes are often the first sites where jaundice can be seen, together with the sclera and the skin of the pinna. Yellow oral mucus membranes are almost always observed in cases of severe icterus, which can be caused by immune-mediated hemolytic anemia, severe hepatobiliary disease, or extrahepatic biliary duct obstruction/rupture.

A septic patient often has **injected, highly vascular mucous membranes** (brick-red), as can also occur in patients with polycythemia, those with acute hepatic or pancreatic disease, or those with severe azotemia. Congestion of mucous membranes may occur in patients with gastrointestinal disease, usually as a manifestation of dehydration. Mucous membranes should also be checked for signs of hemorrhage. Superficial bleeding into the skin or mucous membranes and scleral and vitreal hemorrhage are common manifestations of abnormalities of primary hemostasis. In addition to petechiae or ecchymoses, the animal may also present with hematemesis and/or melena, as well as hematuria. Although infrequent, patients with severe hepatic disease can show bleeding diathesis due to coagulation factor deficiency, disseminated intravascular coagulation (DIC), or portal hypertension. Because of the multiple hemostatic defects present in patients with DIC, they may experience hemorrhage of any type and in any location (cavitary or superficial).

#### 1.2.2.9 Peripheral lymph nodes

Mandibular, prescapular, and popliteal lymph nodes are usually palpable, and they should be evaluated for size, shape, and consistency. In contrast, the axillary and superficial inguinal lymph nodes are not always discernible. Given the close proximity of the mandibular lymph nodes and submaxillary salivary glands, it is essential that the clinician be able to distinguish between these two. Especially in cats, the surrounding subcutaneous fat may make the popliteal lymph nodes seem larger than they actually are. On the other hand, emaciated adult animals may have normal-sized popliteal lymph nodes that appear more prominent because of loss of fat and muscle mass.

Generalized lymphadenopathy usually indicates a systemic disease (e.g., immune-mediated disease, systemic infection, or most commonly neoplasia). Especially in the dog, the presence of markedly enlarged peripheral lymph nodes that are firm and non-painful is highly suggestive of lymphoma.

#### 1.2.2.10 Skin and subcutaneous tissue

The skin should be carefully inspected for areas of alopecia, inflammation, nodularity, and crustiness. Also, examination of mucocutaneous junctions may reveal evidence of systemic immune-mediated disease. Canine systemic lupus erythematosus has occasionally been reported to cause megaesophagus in dogs.[10]




**Fig. 1-10** Hepatocutaneous syndrome

Crusting and ulcers in the periocular region (**a**) and hyperkeratosis of the footpads with ulceration (**b**) in a Welsh terrier with hepatocutaneous syndrome.

Non-seasonal pruritus, erythema, and papules can be attributed to food hypersensitivity or food intolerance in both dogs and cats (▶Chap. 11.1). The concurrent presence of gastrointestinal and dermatological signs in dogs and cats is strongly suggestive of food hypersensitivity.[11]

Dramatic skin lesions (i.e., erythema, crusts, erosions, ulcers, alopecia, or shiny skin) can be seen in high-contact areas and the ventral thorax and abdomen in patients with superficial necrolytic dermatitis due to glucagonoma or, more frequently, hepatocutaneous syndrome, which can rarely occur secondary to liver disease (▶Fig. 1-10).[12] Also, pancreatic carcinoma, bile duct carcinoma, hepatocellular carcinoma, neuroendocrine pancreatic carcinoma, hepatosplenic plasma cell tumor, or colon carcinoma have also been reported as a cause of paraneoplastic alopecia in cats, which is predominantly present in the area of the ventral abdomen and hindlimbs.[13,14]

The integument should also be evaluated for changes in skin turgor, which is assessed in a consistent manner and location, usually on the lateral thorax (see evaluation of mucous membranes for hydration status). The clinician should take into account that the skin turgor is dependent on the amount of subcutaneous fat and elastin, as well as on the interstitial volume. Thus, emaciated and older animals may appear more dehydrated than they actually are. On the other hand, obese animals may appear falsely well-hydrated based on their skin tenting.

Generalized soft tissue swelling or enlargement involving the four limbs, often associated with ascites, may be due to edema. Edema can be easily distinguished from other subcutaneous fluid accumulations or masses because the pressure applied to an edematous area results in an indentation that stays for a short period of time. Subcutaneous edema can occasionally be seen in hypoalbuminemic dogs with PLE, PLN, or severe hepatic insufficiency.

### 1.2.3 Examination of the gastrointestinal tract

The examination of the gastrointestinal or digestive tract begins at the head (i.e., oral cavity), passes through the neck, down to the abdomen, and finishes with a rectal examination.

#### 1.2.3.1 Examination of the mouth and pharyngeal area

Examination of the mouth and pharyngeal area often provides important clues as to the pathogenesis of anorexia, vomiting, regurgitation, or drooling. In particular, drooling, which is best defined either as **ptyalism** (i.e., overproduction of saliva) or **pseudoptyalism** (i.e., dribbling or drooling of saliva that has accumulated in the oral cavity), occurs because animals are unable to swallow or are in too much pain to do so. Drooling commonly occurs during nausea, hepatic encephalopathy (especially in the cat), seizures, stomatitis, glossitis, gingivitis, pharyngitis, tonsillitis, or oral or pharyngeal dysphagia (▶Chap. 4.2). Nasal discharge can also be associated with dysphagia, gagging, or sometimes vomiting.

Swallowing and the **gag reflex** are assessed by placing an index finger at the base of the tongue or by observing the animal while it is drinking or eating. During the first examination in puppies or kittens, evaluation for cleft palate or other



**Fig. 1-11** Sublingual linear foreign body
This picture shows a linear foreign body wrapped around the base of the tongue in a cat.

congenital defects is required. Tonsillitis, an inflammation of the tonsils which is associated with enlargement of the tonsils, mainly in the dog, can cause anorexia, vomiting, or dysphagia and can occasionally be a sign of systemic disease (e.g., lymphoma). However, a complete examination of the tonsils and the oropharynx is rarely possible. Sedation is required if there are indications of an abnormality in the pharyngeal and laryngeal regions. The tongue is examined for color and movement. The sublingual region is checked for masses, linear foreign bodies (in the cat, ▶Fig. 1-11), or a laceration of the frenulum as a result of a string. This type of assessment should be included in every physical examination.

Also, breath odor can be indicative of dental or periodontal disease, as well as uremia or ketonemia.

The high frequency of hyperthyroidism in geriatric cats requires that the clinician carefully palpate the paratracheal area, extending from the caudal larynx to the thoracic inlet, to detect nodular swelling suggestive of thyroid gland enlargement. The normal feline thyroid glands are not usually palpable.

### 1.2.3.2 General examination of the abdomen

The general aspects of the abdomen should first be evaluated, and careful palpation of the abdomen is the most important part of the abdominal examination.

In general, abdominal distension may be due to gas, fluid, organomegaly, or poor abdominal muscle tone. Association with other clinical signs, such as vomiting, diarrhea, abdominal pain, polydipsia, polyuria, polyphagia, or edema, may serve as a clue to the underlying etiology. If a gas-distended abdomen is suspected, digital abdominal percussion should be performed, listening for a tympanic sound. In the dog, gastric tympany results in flaring of the posterior rib cage and the hypochondrium. As gastric distension increases, the posterior abdomen also becomes visibly distended.

A sudden onset gas-distended abdomen, shock, and even sudden death are often observed in dogs with intestinal volvulus.

If an enlarged abdomen is suspected to be due to abdominal fluid, ballottement should be carefully performed to determine if a fluid wave is present. With experience, false positive results are infrequent. **Abdominal effusion** is usually caused by hypoalbuminemia, portal hypertension, or peritoneal inflammation. Effusion due to gastrointestinal disease is primarily caused by PLE, hepatic failure, rupture of the alimentary tract, or leakage following an anastomosis.[15–17] PLE in a young dog with chronic intermittent diarrhea, without hookworms, should prompt suspicion of a chronic intussusception, and an abdominal ultrasound should be performed.[17]

Pyogranulomatous inflammation of the abdominal or thoracic cavity that is associated with a characteristic effusion is typical for the effusive form of FIP.

**Malignant abdominal tumors** may lead to obstruction of lymphatic flow, increased vascular permeability, leading to effusions that can be characterized as a modified transudate or can be exudative.[18] Hepatobiliary malignancies or other intra-abdominal malignant neoplasia that have spread to the peritoneum can elicit an inflammatory reaction, with subsequent exudation of lymph, fibrin, and blood. The resulting peritoneal effusion may be serosanguinous, hemorrhagic, or pseudochylous in appearance. Modified transudates can also result from hepatic or cardiac disease.

An increased abdominal size due to enlarged organs are usually related to the liver, spleen, and occasionally, the kidneys. Alternatively, single neoplastic masses of other organs can also lead to abdominal distention.

### 1.2.3.3 Abdominal palpation

Abdominal palpation is the cornerstone of the physical examination in both dogs and cats with clinical signs of gastrointestinal disease. This can be a most informative procedure

in the cat because of the ease with which most of the viscera can be palpated in this species.

Some animals tense their abdominal muscles in response to palpation. The clinician should distinguish between a normal frightened patient from one with referred spinal pain, abdominal pain, or generalized pain. It is worth noting that if an animal arches its back during abdominal palpation, the primary problem may be in the spinal cord.

More significance is attributed to the pain response elicited in stoic animals and to pain that is localizable, repeatable, and evident after minimal manipulation. It is necessary to determine whether the painful area is superficial, located in the cranial or caudal abdomen, and if it originates from a specific viscus. Cranial abdominal pain is commonly observed in dogs with pancreatitis but less commonly observed in cats. Generalized abdominal pain with the rigidity of the abdominal musculature suggests generalized peritonitis. An acute abdomen requires an urgent workup including history, clinical examination, and additional diagnostic testing (e.g., radiography, abdominal ultrasound, and laboratory tests).

An empty **stomach** in cats and dogs is usually only palpable in thin patients, although after being distended with food, the stomach can be palpated in the upper left abdominal quadrant in most patients (i.e., left medial epigastrium). The **gallbladder and pancreas** are not normally palpable. However, in patients with pancreatitis, pancreatic neoplasia, or a pancreatic pseudocyst (▶Chap. 10.3), an abdominal mass and pain associated with palpation of that mass may be observed in the right cranial quadrant of the abdomen (i.e., right medial epigastrium).

The **small intestine** can easily be palpated as a thin-walled and smooth object that fills much of the mid-abdomen (i.e., mesogastrium) and slides through the fingers.



In the cat, the ileocecal area can often be palpated as a firm, knot-like structure in the mid-cranial abdomen (i.e., medial mesogastrium) and should not be confused with an abdominal mass.

The bowel should be carefully evaluated for thickness, rigidity, and irregular masses. A thickened intestinal wall may be felt in patients with intestinal infiltration by inflammatory or neoplastic cells and in patients with intestinal smooth muscle hypertrophy.[19]

Masses (e.g., lymph node enlargements, foreign bodies, omental steatitis, neoplasia, intussusception, or focal granulomatous lesions, such as those that can be seen in patients with a non-effusive form of FIP) can cause partial or total intestinal obstruction but may go undetected during physical examination because of their small size. Fluid-distended small bowel loops are often palpable in patients with acute enteritis.



Aggregated or accordion-like small bowel loops are characteristic of a linear foreign body obstruction in cats.

Palpable **mesenteric lymph node enlargements** are often associated with tumors, granulomas, or inflammation (with or without foreign body obstruction). Massive mesenteric lymphadenopathy is often typical of dogs and cats with alimentary tract lymphoma (▶Chap. 11.3), but modest lymphadenopathy can also be found in patients with inflammatory bowel disease (IBD, ▶Chap. 11.2) or other chronic intestinal diseases.

A sick animal that vomits shortly after abdominal palpation should be suspected of having a GI obstruction, severe GI tract inflammation, or pancreatitis.

The transverse and descending **colon** are often full of fecal material and can easily be identified by palpation of the mid-posterior abdomen (i.e., medial and dorsal meso-hypogastrium), just ventral to the spine. An impacted colon (the colon must be at least twice its normal diameter before megacolon can be considered) is caused by intestinal obstruction or dysmotility.

The **liver** can be routinely palpated just caudal to the costal arch, along the ventral body wall in both canine and feline patients but may not be palpable in some cases. If the liver is not palpable, it does not automatically mean that it is abnormally small. Microhepatia is mainly seen in patients with a congenital portosystemic shunt or those with chronic hepatic disease with progressive loss of hepatocytes (▶Chap. 9.5). However, hepatic size is better evaluated by radiography. In lean cats, it is possible to palpate the diaphragmatic surface of the liver. In animals with pleural effusion or other diseases that expand the thoracic volume, the liver may appear enlarged due to its caudal displacement. The pattern of hepatic enlargement may be generalized or focal, depending on its cause. Infiltrative and congestive diseases tend to result in smooth, firm, and diffuse hepatomegaly. Primary or metastatic neoplasia, nodular hyperplasia, and some chronic hepatic diseases associated with nodular regeneration can cause focal or asymmetric hepatic enlargement.

In icteric dogs and cats, hepatosplenomegaly may be attributable to mononuclear-phagocytic cell hyperplasia and extramedullary hematopoiesis secondary to immune-mediated hemolytic anemia or infiltrative processes such as systemic mast cell disease, lymphoma, or myeloid leukemia.

Palpation of the **spleen** is not always possible, but it is easier in the cat. Sometimes the free distal portion is palpable on the floor of the mid-abdomen. The spleen is palpated to identify an increase in size and nodules and larger masses. In patients with severe splenomegaly, the spleen may occupy the entire ventral abdominal floor. When the enlarged spleen is folded over, it could be mistaken for a mass. In some cases, the clinician might be able to unfold the spleen with his or her thumb and evaluate the true size and shape of the organ.

In cats, an enlarged spleen suggests mast cell disease, lymphoma, or another neoplastic process. In dogs, splenomegaly with irregular margins strongly suggests hemangiosarcoma or hematoma, but other causes of splenic enlargement must also be considered.

The **kidneys** can be more easily palpated in cats compared with dogs because they are more loosely attached. The kidneys are normally located in the retroperitoneal space, and the right kidney is positioned slightly more cranial than the left one. The kidneys are evaluated for size, shape, location, firmness, pain, and surface irregularities. The left kidney (the only one that can be palpated in some dogs) is especially movable and can easily be mistaken for an abdominal mass. Enlarged, abnormally-shaped kidneys may be due to acute renal failure, renal neoplasia, renal cysts, abscesses, granulomatous nephritis due to FIP, hydronephrosis, or a hematoma. In contrast, small renal size is often associated with chronic renal disease.

During abdominal palpation of intact female animals, the normal non-gravid **uterus** is usually non-palpable. Massive uteromegaly caused by pregnancy, pyometra, mucometra, or hydrometra can sometimes give the mistaken impression of ascites and must be carefully differentiated.

#### 1.2.3.4 Abdominal auscultation

Lastly, abdominal auscultation may sometimes be helpful. Intestinal sounds (i.e., borborygmus) come from waves of peristaltic contractions that move digesta aborad along the GI tract. Borborygmus can be hypoactive, normoactive, and hyperactive, but its interpretation is somewhat subjective and for this reason, the historical and clinical context should always be taken into account. However, being able to interpret trends in gut sounds can offer a valuable aid in differentiating a healthy subject from an unhealthy one. Dogs or cats with chronic clinical signs of small bowel disease with hyperactive sounds may have a malabsorption syndrome. A dog or a cat with anorexia and vomiting with hypoactive borborygmus may have an intestinal obstruction.

Usually, failure to detect intestinal sounds after 2–3 minutes of auscultation is suggestive of ileus.

#### 1.2.3.5 Examination of the perineal area

The perineal area should be examined for evidence of diarrhea, including feces caked in the hair coat, masses, herniations, sphincter integrity, masses, and perineal hernia. Rectal examination must always be performed, and the clinician should be able to identify and evaluate the colonic mucosa, anal sphincter, anal sacs, pelvic canal bones, urogenital tract, and luminal contents. Mucosal polyps can easily be misinterpreted as mucosal folds, and it is possible to miss partial strictures that are large enough to allow a single finger to pass through.

Pelvic canal obstruction due to congenital and acquired causes can lead to constipation and megacolon, especially in cats.

Rectal discomfort, hematochezia, and mucous can be found in patients with colitis, proctitis, or large bowel neoplasia.

During rectal examination, the prostate of all mature male dogs must be evaluated for size, symmetry, surface structure, and pain. If enlarged, the prostate may extend slightly over the brim of the pelvis or fall into the abdomen. In this latter situation, the prostate can be palpated in the caudal abdomen ventral to the colon and caudal to the urinary bladder. To assist in rectal palpation, the other hand of the examiner should be used to gently push the prostate into a more dorsal and caudal position via abdominal palpation.

Also, to complete the physical examination, the clinician should observe the act of defecation whenever possible, especially if there is a history of dyschezia or tenesmus.

Whether tenesmus occurs before or after defecation can also aid in the differentiation of an underlying disease process. Obstructive disorders are more commonly associated with tenesmus before the evacuation of feces, whereas inflammatory disorders are often associated with persistent tenesmus after the evacuation of feces.

**KEY FACTS**

- Life-threatening volumes of blood can accumulate within the gastrointestinal tract, with little or no visible signs of external blood loss.
- Abdominal distension may be due to gas, fluid, organomegaly, or poor abdominal muscle tone.
- Protein-losing enteropathy (PLE) in a young dog with chronic intermittent diarrhea, without hookworms, should prompt a suspicion for a chronic intussusception.
- Aggregated (accordion-like) small bowel loops on abdominal palpation are characteristic of a linear foreign body obstruction in cats.
- A sick animal that vomits shortly after abdominal palpation should be suspected of having a gastrointestinal (GI) obstruction, severe GI tract inflammation, or pancreatitis.
- A rectal palpation should be performed in every patient presenting for evaluation of gastrointestinal disease.

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
svg.to/9842-01-02

## 1.3 Laboratory tests

### 1.3.1 Diagnosis of gastric disease

Craig G. Ruaux

#### 1.3.1.1 Introduction

There are no findings on routine laboratory tests that are specific for gastric disease. However, routine clinical chemistry remains important in the assessment of these cases to monitor the overall health of the patient. Routine clinical chemistry panels may be useful to rule out conditions that can lead to similar clinical signs or systemic disorders that can affect the stomach (such as renal or hepatic failure or pancreatitis). Determining packed cell volumes and total protein concentrations allow for evaluation of blood and protein loss in patients with gastric ulcers and hydration status in vomiting patients. Animals with gastric ulcers may have regenerative anemia and decreased total protein concentrations. Chronic vomiting may lead to loss of electrolytes (mainly sodium and potassium) and acid-base disturbances (metabolic alkalosis or acidosis). Anemia, hypoglycemia, and increased liver enzyme activities may be observed in animals with gastric tumors (▶Chap. 6.3.4).

Gastroscopy is currently the gold standard for diagnosing gastric disease (▶Chap. 1.5). In recent years, several new diagnostic tests for gastric disease have been developed. However, at the current time, most of these new tests are employed predominantly in a research setting.

#### 1.3.1.2 Evaluation for gastric parasitism and *Helicobacter*-like organisms

In regions where gastric parasites, such as *Ollulanus tricupsis* (in cats) and *Physaloptera rara* (both dogs and cats), are endemic, patients should be screened for the relevant organisms. *Ollulanus tricuspis* can be detected during microscopic examination of vomitus, while eggs of *Physaloptera rara* can be detected in fecal smears or by fecal sedimentation.[1]

##### 1.3.1.2.1 Diagnosis of *Helicobacter*-like organisms

*Helicobacter*-like organisms (HLOs) can be detected in biopsy specimens obtained during gastroscopy by means of histopathology (Warthin-Starry or modified Steiner stain), immunohistochemistry, polymerase chain reaction (PCR), or rapid-urease tests.[2] Alternatively, an impression smear can be taken from the gastric mucosa using a cytology brush. The brush is then rolled across a microscope slide, and the slide is stained with either May-Grünwald-Giemsa, Gram, or Diff-Quick stains.[2] Many animals show a patchy distribution of *HLO* infestation, and it is crucial that biopsy specimens or impression smears are obtained from several areas of the stomach.[3] Recent publications have described the use of in vivo confocal endomicroscopy to detect gastric colonization by *HLOs*, but this technique could not detect intracellular invasion by the organism.[4]

Minimally invasive detection methods for *HLOs* are easy to perform but are limited in that they cannot identify the presence of gastric disease. Detection of antibodies directed against *HLOs* in serum has a relatively low sensitivity. In addition, antibodies circulate for up to 6 months after the eradication of an organism; thus, these antibody tests cannot be used to monitor therapeutic success.[4] The $^{13}$C-urea breath or blood test is based on the detection of metabolic activity of *Helicobacter* spp.[5] The organisms produce the enzyme urease, which catalyzes the metabolism of orally administered

$^{13}$C-urea. The $^{13}$C is released from the urea, incorporated into $^{13}CO_2$, and can be quantified in either breath or blood samples.[5] This test can be used for both the diagnosis and monitoring of therapy but is not offered commercially at this time.

#### 1.3.1.3 Sucrose permeability testing

Increased gastric permeability has been observed in humans with gastric ulcers and NSAID- or *Helicobacter pylori*-associated gastritis. Gastric permeability has traditionally been evaluated using radioactive markers ($^{51}$Cr-EDTA). Alternatively, the disaccharide sucrose can be used as a specific non-radioactive marker for gastric permeability.[6] Orally administered sucrose is too large to permeate the intact gastric mucosa, and an increase in the urinary sucrose concentration is indicative of increased gastric permeability, which is highly suggestive of gastric mucosal damage. However, this test is not currently commercially available.

#### 1.3.1.4 Minimally invasive markers for gastric disease

Serum gastrin concentrations can be measured in dogs and cats using assays developed for serum gastrin measurements in people. Gastrin is very labile, and serum must immediately be separated from the blood clot, frozen, and shipped on ice.

**NOTE**

Gastric acid suppressants, both $H_2$-receptor antagonists and proton pump inhibitors, induce a compensatory increase in circulating serum gastrin concentrations. However, in patients with severe gastritis or esophagitis, it is ethically questionable to withhold these medications before testing.

A 24-hour-fasted serum gastrin concentration increased to >10 times the upper limit of the reference interval is suggestive of a gastrinoma in dogs. However, this recommendation is based on data from human beings where atrophic gastritis is a common cause of moderate increases in serum gastrin concentrations. Atrophic gastritis has only been reported in the Norwegian lundehund, and other diseases or medications associated with increased serum gastrin concentrations can be easily ruled out in the dog.

C-reactive protein, a highly sensitive but nonspecific marker of inflammation, correlates well with the degree of experimentally induced damage of the gastric mucosa.[7] Increased plasma lactate concentration (>6.0 mmol/L) has been shown to be a negative prognostic marker for post-operative survival time in dogs following gastric dilatation-volvulus.[8] Further studies evaluating the correlation of plasma lactate concentrations with long-term survival are warranted. Measurement of immunoreactive pepsinogen has served as a research tool for the diagnosis of gastritis in dogs but has no diagnostic value in individual patients with spontaneous disease.[10]

#### 1.3.1.5 Analysis of gastric juice

Analysis of gastric juice is rarely performed in veterinary medicine. This is due to both technical complexity and limited standardization. Analysis of gastric juice also shows a poor correlation with endoscopic and histopathological findings.

#### 1.3.1.6 Evaluation of gastric emptying time

Scintigraphy is considered the gold standard for the evaluation of gastric emptying but requires the use of a radioactive marker. Alternatively, a radiopaque marker, such as barium-impregnated polyethylene spheres (BIPS), can be used. These markers have the disadvantage that, depending on their size, they only mimic the emptying of either solid or liquid food.[11] Recent studies have described the use of capsule endoscopy systems (▶Chap. 1.5.6) to determine gastric emptying times in individual dogs.[12]

A common finding with all methods that assess gastric emptying is the high degree of intra-individual variation, which leads to a very wide reference interval and difficulty in interpreting clinical cases.

**KEY FACTS**

- Routine laboratory tests are nonspecific for gastric disease but should be performed to rule out other diseases that are associated with a similar clinical presentation.
- Currently, no laboratory tests are available that are specific for gastric disease.
- Gastroscopy is currently the gold standard for a definitive diagnosis of gastric disease.

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
svg.to/9842-01-03-01

## 1.3.2 Diagnosis of intestinal disorders

Craig G. Ruaux

### 1.3.2.1 Introduction

The clinical investigation and definitive diagnosis of intestinal disorders are complicated by the inaccessibility of much of the intestinal tract to direct examination. While endoscopic examination of the intestinal tract can yield information on discrete lesions and gross alterations in mucosal appearance or architecture, endoscopy requires expensive equipment, a high level of expertise, and general anesthesia of the patient. Histological assessment of the intestinal tract is usually considered the gold standard for the diagnosis of intestinal disease. A high degree of variability in histopathological interpretation has been documented between different observers, and the reliability and consistency of diagnoses based on intestinal histopathology have been questioned.[1]

Laboratory assessment of the intestinal tract is less expensive and invasive than endoscopy or exploratory laparotomy with histopathology. Most clinicians, therefore, will use some form of laboratory assessment of the intestinal tract before proceeding to more invasive procedures.

As described in ▶ Chap. 7.1, the intestinal tract as a whole has five major functions: secretion, digestion, absorption, motility, and barrier function. Secretion of fluid, ions, and enzymes, and nutrient digestion and absorption occur primarily in the small intestine. The large intestine is the major site of water and ion absorption. Clinical signs of intestinal disease result from alterations or disturbances in one or more of these major functions. Decreased digestion or absorption, or increased fluid secretion, will lead to diarrhea, one of the hallmark signs of intestinal disease.

Normal function of the intestine relies upon the presence of a healthy epithelium. Much of the function of the intestinal epithelium depends on subcellular structural elements, such as the microvillar brush border and intercellular tight junctions, which are not assessed by routine histopathological techniques.

Functional assessment of the intestinal mucosa can add useful information in the assessment of animals with gastrointestinal disease, except for water-soluble vitamin measurements, as these techniques are rarely used in clinical practice. Typically, the only functions assessed are mucosal barrier function and absorptive capacity. Intestinal absorptive capacity can be assessed by measuring serum cobalamin and folate concentrations and assessing intestinal function using sugar probes. Intestinal barrier function can be assessed by measuring fecal $\alpha_1$-proteinase inhibitor concentrations and performing radioisotope studies with $^{51}$Cr-EDTA; permeability testing can be assessed using sugar probes. Intestinal motility can be assessed using radiographic or ultrasonographic techniques, but secretion and digestion cannot be readily assessed using non-invasive markers.

### 1.3.2.2 Assessment of serum cobalamin and folate concentrations

Cobalamin (Vitamin $B_{12}$) and folate are water-soluble vitamins with highly specific sites of absorption. Measurement of serum concentrations of these vitamins can provide information about the small intestinal mucosa and the microbiome present in the small intestine.

#### 1.3.2.2.1 Cobalamin

Dietary cobalamin deficiency is highly unlikely in pets consuming commercial diets as these diets are fortified with cobalamin. Even homemade diets for companion animals are usually based on some form of animal protein, and thus provide sufficient cobalamin in most cases. As dietary deficiency of cobalamin is unlikely, alterations in serum cobalamin concentrations most likely represent changes in the ability of the animal's GI tract to absorb cobalamin. Thus, serum cobalamin concentrations can be used as a marker for gastrointestinal disease.

Cobalamin is absorbed through a complex, receptor-mediated mechanism (▶ Fig. 1-12). Dietary cobalamin, initially complexed to protein in the diet, is liberated in the stomach by the action of pepsinogen and gastric acid. The cobalamin is immediately bound to gastric and salivary R-protein, which carries the cobalamin into the duodenum. In the duodenum, the R-protein-cobalamin complex is broken down by pancreatic proteases, and the liberated cobalamin is complexed with another carrier protein, intrinsic factor. The site of intrinsic factor synthesis and secretion varies from species to species. In human beings, the gastric mucosa is the major source of intrinsic factor.



The domestic cat exclusively synthesizes intrinsic factor in the exocrine pancreas.[2,3]



Dogs produce intrinsic factor in the pancreas, and to a lesser degree, in the stomach.[4]

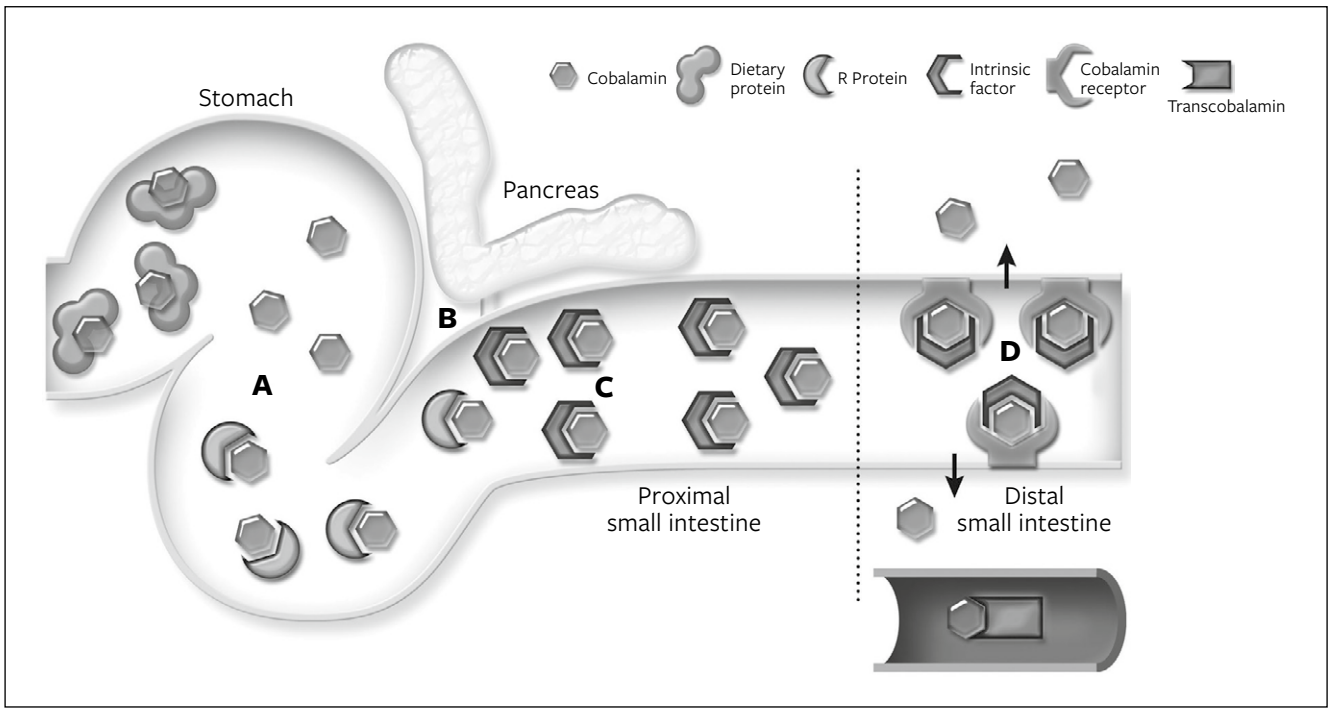



**Fig. 1-12** Cobalamin absorption

Dietary cobalamin is bound to dietary protein. In the stomach, pepsin and hydrochloric acid degrade the dietary protein, releasing cobalamin (**A**). Cobalamin is immediately bound by R-protein, which is produced by the gastric mucosa. In the duodenum, pancreatic proteinases digest the R-protein, releasing the cobalamin. Free cobalamin in the duodenum is bound by intrinsic factor (**B**). In humans, intrinsic factor is produced primarily by the stomach, and, in dogs, it is produced by both the pancreas and, to a lesser degree, the stomach. However, in cats, 99% of intrinsic factor is synthesized by the exocrine pancreas. Cobalamin remains bound to intrinsic factor during its passage through the cranial small intestine (**C**). In the distal small intestine, cobalamin/intrinsic factor complexes are taken up by specific receptors found only on enterocytes in the ileum (**D**). These enterocytes process the cobalamin/intrinsic factor complex and release cobalamin into the circulation, where a final set of binding proteins (transcobalamins) complex the vitamin and carry it to the cells.

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The final site of cobalamin absorption in all species studied to date is the ileum. Highly specialized cobalamin-intrinsic factor complex receptors are expressed on ileal mucosal enterocytes.

As the exocrine pancreas is the only source of intrinsic factor in cats and an important source in dogs, **exocrine pancreatic insufficiency** is commonly associated with cobalamin deficiency in both dogs and cats and should be ruled out in patients with gastrointestinal signs and a decreased serum cobalamin concentration (▶Chap. 1.3.4.2).[5]

Two other major mechanisms can reduce cobalamin availability from the small intestine, decreased mucosal absorptive capacity or **excess utilization of cobalamin by the intestinal microbiome**. Some bacterial species commonly present in the intestinal tract, particularly some members of the *Clostridium* and *Bacteroides* genera, are able to absorb and utilize cobalamin after it has been complexed with intrinsic factor. In normal individuals with a healthy intestinal microbiome, there is sufficient cobalamin in the diet to supply the needs of both the host organism and the microbiome. If the number of bacteria present in the intestine is increased, particularly if *Clostridium* and *Bacteroides* spp. are increased in the cranial part of the small intestine, these organisms can effectively compete with the host for the available cobalamin, ultimately leading to a reduced serum cobalamin concentration in the host.

**Mucosal disease in the ileum** may reduce expression of the cobalamin-intrinsic-factor complex receptor. With reduced expression of this receptor, mucosal uptake of cobalamin in the ileum is reduced. Persistent cobalamin malabsorption leads to the depletion of body stores of cobalamin and, ultimately, reduced serum cobalamin concentrations. The same is true for diffuse intestinal disease as long as the ileum is involved in the disease process. Cobalamin normally undergoes enterohepatic circulation. In gastrointestinal disease, the ability of the intestine to reabsorb cobalamin secreted in the bile is reduced, which can lead to dramatic shortening of the half-life of cobalamin in circulation, particularly in cats.[6]

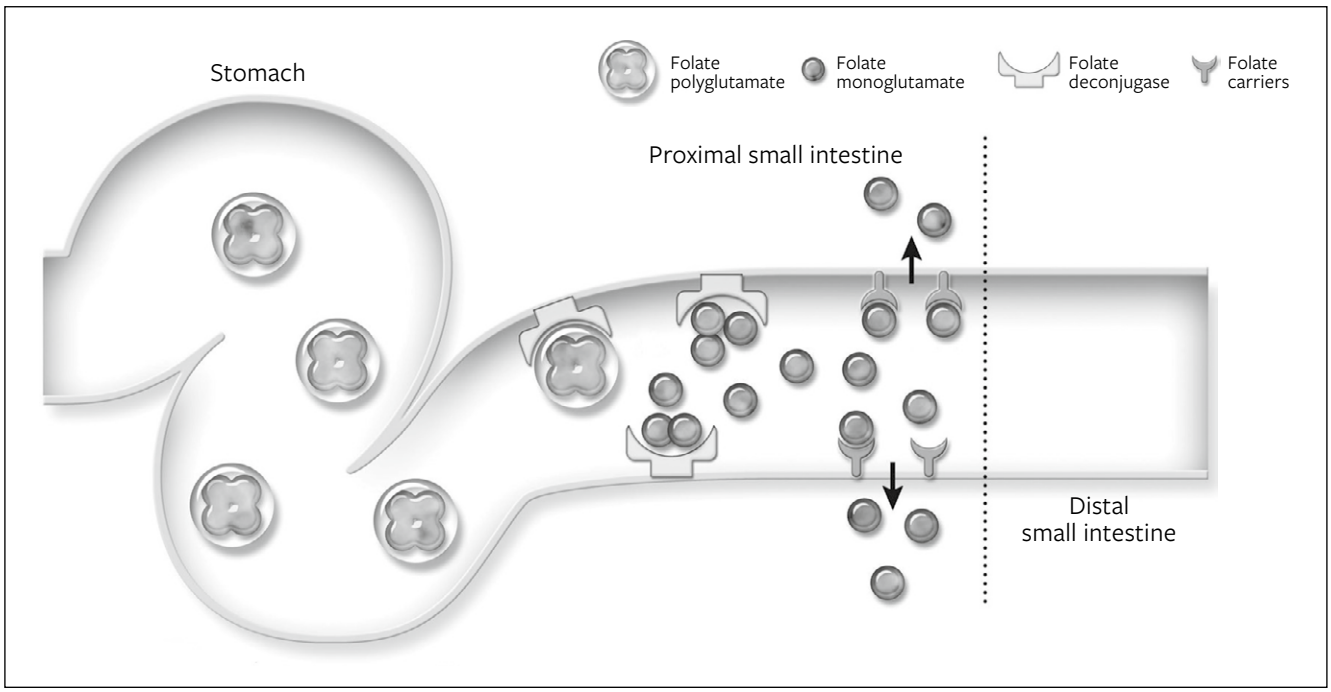



**Fig. 1-13** Folate absorption

Dietary folate enters the gastrointestinal tract predominantly in the polyglutamate form. Folate deconjugase, a brush border enzyme in the cranial small intestine, deconjugates the folate polyglutamate to folate monoglutamate. Specific folate carriers present on enterocytes located in the cranial small intestine subsequently absorb folate monoglutamate. Both the deconjugase and folate carrier molecules are restricted to the cranial small intestine. There is no appreciable absorption of folate in the distal small intestine or the colon.

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Serum cobalamin concentration is not only of diagnostic importance. Cobalamin is essential for many cell functions, and **cobalamin deficiency can lead to gastrointestinal abnormalities**, such as inflammatory infiltration of the mucosa, villous atrophy, and cobalamin malabsorption, as well as systemic abnormalities, such as peripheral and central neuropathies, or immunodeficiencies. Thus, patients with cobalamin deficiency may not respond to therapy of the primary disease process unless supplemented with cobalamin, and measurement of serum cobalamin is crucial in planning a rational therapy for these patients.

#### 1.3.2.2.2 Folate

The normal mechanism of folate absorption is illustrated in ▶Fig. 1-13. Most folate in the diet is present in a poorly absorbable polyglutamate form. Folate deconjugase in the jejunum removes most of the glutamate residues, leaving folate monoglutamate. Specific folate carriers in the upper small intestine then absorb folate monoglutamate.

Gastrointestinal disease may either increase or decrease serum folate concentrations, depending on the type of pathology present. Mucosal disease in the upper small intestine, or diffuse intestinal disease involving the upper small intestine, may reduce folate absorption either by interfering with folate polyglutamate deconjugation or reducing the presence of folate carrier proteins. Also, many intestinal bacteria, particularly those present in the lower small bowel, are able to synthesize folate. These organisms release excess folate into the intestine. Thus, an increase in the number of these organisms in the small intestine can lead to increased serum folate concentrations.[7]

Measurement of serum concentrations of cobalamin and folate is clinically indicated during the assessment of any patient with clinical signs of gastrointestinal disease, such as chronic diarrhea, particularly in those with clinical signs and history suggestive of small bowel diarrhea. Differential diagnoses to be considered with altered serum cobalamin and folate concentrations are summarized in ▶Tab. 1-10. To rule out exocrine pancreatic insufficiency, concurrent measurement of serum trypsin-like immunoreactivity concentration (TLI, ▶Chap. 1.3.4.1.2) is strongly recommended. Red blood cells have very high intracellular concentrations of folate; thus, it is important to avoid hemolysis of samples intended for the measurement of serum folate to reduce the chance of falsely elevated results. Also,

**Tab. 1-10** Interpretation of serum concentrations of cobalamin and folate in companion animals with gastrointestinal diseases

| | | Serum cobalamin | | |
|---|---|---|---|---|
| | | **Elevated** | **Normal** | **Subnormal** |
| **Serum folate** | Elevated | • Increased bacterial numbers in the cranial small intestine<br>• Consider small intestinal dysbiosis | • Increased bacterial numbers in the cranial small intestine<br>• Consider small intestinal dysbiosis | • Small intestinal dysbiosis or ileal mucosal disease<br>• Measure serum TLI concentration to rule out EPI |
| | Normal | • Elevated serum cobalamin concentration with normal serum folate concentration has no known significance | • Normal serum cobalamin and folate concentrations do not rule out small intestinal disease | • Ileal mucosal disease<br>• Measure serum TLI concentration to rule out EPI |
| | Subnormal | • Disease affecting the cranial small intestine<br>• Consider IBD, lymphoma, or fungal disease | • Disease affecting the cranial small intestine<br>• Consider IBD, lymphoma, or fungal disease | • Diffuse mucosal disease<br>• Consider IBD, lymphoma, or fungal disease |

**TLI** = trypsin-like immunoreactivity; **EPI** = exocrine pancreatic insufficiency; **IBD** = inflammatory bowel disease

serum folate is light-sensitive, and serum samples should be protected from light by wrapping them in foil before shipping.

### 1.3.2.3 Assessment of gastrointestinal protein loss

Many small intestinal diseases can lead to loss of protein into the GI tract. Protein loss into the intestine is a significant metabolic drain on the patient and may alter intestinal bacterial numbers by increasing available substrates for bacterial growth. Excess protein loss into the small intestine can lead to loss of plasma oncotic pressure and systemic pathology, such as ascites, thoracic effusion, and edema.

Assessment of protein loss into the small intestine is complicated by the digestive function of the intestine and the presence of bacterial proteolytic enzymes. It is important to quantify **albumin loss** into the GI tract, as albumin is a major contributor to the colloid plasma oncotic pressure. Unfortunately, albumin present in the GI tract is rapidly degraded by digestive and bacterial proteases; therefore, it is not possible to accurately measure albumin in feces or chyme.

**Alpha$_1$-proteinase inhibitor ($\alpha_1$-PI)** is a serum protein that is similar in molecular mass and size to albumin and thus is lost into the intestine at a similar rate as albumin. As $\alpha_1$-PI is a proteinase inhibitor, it is able to resist proteolytic degradation in the intestine and is passed undamaged in the feces.[9] Following extraction from fecal samples, $\alpha_1$-PI can be measured by use of an enzyme-linked immunosorbent assay (further information is available https://vetmed.tamu.edu/gilab/).

The fecal $\alpha_1$-PI test can detect significant protein loss before serum/plasma proteins are markedly reduced and before the onset of severe clinical signs related to hypoproteinemia. For example, soft-coated wheaten terriers that have a familial protein-losing enteropathy (PLE)/nephropathy have increased fecal $\alpha_1$-PI concentrations long before any clinical signs are present. Also, some patients with hypoalbuminemia due to PLE may not show signs of gastrointestinal disease; measurement of fecal $\alpha_1$-PI concentrations may help to diagnose the presence of gastrointestinal disease in these patients (▶Chap. 7.3.8). At the current time, only an assay for the measurement of $\alpha_1$-PI in dogs is commercially available.

### 1.3.2.4 Non-invasive assessment of intestinal mucosal inflammation

Documenting the presence of inflammation within the gastrointestinal mucosa remains challenging. Yet, appropriate evidence-based practice requires an objective marker for gastrointestinal inflammation before defining a chronic enteropathy as inflammatory in origin.

Inflammatory enteropathies can feature mucosal infiltration by a variety of inflammatory and immune system effector cells, ranging from patients with severe neutrophilic infiltrates in patients with some viral or bacterial pathogen-associated diseases to chronic lymphocytic or lymphoplasmacytic inflammation in "lower grade" immune-mediated or food-responsive enteropathies. Infiltration with eosinophils and the activity of mast cells may be important in other patients with clinical signs of gastrointestinal disease.

Immunological effector cells release a variety of compounds into the local mucosal environment. Direct measurement of these effector compounds, or metabolic end products of their degradation, can provide a minimally invasive technique for assessment of the types and severity of inflammation present.

Measurement techniques for several biomarkers of inflammatory cell activity in companion animals have been developed and validated in the last 5–10 years. Measuring these biomarkers in the systemic circulation can provide an integrated assessment for the presence of systemic inflammation in a patient; however, this lacks specificity for evaluating gastrointestinal inflammation. Acute phase proteins such as C-reactive protein and serum amyloid A, and various pro- and anti-inflammatory cytokines have been investigated in animals with chronic inflammatory enteropathies, and these are often different in diseased patients when compared with healthy controls, but they are all hampered by lower overall specificity and a high degree of intra-individual variability due to the effects of other systemic factors. Fortunately, several recently developed biomarkers for inflammatory cell activity can be extracted and measured from fecal samples, allowing a more specific assessment of gastrointestinal mucosal inflammation in animals with chronic inflammatory enteropathies.[10]

#### 1.3.2.4.1 Calprotectin and Calgranulin C

**Calprotectin**, also known as S100A8/A9, is a damage-associated molecular pattern (DAMP) molecule. This class of molecules accumulates at the site of active inflammation, having been released by effector cells in the inflammatory environment. The most important inflammatory effector cells responsible for the majority of calprotectin release in inflammatory conditions are activated macrophages and neutrophils. Measurement of calprotectin within the systemic circulation has been described in dogs with chronic enteropathies and has been shown to be significantly increased in these patients.[11]

Calprotectin survives transit through the GI tract and may be measured in fecal extracts. Measurement of calprotectin in fecal samples has been shown to be an acceptable surrogate marker of disease severity in dogs with chronic inflammatory enteropathies and may predict response to therapy in these patients.[12,13]

**Calgranulin C**, also known as S100A12, is another DAMP molecule that is released and accumulates in areas of active inflammation and is released by the same cells as calprotectin. Measurement of this protein in fecal extracts provides a sensitive and specific indicator of mucosal inflammation. Interestingly, fecal concentrations of calgranulin C correlate with the severity of clinical signs and endoscopic lesions in the GI tract of dogs but not with histological severity.[13]

Fecal assays for calprotectin and calgranulin C show significant promise as minimally invasive biomarkers of gastrointestinal inflammation in dogs and cats.

#### 1.3.2.4.2 N-methylhistamine and 3-Bromotyrosine

N-methylhistamine (NMH) and 3-bromotyrosine (3-BrY) are markers of mast cell and eosinophil activity, respectively. These compounds have been evaluated in the circulation (NMH, 3-BrY) and fecal samples (NMH) of canine patients. Concentrations of these biomarkers have been shown to be altered in dogs with chronic inflammatory enteropathies. Higher serum concentrations of 3-BrY are seen in dogs that require anti-inflammatory or immunosuppressive therapy compared with dogs that respond to dietary modification for food-responsive enteropathy, suggesting that this may be a useful marker to guide therapy, but further data is needed. The sensitivity, specificity, and diagnostic utility of these compounds are less well-defined than those of calprotectin and calgranulin C.

### 1.3.2.5 Assessment of intestinal permeability and barrier function

Intestinal barrier function, and the maintenance of normal intestinal permeability, are both critical aspects of gastrointestinal health. Alterations in permeability and barrier integrity may have important functional and pathological impacts, yet this aspect of intestinal functional assessment remains highly challenging.

The use of **sugar probes** to assess intestinal mucosal permeability and absorptive capacity has been described in dogs and cats. The most common probes used for this type of study are mixtures of simple sugars, with the quantification of these sugar probes in either urine or serum.[14–16] However, due to the methodological complexity of these tests, they are typically only used in research settings.

**Radioisotope studies** using $^{51}$Cr-EDTA have been described to assess gastrointestinal protein loss and intestinal permeability. Parenterally administered $^{51}$Cr-EDTA binds to (among others) albumin in the circulation, and quantification

of fecal recovery of the radiation allows assessment of protein loss. Similarly, orally administered solutions of $^{51}$Cr-EDTA, followed by measurement of recovery of radiation in serum or urine samples, provides a method for determination of intestinal barrier function.[17] The use of $^{51}$Cr-EDTA involves the production and management of radioactive waste, limiting the use of these techniques to research environments.

Recently, the use of the non-radioactive iodinated contrast agent **iohexol** as a probe for intestinal permeability has been described.[17] Iohexol recovery in serum samples correlates well with $^{51}$Cr-EDTA recovery. The use of oral iohexol recovery testing to assess intestinal permeability has been reported in dogs.[18] This technique requires more investigation to determine its diagnostic and clinical utility, but it shows promise as a minimally invasive, non-radioactive method to assess intestinal barrier function in small animal patients.

**KEY FACTS**

- Non-invasive serum and urine tests often yield clinically useful information for assessment of the small intestine.
- Functional assessment of the intestine may reveal disease when histopathology is normal.
- Serum concentrations of cobalamin and folate can aid in localizing intestinal disease and may indicate the presence of an altered intestinal microbiota.
- Fecal concentrations of alpha$_1$-proteinase inhibitor ($\alpha_1$-PI) are often increased in animals with protein-losing enteropathy before hypoproteinemia develops.
- Non-invasive markers of intestinal inflammation, measured in fecal samples, may aid in the characterization and management of chronic enteropathies.
- Minimally invasive assessment of intestinal barrier integrity using recovery of orally administered iohexol shows promise for the assessment of this critical intestinal function.

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
svg.to/9842-01-03-02

## 1.3.3 Diagnosis of liver and biliary tract disease

Ben Harris

### 1.3.3.1 Introduction

Laboratory testing allows screening for, diagnosing, and monitoring of hepatobiliary disease in a minimally invasive way – generally by application of blood tests. As these tests are mostly surrogate markers of damage to, or function of, the liver and biliary tree, it is important to understand their basis and, therefore, the strengths and limitations before using them to inform prognosis or to guide surgical or medical therapy.

Without such laboratory testing, diagnosis of hepatobiliary disease would often be delayed to the point of advanced clinical signs, at which point the prognosis may already be poor. The early and targeted application of laboratory tests may allow earlier diagnoses and interventions, thereby allowing for better prognoses.

There are few stand-alone laboratory tests that permit definitive diagnosis or accurate prognostication with a single test, but some tests may indicate when diagnostic imaging, biopsies, surgery, medications, or serial monitoring of values may be valuable.

#### 1.3.3.1.1 Accuracy of testing

Laboratory tests may be performed on benchtop analyzers in practice or at external laboratories, some of which may be accredited. Accreditation (ISO 17025) of a laboratory indicates that they have robust procedures, technical competence, quality assurance and therefore reliable, repeatable results. Reference interval values ("normal range") for each parameter will vary between laboratories, meaning that serial or follow-up monitoring is best done using the same analyzer or laboratory. Benchtop analyzers usually use simpler technologies (e.g., dry colorimetric tests) that allow use by individuals with minimal training, but these technologies may be more prone to error. In-house laboratory quality control is crucial to give the clinician confidence in the accuracy of the results upon which they will base their diagnostic and therapeutic decisions.

#### 1.3.3.1.2 Reference intervals

The term "reference interval" or "reference range" is preferred over the use of "normal range." By definition, only 95% of healthy individuals will have values within the "reference

interval." The other 5% are "normal outliers." If the reference interval was broadened to include all normal individuals, then the sensitivity of the test for detecting pathologic changes would suffer. Each laboratory should establish their own "reference intervals" – one cannot expect that a reference interval established by the manufacturer of a machine in one country will necessarily reflect the normal population in another country. A minimum of 40 healthy individuals is generally required to establish a reference interval.

Hepatobiliary laboratory biochemical testing is broadly divided into three categories:

1. Hepatocellular markers
2. Cholestatic markers
3. Functional markers

It should also be noted that there are various laboratory interferences that can affect markers of hepatobiliary disease (▶Tab. 1-11).

**Tab. 1-11** Laboratory interferences

| Condition | Laboratory parameters falsely increased | Laboratory parameters falsely decreased |
|---|---|---|
| Lipemia | Bilirubin | Sodium, chloride |
| Hemolysis | AST, phosphate, CK | Hematocrit; hemoglobin parameters |
| Icterus | ALT | Creatinine, total protein |

**AST** = aspartate aminotransferase; **CK** = creatine kinase; **ALT** = alanine aminotransferase

Hematology and urinalysis are also commonly used in the diagnosis and monitoring of hepatobiliary disease.

Cytology and histopathology are discussed in ▶Chap. 1.7.3 and ▶Chap. 1.8.2, respectively.

### 1.3.3.2 Hepatocellular damage markers

**Alanine aminotransferase (ALT)** is a transaminase enzyme essential for the metabolism of hepatocytes, as well as other tissues. ALT is present in high concentrations in hepatocytes, lower concentrations in skeletal and cardiac myocytes, and relatively insignificant concentrations in other cells and plasma. The normal ALT activity present in plasma is primarily due to leakage from senescent cells. When hepatocellular damage or death occurs, a large degree of leaked cytoplasm releases large concentrations of ALT into the extracellular space and, thus, the plasma. The greater the extent of cellular damage, the greater the release of cytoplasm, and the higher the rise of ALT activity in plasma (or serum). This applies to the level of cellular damage (e.g., mild membrane damage due to inflammation or cell death from hyperthermia) or to the liver volume affected (e.g., a small neoplastic lesion vs. torsion of an entire liver lobe).



**NOTE**

While the severity or extent of damage is reflected by the magnitude of ALT activity, this does not necessarily indicate the reversibility of the change, particularly as the liver has a strong capacity for regeneration.

Increased ALT activity can be caused by inflammation, infection, heat stress, hypoxia, toxins, endocrine disease, and neoplasia.

As a broad rule of thumb, an increase in ALT activity warrants further investigation; the urgency of the further investigation is determined by the magnitude of the rise, the persistence of the rise, and the clinical presentation of the patient. For example, a 10% rise in ALT activity above the reference interval found on a "senior health check" of a dog with no perceived problems and no breed predisposition to hepatic disease would not raise great concern – a follow-up test within a few months would be appropriate. A 10% rise in ALT in a middle-aged female Doberman pinscher with a slightly reduced appetite should trigger further investigation such as abdominal ultrasonography, possibly followed by liver biopsy, in rapid order (Doberman pinscher chronic hepatitis has a late presentation and rapid course). A 50% rise in an icteric, vomiting cat demands immediate hepatobiliary-centered investigation, whereas a 10–20% rise in an older cat with weight loss and infrequent vomiting should first prompt blood tests to rule out endocrinopathies (hyperthyroidism; ▶Tab. 1-12).

**Tab. 1-12** Non-hepatic causes of liver enzyme elevations

| Enzyme | Cause |
|---|---|
| ALT | Hyperthyroidism (C) |
| AST | Muscle damage, hemolysis, hyperthyroidism (C) |
| ALP | Hyperthyroidism (C) (bone isoenzyme), hyperadrenocorticism, diabetes mellitus |

**ALT** = alanine aminotransferase; **AST** = aspartate aminotransferase; **ALP** = alkaline phosphatase; **C** = applies only to cats

The half-life of ALT in plasma in dogs is approximately 2–3 days, whereas, in cats, it is 3.5 hours (▶Tab. 1-13).

**Tab. 1-13** Plasma half-lives of liver enzymes

| Enzyme | Half-life (dogs) | Half-life (cats) |
|---|---|---|
| ALT | 2–3 days | 3.5 hours |
| AST | 22 hours | 1 hour |
| ALP | 3 days | 5.8 hours |
| GGT | Not determined | Not determined |

**ALT** = alanine aminotransferase; **AST** = aspartate aminotransferase; **ALP** = alkaline phosphatase; **GGT** = gamma glutamyl transferase

As the enzyme is cleared so rapidly in cats, any elevation should be considered relevant as a sign of ongoing liver damage.

**Aspartate aminotransferase (AST)** is another transaminase enzyme. It is found in the highest concentration in skeletal muscle, but also in the liver and cardiac muscle. The half-life of AST is approximately 22 hours in dogs and one hour in cats (▶Tab. 1-13). More marked elevations tend to be seen in muscular injury or inflammation than in liver disease. If AST concentrations are increased, but ALT is within normal limits, then the origin is likely skeletal muscle (▶Tab. 1-12). A corresponding increase in creatine kinase (CK) further supports muscle as the likely origin. AST may be more sensitive than ALT for the detection of hepatic inflammation in cats.

### 1.3.3.3 Cholestatic markers

Certain liver enzymes are located in the bile duct epithelium and within the canalicular membrane of hepatocytes. Damage to these cells or cholestasis (intra- or extrahepatic) releases the enzymes, allowing their detection in blood. Therefore, disease of the biliary tree will cause an elevation in these so-called "cholestatic markers." Frequently, there is a concomitant increase of hepatocellular enzymes and cholestatic enzymes, as disease processes are seldom limited to one region.

The principal cholestatic enzymes used in diagnosing canine and feline hepatopathies are alkaline phosphatase and gamma-glutamyl transferase.

**Alkaline phosphatase (ALP)** is found not only in biliary epithelial cells, but also as different isoenzyme forms – in bone and, to a lesser extent, in intestinal cells, kidneys, leukocytes, and placental tissue.



Dogs, unlike cats, also possess a form of ALP that is induced by corticosteroids (both endogenous and exogenous), though the degree of induction of that isoenzyme is highly dependent upon the individual.

**Gamma-glutamyl transferase (GGT)** is only found in significant concentrations in the liver. Increased leakage of GGT into the circulation is triggered by cholestasis or is drug-induced (▶Tab. 1-14). Because of the various isoenzymes of ALP in dogs, GGT is more specific but less sensitive than ALP is for hepatobiliary disease. In cats, however, GGT is generally more sensitive but less specific for hepatobiliary disease than ALP. The exception here is that GGT activity increases are relatively limited compared with ALP rises in cats with hepatic lipidosis. Up to 11% of cats with hepatic disease may have both ALP and GGT concentrations within the reference interval.[1]

**Tab. 1-14** Drugs affecting serum liver enzyme activities

| Drugs | Laboratory parameters increased |
|---|---|
| Phenobarbital, primidone (and other anticonvulsants) | ALT, ALP, AST |
| Corticosteroids | ALP, ALT, GGT |
| Cyclosporine | ALT |

**ALT** = alanine aminotransferase; **ALP** = alkaline phosphatase; **AST** = aspartate aminotransferase; **CK** = creatine kinase; **GGT** = gamma glutamyl transferase

ALP (hepatic) has a half-life of 5.8 hours in cats[2] but approximately 3 days in dogs (▶Tab. 1-13).[3]

Increases of ALP and GGT activity in isolation, or increases in the activity of these enzymes without a concomitant increase in the activity of hepatocellular enzymes, suggests minimal involvement of the hepatic parenchyma (▶Tab. 1-12). In addition to ruling out endocrinopathies, investigations should center around the biliary system, considering differential diagnoses such as pancreatitis, pancreatic neoplasia, cholecystitis, cholangitis, cholelithiasis, biliary mucocele, and biliary neoplasia (▶Chap. 9.4, ▶Chap. 9.5). Some further blood tests may be necessary, such as measuring pancreatic lipase (▶Chap. 1.3.4.1.1), but generally, the investigation requires abdominal ultrasonography and possible further sampling (fine needle aspirates, cholecystocentesis).

**CLINICAL PEARLS**

Scottish terriers commonly have an increased ALP concentration with consistent signs of corticosteroid excess (polyuria, polydipsia, vacuolar hepatopathy) but with normal cortisol concentrations after ACTH stimulation. These affected dogs have a SNP (single nucleotide polymorphism) adjacent to the *HSD17B2* gene – a gene involved in sex hormone inactivation.[4]

#### 1.3.3.4 Cholesterol

Cholesterol is mainly synthesized by the liver and excreted in bile. Cholesterol is neither sensitive nor specific for hepatobiliary disease – concentrations may be increased, decreased, or normal. In advanced hepatic disease, the reduced synthetic capability of the liver may result in hypocholesterolemia (e.g., end-stage chronic hepatitis and portosystemic vascular anomalies). Cholestasis can result in hypercholesterolemia; though the mechanism is not clear, this may be due to the production of lipoprotein X. Some studies have shown that plasma concentrations of biliary lipoproteins increase during cholestasis, resulting in increased synthesis of lipoprotein X (for which biliary lipoprotein is a precursor).[5]

#### 1.3.3.5 Bilirubin

Bilirubin is the pigment that derives from the breakdown of heme complexes, such as the degradation of hemoglobin by macrophages. After the release of bilirubin from macrophages, it enters the plasma in its unconjugated, hydrophobic state and binds to plasma proteins (albumin). After absorption by hepatocytes, it complexes with glucuronic acid (a process known as "conjugation") and becomes water soluble. In this conjugated state, bilirubin is excreted in bile and reaches the intestines where it is degraded by commensal bacteria into urobilinogen and then stercobilin.

Accordingly, plasma concentrations of bilirubin may be elevated by excessive production, impaired conjugation or impaired excretion. A common example of increased bilirubin synthesis is hemolytic anemia: Though the amount of bilirubin produced should be easily conjugated by the liver, the concomitant hypoxic injury to hepatocytes (due to anemia) impairs this process. Other processes than hypoxic hepatocyte injury may impair the liver's ability to conjugate and excrete bilirubin, such as marked liver dysfunction (e.g., advanced chronic hepatitis or acute hepatopathies, such as leptospirosis; ▶Chap. 9.5.2.2). In these diseases, there is usually an accompanying increase in liver enzymes, though in end-stage cirrhotic liver disease, the reduced hepatic mass indicates that there is no great increase in hepatocellular enzyme leakage. Impaired excretion of bilirubin can occur with biliary tract obstruction, which can be caused by disease processes of the duodenal papilla (where the common bile duct enters the duodenum), gallbladder mucocele, cholelithiasis, cholangitis, pancreatitis (in which the swelling of the pancreas in the proximity of the common bile duct can cause obstruction) or neoplastic processes which compress the common bile duct (e.g., pancreatic neoplasia; ▶Chap. 9.6.1, ▶Chap. 9.6.4). Two unusual causes of post-hepatic hyperbilirubinemia, which the author has seen in cats, are obstruction of the duodenal papilla by a foreign body (an earplug) and a helminth.

Hyperbilirubinemia is termed "jaundice," which specifically refers to the yellow appearance of the mucous membranes or skin, or "icterus," which is a more clinical term that describes the yellow appearance of these tissues, blood plasma, or serum (e.g., "icteric serum sample"). Icterus only becomes apparent to the human eye at bilirubin concentrations of more than 25–40 mmol/L, but this depends upon the patient's skin pigmentation. Visible jaundice may persist even after the serum concentrations of bilirubin have returned to normal, as bilirubin can bind irreversibly to protein in the tissues.

Though the relative concentrations of conjugated and non-conjugated bilirubin can be measured, there is no useful clinical application of this in cats and dogs. The presence of increased bilirubin concentrations in blood may lead to errors in assays of other blood parameters (▶Tab. 1-11).

#### 1.3.3.6 Bile acids

Bile acids are derived from cholesterol in the liver and secreted into bile, usually conjugated to amino acids (e.g., taurine). Bile acids emulsify fats in the intestine, aiding their absorption. After storage in the gallbladder, bile containing the bile acids is excreted into the small intestine in response to cholecystokinin. Cholecystokinin is produced in the "I"-cells of the duodenum and released into the circulation when triggered by the detection of food (fatty acids and some amino acids) in the duodenum. Bile acids are reabsorbed in the ileum after binding to specific intestinal bile acid transporters; approximately 10% of bile acids are not reabsorbed here but remain in the intestines where they are degraded (deconjugated) by commensal bacteria and absorbed in the colon. In healthy animals, less than 5% of the total quantity of bile acids is excreted in feces. Those that are reabsorbed enter the portal circulation, where they are efficiently absorbed by

the liver and enter the secretion-reabsorption cycle again – a process known as enterohepatic circulation.

A slightly increased serum bile acids concentration occurs post-prandially in normal patients due to gallbladder contraction. If the hepatic re-uptake of bile acids is impaired (e.g., reduced hepatic function, portosystemic shunting, or portal hypertension), then serum bile acid concentrations (in particular, postprandial concentrations) increase further.

If bilirubin is increased in a non-anemic patient (potentially indicating cholestasis or advanced hepatic disease), testing for bile acids adds little further information.

#### 1.3.3.6.1 Bile acid stimulation test

To complete a bile acid stimulation test, a baseline serum sample is taken from the fasted patient, the patient is then fed, and a postprandial serum sample is taken 1–2 hours later. Bile acids are assayed on both samples. A bile acid stimulation test is used in two situations: One is in a patient with increased liver enzymes or other markers of hepatic dysfunction to establish whether a patient has **hepatic impairment** or not. If the bile acids released in response to feeding are not efficiently reabsorbed by the liver, then the post-prandial bile acids should be significantly increased. It is possible for dogs with liver disease, such as chronic hepatitis, to have normal preprandial and postprandial bile acids.

Bile acids can also be assessed to detect **portosystemic shunting** – if the portal blood is shunted around or through the liver (microscopically or macroscopically) without being exposed to the sinusoidal system. Then, the liver will not have the opportunity to re-uptake the bile acids, and high bile acids concentrations will be found in the post-prandial sample.

Elevated fasting bile acids assay may be useful without performing a stimulation test. However, a recent study[6] of a population of dogs with compatible clinical signs showed that increased fasting bile acids had a sensitivity of 98% and a negative predictive value of 96% for a diagnosis of portosystemic shunt.

### 1.3.3.7 Ammonia

Ammonia is produced by muscle catabolism (from amines and amino acids) and the degradation of amino acids by bacteria in the large intestine; the latter being by far the greatest contribution. Gut-derived ammonia is transported from the gut by the portal system and delivered to the liver, where the urea cycle converts it into urea. Urea is subsequently returned to the gut or excreted in the urine. By virtue of the efficiency of portal circulation and hepatic conversion, circulating ammonia levels remain low in healthy animals. In patients with portosystemic shunts, the ammonia does not reach the liver to be converted; instead, it reaches the systemic circulation. In patients with significant liver dysfunction or urea cycle deficiencies, ammonia may pass through the liver but is not efficiently converted into urea.

Ammonia has toxic effects, particularly in the central nervous system, where increased concentrations manifest as hepatic encephalopathy.

Ammonia is a highly labile substance that must be handled under stringent conditions. Blood samples should be stored on ice before analysis, even when an in-house analysis is planned. Ammonia concentrations may be artifactually increased by hemolysis or by delayed separation of plasma (▶Tab. 1-11).

Samples (heparin or EDTA) should be centrifuged immediately, or at the most, within 15 minutes of collection, and then the plasma stored on ice, if analysis is delayed further. If samples are to be shipped to a laboratory for analysis, then the separated plasma should be frozen rapidly and the samples shipped on dry ice to avoid thawing before reaching the laboratory (▶Tab. 1-15).

The fasting bile acid concentration has a sensitivity of 98% for detecting portosystemic shunts (PSS, ▶Chap. 9.5.3.2), and assaying for ammonia 40 minutes after the ammonia tolerance test has a sensitivity of 100%.[6] If these tests are within normal limits, there is a high degree of confidence for ruling out PSS.

**Tab. 1-15** Specific sample requirements

| Assay | Anticoagulant | Sample required | Other requirements |
|---|---|---|---|
| Hematology | EDTA | Whole blood | Recommend submitting with fresh blood smear at time of collection |
| Cholesterol | Heparin or EDTA or none | Plasma or serum | Fast patient for 12 hours before the test |
| Serum biochemistry | Heparin or EDTA or none | Plasma or serum | Separate cells soon after sampling |
| Ammonia | Heparin or EDTA | Plasma | Run test without delay; keep sample on ice and separate cells within 15 minutes; run assay within 3 hours. Alternatively, freeze after separation and store frozen. |

The combination of increased fasting ammonia and increased fasting bile acids has a positive predictive value of 97% for PSS (i.e., it is a highly specific test).[6]

Ammonia is generally only increased in patients without portosystemic vascular anomalies if liver function is significantly impaired (<40% residual function), so while it may be a marker of advanced hepatic dysfunction, it is not a useful screening test for hepatic parenchymal disease.

Ammonia is increased in cats with urea cycle deficiencies (e.g., due to arginine deficiency) and in dogs with severe hypocobalaminemia and methylmalonic aciduria.

**CLINICAL PEARLS**

Use of L-asparaginase (for treatment of lymphoma) may cause hyperammonemia that can result in signs of encephalopathy.

#### 1.3.3.7.1 Ammonia tolerance test

As mentioned above, the ammonia tolerance test is highly sensitive for PSS and has a negative predictive value of 100%. The test is performed by administering 2 ml/kg of 5% ammonium chloride rectally and then measuring serum ammonia concentration at 20 and 40 minutes.

### 1.3.3.8 Functional markers – hepatic synthetic capacity

In significant liver impairment, hepatic protein synthesis may be reduced, resulting in decreased concentrations of albumin, coagulation factors and fibrinogen. While albumin and fibrinogen are measured directly, coagulation factors are assessed by means of coagulation times (prothrombin time [PT] and activated partial thromboplastin time [APTT]). These various parameters are not specific, however, and should be viewed considering other tests.

Patients with hepatic insufficiency or portosystemic shunting may have severe hypoalbuminemia. However, this can also be caused by protein-losing enteropathy or protein-losing nephropathy, and dogs with a normal serum albumin concentration can have liver disease. Dogs with liver disease usually have serum globulin concentrations within the reference interval or they may be increased in those with inflammatory liver disease.

Patients with reduced functional hepatic parenchyma may be coagulopathic due to reduced production of the coagulation factors. Patients with cholestasis may be coagulopathic due to reduced vitamin K concentrations, as vitamin K is required for activation of factors II, VII, IX, and X. Cholestasis leads to reduced bile secretion in the duodenum, meaning less emulsification and absorption of fat and therefore the fat-soluble vitamins such as vitamin K. Prothrombin time is generally affected first, as factor VII has the shortest half-life (and is therefore depleted first), and the extrinsic pathway relies upon factor VII.

Hepatic lipid handling may also be affected, resulting in hypocholesterolemia in some patients. Similarly, cholesterol assay is not a screening test for liver disease (see above).

Reduced or low hepatic functional mass means there is a smaller amount of tissue for gluconeogenesis, so in advanced hepatic failure or significant portosystemic shunting, hypoglycemia may occur.

### 1.3.3.9 Hematology

Acanthocytes may be seen in blood smears of hepatic patients due to the disruption of lipid synthesis that affects the erythrocyte membrane. Variable erythrocyte shapes (poikilocytosis) may particularly be seen in cats with liver disease. Schistocytes may be seen in patients with portosystemic shunts, due to the shear stress of erythrocytes.

### 1.3.3.10 Urinalysis

Normal dogs have a small amount of detectable bilirubin in their urine due to production in and loss from the renal tubular cells. Normal cats, however, should have no bilirubin in their urine.

Increased ammonia concentrations in the blood causes increased ammonium in urine, and this combined with uric acid forms ammonium urate crystals and uroliths. The finding of ammonium urate uroliths or crystals in the urine should prompt investigation for possible portosystemic shunting unless there is another clear underlying cause. Mutation of the *SLC2A9* gene in dogs (heritable in English bulldogs, Dalmatians, and black Russian terriers) causes dysfunction of the urate transporter and causes hyperuricosuria and, consequently, urate urolithiasis.

**KEY FACTS**

- Liver enzymes are of two main types – those associated with the hepatocytes (ALT, AST) and those from the biliary tree (ALP, GGT).
- The magnitude of liver enzyme increases reflects the number of cells damaged, but does not indicate the reversibility of the problem.
- Liver enzymes may be increased by primary hepatobiliary disease or by systemic or exogenous factors.
- The combination of increased fasting ammonia and increased fasting bile acids has a positive predictive value of 97% for portosystemic shunts.
- Bile acid concentrations should be interpreted with caution in patients with hyperbilirubinemia.

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
svg.to/9842-01-03-03

## 1.3.4 Diagnosis of exocrine pancreatic disorders

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### 1.3.4.1 Laboratory tests for pancreatitis

Several serum tests have been developed and evaluated, but most have shown no or only limited usefulness for the diagnosis of pancreatitis in dogs and cats. Although histopathology of the pancreas is widely considered a gold standard for the diagnosis of canine and feline pancreatitis, it is associated with several limitations.[1] For example, histopathologic changes can be highly localized, and failure to find changes may not exclude pancreatitis. Also, the normal histology of the exocrine pancreas is still being debated, making the characterization of the clinical relevance of abnormal findings difficult (▶Chap. 1.8.3.3). Therefore, the results of the studies discussed in the following sections should be interpreted with caution and the understanding that they often rely upon an imperfect gold standard. It also must be noted that it is difficult, or even impossible, to determine a single cut-off that corresponds to the exact sensitivity of a diagnostic test for pancreatitis because the sensitivity varies depending upon several factors, including the type of study, the criteria for pancreatitis used (i.e., based on histopathological confirmation, ultrasonographic findings, or comprehensive clinical information available), the type of pancreatitis (i.e., acute or chronic, mild or severe), and the cut-off values used. Therefore, direct comparison of the results among different studies is challenging. ▶Tab. 1-16 and ▶Tab. 1-17 provide an overview of selected studies evaluating the sensitivity and/or specificity of different laboratory tests to diagnose pancreatitis in dogs and cats.

#### 1.3.4.1.1 Pancreatic lipase immunoreactivity assays

Pancreatic lipase immunoreactivity (PLI) assays are currently considered the most sensitive and specific serum tests for diagnosing pancreatitis in dogs and cats. The main advantage of PLI assays over traditional lipase activity assays is that, in contrast to the traditional activity assays for lipase, which indiscriminately measure the activities of lipases of multiple origins, immunoassays that are used to measure pancreatic lipase concentration in serum (i.e., PLI assays) quantify lipase of pancreatic origin exclusively based on its unique three-dimensional structure[2–6] Therefore, PLI assays have inherent advantages over the traditional serum lipase activity assays that make them more suitable for specific evaluation of the exocrine pancreas in dogs and cats.

The originally developed and analytically validated immunoassays for the specific measurement of serum pancreatic lipase in dogs (canine PLI) and cats (feline PLI)[7–9] have been replaced by more widely available, fully validated immunoassays (Spec cPL® for dogs and Spec fPL® for cats) that demonstrate similar clinical performance to the original PLI assays and are available through IDEXX Laboratories and the Gastrointestinal Laboratory at Texas A&M University.[10,11] The reference interval for Spec cPL is 0–200 µg/L and for Spec fPL 0–4.4 µg/L. Both assays incorporate a gray zone in interpreting the results (201–399 µg/L for Spec cPL and 4.5–8.7 µg/L for Spec fPL); values in the gray zone are non-diagnostic, and further testing or retesting is recommended. Concentrations ≥400 µg/L (Spec cPL) or ≥8.8 µg/L (Spec fPL) are considered highly suggestive of pancreatitis. A recent study suggested that serum Spec fPL concentrations have a high individuality, and population-based reference intervals may fail to detect clinically significant differences in pancreatic physiology.[12] Thus, subject-based reference intervals might be more useful for this test, but this requires further research.[12] At the current time, population-based reference intervals continue to be used.

In addition to the above-validated immunoassays, several other assays measuring PLI in dogs and cats are available, respectively. Laboklin Laboratories in Europe offers a PLI assay for dogs and also one for cats, but these assays were

**Tab. 1-16** Summary of the diagnostic accuracy of immunological and activity-based lipase assays in dogs.

| Study | Number of animals | Gold standard | Immunological assays | | Activity assays | |
|---|---|---|---|---|---|---|
| | | | Sensitivity | Specificity | Sensitivity | Specificity |
| Graca et al. (2005)[20] | 30 | Clinical assessment | N/A | N/A | **1,2 DiG**<br>• 73% (cut-off ≥500 U/L)<br>• 60% (cut-off ≥699 U/L)<br><br>**DGGR**<br>• 93% (cut-off ≥120 U/L)<br>• 73% (cut-off ≥180 U/L) | **1,2 DiG**<br>• 73% (cut-off ≥500 U/L)<br>• 73% (cut-off ≥699 U/L)<br><br>**DGGR**<br>• 53%(cut-off ≥120 U/L)<br>• 67% (cut-off ≥180 U/L) |
| Steiner et al. (2008)[11] | 22 | Gross pathology and histo-pathology | **cPLI** (in-house ELISA) 64%<br><br>**Spec cPL** (cut-off ≥400 µg/L) 64% | N/A | **1,2 DiG** 14% (cut-off 3× upper reference limit) | N/A |
| Neilson-Carley et al. (2011)[3] | 64 | Histo-pathology | N/A | **Spec cPL** (cut-off ≥400 µg/L) 98% | N/A | N/A |
| Trivedi et al. (2011)[18] | 70 | Histopa-thology | **Spec cPL** (cut-off ≥400 µg/L)<br>• mild: 21%<br>• moderate/ severe: 71% | **Spec cPL** (cut-off ≥400 µg/L)<br>• mild: 100%<br>• moderate/ severe: 100% | **1,2 DiG** (cut-off ≥750 U/L)<br>• mild: 54%<br>• moderate/ severe: 71% | **1,2 DiG** (cut-off ≥750 U/L)<br>• mild: 43%<br>• moderate/ severe: 43% |
| McCord et al. (2012)[17] | 54 | Clinical assessment | **SNAP cPL** 92–94%<br><br>**Spec cPL** (cut-off ≥400 µg/L) 72–78% | **SNAP cPL** 71–78%<br><br>**Spec cPL** (cut-off ≥400 µg/L) 81–88% | **1,2 DiG** (cut-off ≥750 U/L) 43–54% | **1,2 DiG** (cut-off ≥750 U/L) 89–93% |
| Haworth et al. (2014)[21] | 38 | Clinical assessment | **SNAP cPL** 82%<br><br>**Spec cPL** (cut-off ≥400 µg/L) 70% | **SNAP cPL** 59%<br><br>**Spec cPL** (cut-off ≥400 µg/L) 77% | N/A | N/A |
| Cridge et al. (2018)[22] | 55 | Clinical assessment | **SNAP cPL** 74–100%<br><br>**Spec cPL** (cut-off ≥400 µg/L) 81–91%<br><br>**VetScan cPL*** | **SNAP cPL** 72–78%<br><br>**Spec cPL** (cut-off ≥400 µg/L) 74–81%<br><br>**VetScan cPL*** | **DGGR** (cut-off ≥216 U/L) 86–91% | **DGGR** (cut-off ≥216 U/L) 64–74% |
| Goodband et al. (2020)[23] | 18 | Histo-pathology | **Spec cPL** (cut-off ≥400 µg/L)<br>• 33% (AP)<br>• 42% (CP) | **Spec cPL** (cut-off ≥400 µg/L)<br>• 100% (AP)<br>• 100% (CP) | **DGGR** (cut-off ≥245 U/L)<br>• 0% (AP)<br>• 57% (CP) | **DGGR** (cut-off ≥245 U/L)<br>• 100% (AP)<br>• 100% (CP) |

* values not reported because the assay failed analytical validation

**1,2 DiG** = 1,2-diglyceride; **DGGR** = 1,2-o-dilauryl-rac-glycero-3-glutaric acid-(6'-methylresorufin) ester; **cPLI** = canine pancreatic lipase immunoreactivity; **Spec cPL** = specific canine pancreatic lipase; **AP** = acute pancreatitis, **CP** = chronic pancreatitis; **N/A** = not available

**Tab. 1-17** Summary of the diagnostic accuracy of immunological and activity-based lipase assays in cats.

| Study | Number of animals | Gold standard | Immunological assays | | Activity assays | |
|---|---|---|---|---|---|---|
| | | | Sensitivity | Specificity | Sensitivity | Specificity |
| Forman et al. (2004)[34] | 29 | Histo-pathology | **fPLI** (in-house RIA*)<br>• mild: 54%<br>• moderate/ severe: 100%<br>• combined: 67% | **fPLI** (in-house RIA*)<br>• symptomatic: 67%<br>• asymptomatic: 100% | N/A | N/A |
| Forman et al. (2009)[35] | 141 | Clinical assessment | **Spec fPL** (cut-off ≥5.4 µg/L) 79% | **Spec fPL** (cut-off ≥5.4 µg/L) 82% | N/A | N/A |
| Oppliger et al. (2013)[43] | 31 | Histo-pathology | **Spec fPL** (cut-off ≥5.4 µg/L) 57% | **Spec fPL** (cut-off ≥5.4 µg/L) 63% | **DGGR** (cut-off ≥26 U/L) 48% | **DGGR** (cut-off ≥26 U/L) 63% |
| Oishi et al. (2015)[44] | 138 | **Spec fPL** ≥5.4 µg/L | N/A | N/A | **Triolein** (cut-off ≥30 U/L) 66.7% | **Triolein** (cut-off ≥30 U/L) 93.2% |
| Oppliger et al. (2016)[45] | 60 | Histo-pathology | **Spec fPL** (cut-off ≥5.4 µg/L)<br>• 42%<br>• 61%[a] | **Spec fPL** (cut-off ≥5.4 µg/L)<br>• 100%<br>• 6%[a] | **DGGR** (cut-off ≥26 U/L)<br>• 37%<br>• 67%[a] | **DGGR** (cut-off ≥26 U/L)<br>• 100%<br>• 79%[a] |

* The cut-off value for the original in-house fPLI-RIA for a diagnosis of pancreatitis was ≥10.0 µg/L, which is equal to the current cut-off value of the Spec fPL of ≥8.8 µg/L.

**a**: when up to 10% lymphocytic inflammation is considered normal; this criterium has not been verified by any study

**DGGR** = 1,2-o-dilauryl-rac-glycero-3-glutaric acid-(6'-methylresorufin) ester; **RIA** = radioimmunoassay; **fPLI** = feline pancreatic lipase immunoreactivity; **Spec fPLI** = specific feline pancreatic lipase; **N/A** = not available

reported to have failed analytical validation.[13] The assay lacked dilutional parallelism, and results were different from Spec cPL and Spec fPL assays, even though the reference interval and cut-off values reported are the same as the Spec assays. Two papers have been published utilizing these assays, but no information is available on how these assays have been improved since previously failing analytical validation, and only some summary data regarding analytical validation have been reported.[14,15] The second assay is available through Zoetis, Parsippany, USA (Abaxis VETSCAN Canine Pancreatic Lipase [cPL] Rapid Test) as a rapid semiquantitative test for samples from dogs run on an in-house analyzer. This assay has much lower repeatability than the Spec cPL assay and showed disagreements of interpretation with repeat measurements.[16] Another in-house assay (Vcheck® cPL and fPL; Bionote, Minnesota, USA) is available in parts of Asia for dogs and cats. Analytical validation of the Vcheck® cPL assay has not been published, and the VetScan® assay had much lower repeatability than the Spec cPL assay and showed disagreements of interpretation with repeat measurements.[16]

## Canine pancreatic lipase immunoreactivity

Both clinical[17] and histopathological,[11,14,18,19] studies concerning canine pancreatic lipase immunoreactivity (cPLI) for canine pancreatitis have been published, and all generally agree that serum cPLI is currently the most sensitive and specific serum marker for pancreatitis in dogs (▶Tab. 1-16). In a large clinical study including 84 dogs, the sensitivity of cPLI measured by Spec cPL (IDEXX Laboratories, Westbrook, ME) ranged between 72–78%.[17] In a recent necropsy study, the sensitivity of cPLI was reported at 91% for moderate or severe pancreatitis.[14] Three older necropsy studies [11,18,19] determined the sensitivity of cPLI to range from 21% for mild and potentially clinically insignificant pancreatitis to 71% for histopathologically moderate to severe pancreatitis (▶Tab. 1-16). The wide overall range of sensitivities reported for cPLI (21–91%) is also seen with other markers for pancreatitis, reflecting the inherent differences in the study design, methodology, and dog population included in each particular study. However, in these studies, cPLI consistently showed

the best performance (sensitivity and specificity) compared with other serum markers evaluated.[11,17–19]

Evidence from recent studies [11,18,19] and the fact that histopathological lesions associated with chronic pancreatitis (e.g., pancreatic fibrosis and atrophy) are not expected to be associated with leakage of pancreatic enzymes into the vascular space[3] suggests that the sensitivity of cPLI is lower for chronic pancreatitis than for acute pancreatitis. In one study of 14 dogs with chronic pancreatitis,[19] the sensitivity of cPLI ranged between 26–58% (depending on the cut-off value applied), further supporting this hypothesis. However, five of the 14 dogs in this study had exocrine pancreatic insufficiency (EPI), where serum cPLI concentration would have been expected to be low.

The measurement of serum cPLI concentration is also considered to have the highest specificity for pancreatitis compared with any other serum test currently available, with specificities ranging between 81–100%.[3,14,17,18,24–29] In the clinical study mentioned above, the specificity of cPLI ranged between 81–88%.[17] In two necropsy studies, including dogs that died or were euthanized for various reasons and had a normal pancreas on histopathology, serum Spec cPL showed a specificity of 100%[18] and 90%.[25] In another necropsy study, the specificity of Spec cPL using the recommended cut-off of 400 µg/L was 98%.[3] Experimentally induced chronic renal failure[27] and long-term prednisone administration[28] were not found to have any clinically significant effect on serum cPLI concentration. Also, pancreatic sampling by ultrasound-guided fine-needle aspiration (FNA) or surgical biopsy did not cause any increases in serum cPLI concentrations in healthy dogs.[30]

A rapid, in-clinic, semiquantitative, visually-read test for estimating canine pancreatic lipase in serum is available.[31] The results of this rapid assay are considered either normal or abnormal (▶Fig. 10-9). In the latter case, the actual PLI concentration may be in the gray zone (200–400 µg/L) or consistent with the diagnosis of pancreatitis (>400 µg/L),[31] but the two cannot be differentiated without quantitative evaluation by measurement of Spec cPL. One study showed a 90–100% agreement between the SNAP cPL and the reference Spec cPL.[31] Another study reported that SNAP cPL has a sensitivity for pancreatitis between 91–94% and a specificity between 71–78%.[17] However, the main use of this diagnostic tool is to rule out pancreatitis (i.e., a normal result makes a diagnosis of pancreatitis very unlikely). Thus, the sensitivity of the SNAP cPL is more important than its specificity.

Other assays measuring serum pancreatic lipase concentrations have been or are in the process of being developed. One such assay is the in-house VetScan® cPL Rapid Test (Abaxis), a semiquantitative in-house assay that provides rapid point-of-care results. In a recent study, this assay was reported to have a good agreement with the Spec cPL assay, and a specificity of 74–83% and a specificity of 77–84%.[22] However, in this study, the assay was not performed under field conditions. In a more recent study, the VetScan® cPL assay failed basic analytical validation and did not adhere to the manufacturer's specifications.[32] Another study reported that this assay has lower repeatability than the Spec PL assay and often provides discrepant categorical results ("pancreatitis" vs. "equivocal" vs. "not pancreatitis") for the same sample.[16] Another patient-side assay, the Vcheck® cPL, is available in parts of Asia. Similar to the VetScan® cPL assay, the Vcheck® cPL assay had lower repeatability than the Spec cPL assay and often provided discrepant categorical results ("pancreatitis" vs. "equivocal" vs. "not pancreatitis") for the same sample. Both in-house assays (VetScan® cPL and Vcheck® cPL) resulted in lower mean pancreatic lipase concentrations than the Spec cPL assay, even though the stated reference interval for both assays is equivalent to that reported for the Spec cPL assay.[16]

### Feline pancreatic lipase immunoreactivity

Multiple studies in cats with experimental or spontaneous pancreatitis have reported that serum feline pancreatic lipase immunoreactivity (fPLI) concentration is the most sensitive and specific serum marker for feline pancreatitis currently available (▶Tab. 1-17).[15,33–41] In a recent retrospective study of 274 cats, Spec fPL had a sensitivity of about 76% in cats with definite or probable pancreatitis.[37] In another clinical study that included 182 cats, the sensitivity of serum Spec fPL concentration was 79%.[35] In a study that included cats primarily with chronic pancreatitis and an acute histopathological component, serum fPLI concentration was 100% sensitive for moderate to severe pancreatitis based on histopathology.[34] In the same study, the sensitivity of fPLI was 54% for histopathologically mild pancreatitis, with an overall sensitivity of 67%. For comparison, the overall sensitivity of feline trypsin-like immunoreactivity (fTLI, ▶Chap. 1.3.4.2.1) in the same study was only 28%.[34] Similar results were reported in a histopathologic study from Germany, where fPLI sensitivity ranged from 57–82%, depending on the histopathologic severity of pancreatitis and the cut-off for fPLI concentration.[15]

**NOTE**

Patients with end-stage chronic pancreatitis, where pancreatic fibrosis and atrophy are the predominant histopathologic feature, may not show leakage of pancreatic enzymes. Therefore, the sensitivity of feline pancreatic lipase immunoreactivity is believed to be lower for chronic pancreatitis than for acute disease,[42] and false-negative results may occur, especially in cats with end-stage or mild chronic pancreatitis.[15]

Similar to its sensitivity, the specificity of serum fPLI concentration for feline pancreatitis is very high, with reported values ranging between 67–100% (▶Tab. 1-17).[34,35,37] In a recent clinical study that included 274 cats, Spec fPL had a specificity of about 90%.[37] In another clinical study of 182 cats, the specificity of fPLI was 82%.[35] Azotemia resulting from experimentally induced chronic renal failure did not have any clinically relevant effect on serum fPLI concentrations.[46] Other exocrine pancreatic conditions, such as pancreatic neoplasia, often associated with concurrent pancreatitis, can lead to increased serum fPLI concentrations.[15] However, pancreatic adenocarcinoma (▶Chap. 10.3.3), while more common in cats than in dogs, is still a rare disease in cats, and thus misdiagnosis of pancreatitis in cats with a pancreatic adenocarcinoma would be rare.

A rapid, in-clinic, semiquantitative test for estimating feline pancreatic lipase in serum is available.[1,47] The results of this rapid assay are considered either normal or abnormal (▶Fig. 10-9). In the latter case, serum fPLI concentration would be expected to be in the gray range or consistent with a diagnosis of pancreatitis. Neither can be distinguished with certainty; however, using the in-clinic assay alone and further testing using the quantitative reference method is recommended. The manufacturer indicates that this test has an 82–92% agreement with the Spec fPL assay. In a recent clinical study, the agreement between SNAP fPL and Spec fPL was 97.5% for negative results and 90% for positive results, suggesting an overall high agreement between the two methods.[39] In that study, it was concluded that SNAP fPL was a valuable tool to exclude or include pancreatitis as a differential diagnosis in an emergency setting.[39] Another patient-side assay, the VCheck® fPL, is available in parts of Asia, but currently, there are no published data on its analytical validation or clinical performance.

#### 1.3.4.1.2 Trypsin-like immunoreactivity

Trypsin-like immunoreactivity (TLI) assays are immunoassays that measure trypsinogen and trypsin concentrations in serum and are of limited usefulness for diagnosing canine and feline pancreatitis. The sensitivity of serum cTLI for the diagnosis of spontaneous pancreatitis is low (36–47%), possibly due to the short half-life of trypsinogen and trypsin in serum.[11,24,27] In addition, although there is strong evidence that trypsinogen is exclusively of pancreatic origin in healthy animals,[48] serum cTLI concentration can be increased in dogs with renal failure.[24,26] This is likely because trypsinogen and trypsin are small, positively charged molecules that are at least partially filtered by the glomerular membrane. Feline TLI (fTLI) has been evaluated for the diagnosis of spontaneous feline pancreatitis, and several cut-off values for pancreatitis have been suggested.[36,40] The main limitation of fTLI is that when cut-off values allowing adequate specificity of the assay are used (e.g., 100 µg/L), the sensitivity of fTLI for the diagnosis of pancreatitis in cats is low (28–33%).[34,36,40,42] Although serum fTLI is considered to be specific for pancreatitis (i.e., trypsin is theoretically produced exclusively by the pancreatic acinar cells), its specificity has been questioned because increased TLI concentrations have been reported in cats with no demonstrable pancreatic disease (although localized lesions might have been missed on histopathology) that had other gastrointestinal disorders (e.g., chronic inflammatory enteropathy or gastrointestinal lymphoma) or azotemia.[40,49]

#### 1.3.4.1.3 Serum amylase and lipase activities

Serum amylase and lipase activities have long been considered markers for pancreatitis in dogs.[29,50] Although serum activities of these two enzymes increase during experimental canine pancreatitis, several studies have shown that these markers, when measured with the traditional assay methodologies, are not useful for the diagnosis of spontaneous canine pancreatitis due to their low sensitivity and specificity.[11,26,29,48,50–52] Many tissues other than the exocrine pancreas synthesize amylases and lipases,[6,48] and traditional catalytic assays are not able to differentiate amylases and lipases according to their tissue of origin. In one study, approximately 50% of dogs with an increased serum activity of either amylase or lipase activity did not have pancreatitis based on histopathological examination of the pancreas.[29] In another, more recent study investigating the specificity and sensitivity of a new serum lipase activity assay based on 1,2-o-dilauryl-rac-glycero glutaric acid-(6′-methylresorufin) ester (DGGR) as a substrate, the specificity was similar (53%).[20]

The sensitivity of serum amylase and lipase activities for spontaneous canine pancreatitis varies but is generally low (14–73% for lipase activity and 18–69% for amylase activity).[11,27,53] Thus, many dogs with pancreatitis may have normal serum activities of these enzymes and, therefore, normal serum amylase and/or lipase activities cannot be used to definitively rule out pancreatitis.[29,53]

Serum amylase and lipase activities have been evaluated in both experimental and spontaneous feline pancreatitis.

Results of clinical studies suggest that traditional catalytic assays for the measurement of serum amylase and lipase activities are of very little clinical value in cats and should not be used for the diagnosis of feline pancreatitis due to unacceptably low specificity and sensitivity.[42,54,55]

More recently developed colorimetric lipase activity assays (such as those based on DGGR as a substrate) have shown better performance than traditional catalytic assays. Supposedly, this substrate is more specific for pancreatic lipase than traditional catalytic assays, and some studies have compared DGGR-based assays with PLI assays and suggested similar performance between the two.[22,43,45,56,57] A study in 142 dogs found high agreement between a specific DGGR-based lipase assay and the Spec cPL assay, with the best agreement ($\kappa$ = 0.80) for a cut-off of this DGGR-based lipase activity assay of >216 U/L.[56] When specific cut-offs are used in cats, there was good agreement between one of these assays and the Spec fPL assay.[43] Specifically, in this study of 250 cats, the best agreement ($\kappa$ = 0.76) was found for a cut-off of DGGR lipase activity of >34 U/L. However, it should be noted that an agreement of 0.76 is not very high for two assays that supposedly measure the same analyte. For example, two assays measuring serum creatinine concentrations would be expected to have an agreement ($\kappa$) close to 1. Also, there are various DGGR-based assays for the measurement of serum lipase activity, and these differ dramatically due to changes in added compounds (e.g., colipase, bile acids) and assay conditions (e.g., pH). Also, the analyzer used can have an impact on test results. Regardless, none of the currently available DGGR-based assays are consistently any more specific for the measurement of pancreatic lipase than more traditional serum lipase activity assays. For example, a recent experimental study in both dogs and cats showed that DGGR is hydrolyzed by pancreatic lipase and lipoprotein lipase, hepatic lipase, or both.[58] These extrapancreatic lipases may contribute to a lack of analytic specificity for this assay.[58] In the same study, no significant effect was shown for serum cPLI or fPLI concentrations.[58] Therefore, further studies are needed before DGGR lipase assays can be recommended for the routine diagnosis of pancreatitis in either dogs or cats.

#### 1.3.4.1.4 Other laboratory markers

Several other diagnostic markers for pancreatitis have been developed and studied. However, none of those can currently be recommended for the routine diagnosis of canine and feline pancreatitis in clinical practice, either because their diagnostic performance has not been sufficiently evaluated clinically or because they have been shown to have low sensitivity and/or specificity. In addition, the availability of most of these diagnostic tests is currently limited. Such tests include serum concentrations of pancreatic elastase-1,[59] phospholipase A2, trypsin-$\alpha_1$-antitrypsin complexes,[11,60] $\alpha_2$-macroglobulin,[61] plasma and urine concentrations of trypsinogen activation peptide (TAP),[62] and lipase activity in peritoneal fluid.[33,63]

### 1.3.4.2 Laboratory diagnosis of exocrine pancreatic insufficiency

#### 1.3.4.2.1 Trypsin-like immunoreactivity

Trypsin-like immunoreactivity (TLI) is the test of choice for EPI diagnosis in both dogs and cats. This test is highly sensitive and specific for the diagnosis of EPI. Animals with EPI produce and secrete lower than normal trypsinogen amounts, leading to a subnormal serum TLI concentration. In a dog or cat with compatible clinical signs, a severely decreased serum TLI concentration (≤5.5 µg/L in dogs or ≤8 µg/L in cats) is sufficient to make a diagnosis of EPI. A TLI result within the reference interval is sufficient for excluding EPI in the vast majority of cases. It should direct clinicians toward the investigation of other disorders as the cause of the observed clinical signs.

One exception to this rule is isolated pancreatic lipase deficiency, where the patient has clinical signs of EPI, but the secretion of trypsin and trypsinogen is normal, and therefore, serum TLI concentration is also normal. This form of EPI has been described in a single dog and suspected in a few other dogs but has not been reported yet in cats.[64] In such cases,

the diagnosis of EPI is challenging. The current assays for the measurement of pancreatic lipase concentration are not suitable for the accurate measurement of pancreatic lipase concentrations at subnormal concentrations. Therefore, isolated pancreatic lipase deficiency cannot be diagnosed using these assays.

Single serum TLI results within the equivocal range in animals with clinical signs of gastrointestinal disease need to be interpreted with caution. In these patients, subsequent retesting of serum TLI may show either a normal serum TLI concentration or progression toward EPI. Therefore, patients with serum TLI results in the equivocal range should be investigated for chronic intestinal disease, and repeat measurement of serum TLI concentration should be performed a few weeks later.

Some dogs with no clinical signs characteristic of EPI are reported to have repeatedly subnormal serum TLI concentrations. At least in dogs, these patients have been shown to have subclinical EPI. Some dogs and cats with subclinical EPI may develop clinical signs later but little is known about such progression.

**NOTE**

Clinically, subclinical exocrine pancreatic insufficiency is not relevant as there is no need for therapy in these patients.

Because renal disease might increase serum TLI concentrations and obscure a diagnosis of EPI, re-evaluation of non-diagnostic serum TLI concentrations in azotemic animals suspected of having EPI is recommended. Similarly, concurrent pancreatitis might slightly increase serum TLI concentration, potentially leading to missing the diagnosis in some patients. However, this has not been reported but is anecdotally seen in clinical patients.

**CLINICAL PEARLS**

Measurement of serum TLI concentration is species-specific. Using a canine assay in cats and vice versa will invariably lead to a false positive diagnosis of exocrine pancreatic insufficiency. Also, food should be withheld prior to measurement of serum trypsin-like immunoreactivity (TLI) concentration (at least for 12 hours), as feeding can lead to slight increases in serum TLI concentrations.

Although there are currently two assays for measuring fTLI in serum available (one radioimmunoassay that is available in the USA and one ELISA that is available in Europe), only the radioimmunoassay has been analytically validated in the literature. This assay is available through the Gastrointestinal Laboratory at Texas A&M University. The reference interval of this assay is 12–82 µg/L, with values ≤8 µg/L being considered diagnostic for EPI. Some cats with signs of gastrointestinal disease have serum fTLI concentrations in the questionable range (8–12 µg/L). These cats should be retested a few weeks or months after the initial measurement to check whether fTLI concentrations have normalized or are in the diagnostic range for EPI.

Similar to dogs, it can be recommended that non-diagnostic serum fTLI concentrations in azotemic cats suspected of having EPI be re-evaluated because renal disease might falsely increase serum fTLI concentrations. The same is true for cats with concurrently increased serum feline pancreatic lipase (fPLI, Spec fPL) concentrations, indicating pancreatitis. While this has not been reported in either dogs or cats, the authors have observed two cats in which serum fTLI fluctuated around the cut-off value for a diagnosis of EPI and were suspected of having concurrent pancreatitis.

TLI testing can be performed in animals that are already on enzyme supplementation without this affecting the results. TLI assays are species-specific and do not measure trypsinogen and trypsin of other species. Also, very little of the trypsinogen contained in the pancreatic enzyme supplement would be expected to be absorbed intact and reach the serum.

#### 1.3.4.2.2 Fecal pancreatic elastase

An ELISA for the measurement of pancreatic elastase in feces is commercially available and marketed in Europe (Shebo Biotech, Giessen, GER) for the diagnosis of canine EPI. It is considered sensitive for EPI, with limited specificity. One study reported false positive results in 23.1% of dogs with a severely decreased fecal elastase concentration. This test is easy and quick to perform, making it a reasonable initial screening tool for dogs with suspected EPI, but a positive test result must be verified by measurement of a serum TLI concentration. This test might also be useful for EPI cases that are due to pancreatic duct obstruction. However, to date, such cases have only been anecdotally reported in the veterinary literature.

### 1.3.4.2.3 Other tests

Serum amylase and lipase activities have no clinical value in the diagnosis of EPI in either dogs or cats. Canine pancreatic lipase immunoreactivity concentrations are low or undetectable in most dogs with EPI, but commercial assays for the measurement of serum PLI concentration (Spec cPL and Spec fPL) are not useful for diagnosing EPI in dogs and cats, respectively, because they have been optimized to detect changes in the higher ranges of their respective working ranges.

Measurement of the fecal proteolytic activity (FPA) was used in the past for the diagnosis of EPI in dogs and cats, but its use is now limited to species for which a TLI assay is not available. Also, measurement of FPA may be useful in patients where serum TLI concentration is in the normal range (e.g., EPI due to pancreatic duct obstruction), but EPI is heavily suspected based on clinical presentation.

A plethora of other tests, including microscopic examination of feces and the bentiromide absorption (BT-PABA) test, have also been used to diagnose EPI in the past. These tests often give false positive and/or false negative results; many are impractical, expensive, or of limited availability and thus are considered obsolete for the diagnosis of EPI.

**KEY FACTS**

- Serum pancreatic lipase immunoreactivity (PLI) concentration (as measured by Spec cPL in dogs and Spec fPL in cats) is both highly specific and sensitive for pancreatitis in small animals.
- Lipase activity assays are not specific for pancreatic lipase as they also measure activity contributed by non-pancreatic lipases.
- Measurement of serum trypsin-like immunoreactivity concentration is the gold standard for the diagnosis of exocrine pancreatic insufficiency in both dogs and cats.

## References

The complete list of references for this chapter can be downloaded from vetline.de:
svg.to/9842-01-03-04

**Tab. 1-18** Overview of the main characteristics of hereditary gastrointestinal diseases in dogs

| Anatomic location | Disease | Breed | Inheritance | Mutation |
|---|---|---|---|---|
| Oral | Cleft lip and palate | Mastiff/terrier genetic cluster and brachycephalic breeds | - | - |
| Oral | Cleft lip with or without cleft palate | Nova Scotia duck tolling retriever | Autosomal recessive | Chromosome 27 |
| Oral | Maxillary canine-tooth mesioversion | Small Shetland sheepdog | - | *FTJS3*, chromosome 9 |
| Pharyngeal | Cricopharyngeal dysfunction | Golden retriever | Autosomal recessive | - |
| Esophageal | Megaesophagus | German shepherd | - | *CFA12* (several SNPs on Chr 12 are associated with megaesophagus, and a 4.7-Mb haplotype block is present in affected dogs) |

## 1.3.5 Molecular-genetics-based laboratory tests

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### 1.3.5.1 Tests for hereditary conditions

Based on improved diagnostic techniques and increased interest of dog and cat owners, a growing number of canine and feline hereditary diseases has been reported over the last few years. Approximately 430 canine and 180 feline hereditary diseases, as well as 186 key mutations for diseases of dogs, have been reported.[1] Other reports name approximately 100 conditions in cats that appear to have an inherited background.[2,3] Genetic diseases are caused by chromosomal changes or gene mutations, leading to an alteration in the expression, structure, and/or function of the encoded protein. The following databases include the most current information on genetic diseases of small animals and can be used to identify which diseases have been linked to a hereditary cause and which laboratory tests are available:

- The **online mendelian inheritance in Animals** (OMIA) is a comprehensive database for animals that includes detailed information on feline and canine genetic diseases (🔗 https://www.omia.org/).[4]
- The **canine inherited disorders database** gives a list of familial canine diseases by breed or disease process (Patterson 2000; 🔗 https://cidd.discoveryspace.ca/)
- The database 🔗 https://www.icatcare.org gives a list of all breeds with diseases that are suspected of being inherited.[6]

As this chapter will focus on gastrointestinal diseases, ▶Tab. 1-18 and ▶Tab. 1-19 provide a relevant overview of gastrointestinal diseases in small animals that have been reported to have a hereditary basis.

| | Mechanism | Reference(s) | Commercial test available | Clinical symptoms |
|---|---|---|---|---|
| | - | Roman et al.2019[34] | - | Nasal discharge, sneezing, gagging, coughing |
| | Wolf et al.[35] reported a region on canine chromosome 27 that is significantly associated with a risk for cleft lip and palate in Nova Scotia duck tolling retrievers. | Wolf et al. 2015[35] | - | Nasal discharge, sneezing, gagging, coughing |
| | Abrams et al.[36] reported variants in two proximal genes: *FTSJ3*, encoding an RNA methyltransferase, and *GH1*, encoding growth hormone in the Shetland sheepdog with retarded growth and dental anomaly. | Abrams et al. 2020[36] | - | Dental anomaly, reduced body size |
| | - | Davidson et al. 2004[37] | - | Regurgitation, failure to thrive, coughing, aspiration pneumonia |
| | Tsai et al.[38] reported (2012) dilatation and atony in the body of the esophagus, usually associated with asynchronous function of the esophagus and the caudal esophageal sphincter. | Tsai et al. 2012[38] | - | Regurgitation, aspiration pneumonia |

▶▶

**Tab. 1-18** Overview of the main characteristics of hereditary gastrointestinal diseases in dogs (Continuation)

| Anatomic location | Disease | Breed | Inheritance | Mutation | |
|---|---|---|---|---|---|
| Esophageal | Persistent right aortic arch, with subclavian artery and ligamentum arteriosum | German pinschers | - | - | |
| Intestinal | Intestinal cobalamin malabsorption, AMN-related; intestinal cobalamin malabsorption, generic Imerslund-Gräsbeck syndrome; megaloblastic anemia 1 | Giant schnauzer, Australian shepherd, border collie, Hungarian komondor, beagle, shar-pei, Yorkshire terrier, one case in a mixed breed dog[45] | Autosomal recessive | *AMN CUBN* | |
| Intestinal | Gluten-sensitive enteropathy | Irish setter | Autosomal recessive | - | |
| Intestinal | Lundehund syndrome | Norwegian lundehund | Autosomal recessive | *LEPREL 1* | |
| Intestinal | Protein-losing enteropathy | Familial predisposition in soft-coated wheaten terriers | Multifactorial | - | |
| Intestinal | Lipid malabsorption | Australian kelpie | Autosomal recessive | - | |
| Intestinal | Inflammatory bowel disease (IBD) | - | Multifactorial | - | |
| Pancreatic | Pancreatic acinar atrophy | German shepherd, rough-coated collie, Pembroke Welsh corgi[57] | Multifactorial | *DLA-88* | |
| Pancreatic | Pancreatitis | Miniature schnauzer | - | *SPINK 1* | |

| | Mechanism | Reference(s) | Commercial test available | Clinical symptoms |
|---|---|---|---|---|
| | Philipp et al. (2011)[40] reported a region of 3.5 Mb at 32–35.5 Mb on *CFA26* using a comparative mapping strategy in seven affected German pinschers. | Menzel and Distl 2011[39], Philipp et al. 2011[40] | - | Regurgitation, failure to thrive |
| | Gold et al. (2015)[42] performed DNA testing and reported homozygosity of an amnionless mutation (AMN c.3G > A) in a juvenile Australian Shepherd dog with cobalamin deficiency. | Kather et al. 2020[41], Gold et al. 2020[42], Dandrieux et al. 2013[43], Fyfe et al. 2014[44], Sancho et al. 2020[45], Fyfe et al. 2018[46], Fyfe et al. 2013[47] | A DNA test for this disorder is included in the OFA's list at https://ofa.org/all-dna-tests/, which directs inquiries to PennGen at the University of Pennsylvania (http://research.vet.upenn.edu/Default.aspx?alias=research.vet.upenn.edu/penngen) | Diarrhea, failure to thrive, neurologic symptoms, anemia, being prone to infections |
| | - | Garden et al. 2000[48], Donnini et al. 2021[49] | - | Diarrhea, poor weight gain |
| | - | Metzgeret al. 2016[50] | Laboklin | Diarrhea, vomiting, weight loss, edema, apathy |
| | Donnini et al. (2021)[49] performed a GWAS in 106 related Gordon setters and reported regions on six chromosomes contributing to variation in liability, consistent with multifactorial inheritance. | Donnini et al. 2021[49] | - | Diarrhea, weight loss, pleural and/or abdominal effusion |
| | O'Brien et al. (2020)[51] described a deletion of the CFA28 omitting *ACLS 5* gene by a GWAS and PCR causing lipid malabsorption in Australian Kelpies. | O'Brien et al. 2020[51] | - | Stunted growth, steatorrhea, abdominal distension, wiry coat |
| | Peiravan et al. (2016)[52] identified an association between DLA-type and canine IBD, supporting the immunogenetic etiology and immunopathogenesis of this disease; Peiravan et al. (2018)[55] identified 16 candidate genes in GSDs with IBD using a combination of pathway analysis and a list of genes that have been reported to be involved in human IBD. | Kathrani et al. 2010[53], Kathrani et al. 2011[54], Peiravan et al. 2016[52], Peiravan et al. 2018[55] | - | Diarrhea, vomiting, weight loss |
| | - | Tsai et al. 2013[56], Evans et al. 2015[57] | - | Diarrhea, failure to thrive, weight loss |
| | - | Bishop et al. 2010[58] | - | Vomiting, diarrhea, abdominal pain, fever, respiratory distress |

**Tab. 1-18** Overview of the main characteristics of hereditary gastrointestinal diseases in dogs (Continuation)

| Anatomic location | Disease | Breed | Inheritance | Mutation |
|---|---|---|---|---|
| Hepatic | Hepatic copper toxicosis | Bedlington terrier, West Highland white terrier in combination with idiopathic chronic active hepatitis (ICAH)[62] in skye terriers, Dalmatians, Labrador retrievers, and possibly Doberman pinschers | Autosomal recessive (Bedlington, Labrador retriever) | Bedlington:[59,60] copper toxicosis locus has been mapped to canine chromosome 10 at locus CFA 10q28, deletion in the *COMMD1* (previously *MURR1* gene);<br>Mutation in the *ABCA12* gene encoding for the ATP-binding cassette;<br>most likely multiple genes involved;<br>Dutch Doberman pinschers: reduced expression of genes associated with copper efflux and reduced glutathione;[61]<br>*COMMD1* did not play a major role in the etiology of copper-associated hepatitis in Labrador retrievers and Dobermans.[63] Variants of copper transporters *ATP7A* and *ATP7B* are associated with hepatic copper levels in Labrador retrievers. The autosomal semi-dominant *ATP7B* variant c.4358 G > A was implicated in increased hepatic copper levels, while the X-linked recessive *ATP7A* variant c.980C > T appeared to attenuate copper deposition in the liver. Together, these two variants explained only 12.5% of the genetic variability of the hepatic copper score in Labrador retrievers.[64] Therefore, variations in other genes are expected to contribute to the copper storage disorders in Labrador retrievers. Recently, the *ATP7B* variant c.4358 G > A was shown to be associated with increased hepatic copper in Dobermans as in Labrador retrievers.[64] Non-reference allele of the variant NC_006602.3.g.52434480C>T in RETN resulting in amino-acid change p.Leu7Phe was associated with decreased hepatic copper levels.[63] Our findings support the hypothesis that the *ATP7B* DNA test can predict defects in hepatic copper metabolism. Veterinarians can test for the *ATP7B* gene mutation to identify Labrador retrievers at risk for copper toxicosis so that they can take steps to prevent the development of copper-associated chronic hepatitis in their patients.[67] |

| | Mechanism | Reference(s) | Commercial test available | Clinical symptoms |
|---|---|---|---|---|
| | Haywood et al. (2016)[60] described a mutation in the *ABSA12* transport gene in Bedlington terriers leading to hepatic failure due to copper toxicosis. | Van de Sluis et al. 2003[59], Watson 2017[61], Thornburgg et al. 1996[62], Wu et al. 2020[63], Fieten et al. 2016[64], Wu et al. 2019[65], Wu et al. 2020[66], Pindar and Ramirez 2019[67] | IDEXX | Icterus, GI symptoms |

**Tab. 1-18** Overview of the main characteristics of hereditary gastrointestinal diseases in dogs (Continuation)

| Anatomic location | Disease | Breed | Inheritance | Mutation | |
|---|---|---|---|---|---|
| Hepatic | Portovascular anomalies | Single intrahepatic shunts in large breed dogs (Irish wolfhound)[70]; patent ductus venosus (Australian cattle dog); right divisional shunt (Labrador retriever)[61] | Multifactorial; Irish wolfhound intrahepatic shunt familial disorder: digenic, triallelic trait could explain the observed occurrence of IHPSS, but other modes of inheritance cannot be excluded (van Steenbbek et al. 2009)[70] | - | |
| Hepatic | Portovascular anomalies | Single extrahepatic shunts in small breed dogs (cairn terrier, Yorkshire terrier, other terriers) | Single gene autosomal recessive | Most likely polygenic or monogenic with variable expression | |
| Hepatic | Chronic active hepatitis | English springer spaniels | X-linked | DLA class II | |
| Hepatic | Abnormalities in the development of the intrahepatic portal veins (hepatic microvascular dysplasia [MVD]), portal vein hypoplasia, (noncirrhotic portal hypertension) | MVD in small terrier breeds (e.g., Yorkshire, cairn, and Maltese terriers, papillon, toy poodles) most without portal hypertension; noncirrhotic hypertension in large Breed dogs | cairn terrier – autosomal recessive for MVD | - | |
| Hepatic | Autoimmune chronic hepatitis | Doberman, cocker spaniel, West Highland white terrier, English springer spaniel | Association with a DLA class II haplotype possible | - | |
| Hepatic | Gallbladder mucocele | Shetland sheepdog, cocker spaniel, miniature schnauzer | - | Possible *ABCB4* mutation | |
| Metabolic | Hypoadrenocorticism | bearded collies | Multifactorial | *CFA18* | |

**GI** = gastrointestinal; **PCR** = polymerase chain reaction; **SNP** = single nucleotide polymorphism; **AMN** = amnionless; **I-GS** = Imerslund-Gräsbeck-syndrome; **MAG1** = megaloblastic-amenia-1; **GSE** = gluten-sensitive enteropathy; **IBD** = inflammatory bowel disease; **DLA** = dog leukocyte antigen; **GSD** = German shepherd dog; **OFA** = Orthopedic Foundation for Animals; **GWAS** = genome wide association studies; **PAA** = pancreatic acinar atrophy; **ICAH** = idiopathic chronic active hepatitis; **PU** = polyuria; **PD** = polydipsia

| | Mechanism | Reference(s) | Commercial test available | Clinical symptoms |
|---|---|---|---|---|
| | - | Ubbink et al. 1998[68], van Steenbeek et al. 2013[69], Watson 2017[61], van Steenbeek et al. 2009[70] | - | Failure to thrive, gastrointestinal symptoms, neurological symptoms due to hepatoencephalopathy, polyuria and polydipsia, lower urinary tract signs due to urinary calculi |
| | - | Van Straten et al. 2005[71], Tobias 2003[72], Watson 2017[61] | - | Failure to thrive, gastrointestinal symptoms, neurological symptoms due to hepatoencephalopathy, polyuria and polydipsia, lower urinary tract signs due to urinary calculi |
| | - | Bexfield et al. 2012[73] | - | Icterus, hepatic encephalopathy, PU/PD, abdominal distension |
| | Watson et al. (2017)[61] described a congenital and probably inherited disorder of the portal vein architecture; Schermerhorn et al. (1996)[74] described a lack of portal vein branches in small portal triads. | Watson 2017[61], Schermerhorn et al. 1996[74] | - | Failure to thrive, gastrointestinal symptoms, neurological symptoms due to hepatoencephalopathy, polyuria and polydipsia, lower urinary tract signs due to urinary calculi |
| | - | Watson 2017[61], Schermerhorn et al. 1996[74] | - | - |
| | The underlying mutation is controversial. | Watson 2017[61], Mealey et al. 2010[75], Cullen et al. 2014[76] | - | - |
| | - | Gershony et al. 2020a[77], Gershony et al. 2020b[78] | - | - |

**Tab. 1-19** Overview of the main characteristics of hereditary gastrointestinal diseases in cats

| Anatomic location | Disease | Breed | Inheritance |
|---|---|---|---|
| Hepatic | Primary copper associated hepatopathy | Domestic cats | - |
| Hepatic | Deficient acetaminophen glucuronidation | Domestic cats | Autosomal recessive |
| Hepatic | Portosystemic shunt | Domestic shorthair cats, Persian, British shorthair, ragdoll, domestic longhair cats, Birman, British blue, Tonkinese;[83] Siamese, Himalayan, and Burmese cat – more common extra-hepatic, but not exclusively[84] | - |
| Hepatic | Amyloidosis | Domestic cats | - |
| Esophageal | Persistent right aortic arch | Domestic cats | - |
| Intestinal | Peritoneopericardial hernia | Himalayan and domestic longhair cats | - |
| Intestinal | Atresia coli | - | - |
| Intestinal esophageal | - | - | - |

### 1.3.5.2 Tests for non-hereditary conditions

#### 1.3.5.2.1 Molecular clonality testing

##### General purpose

Neoplasms emerge from a single transformed cell, which means that monoclonal cell proliferation is a typical finding for neoplastic tissue. In contrast, inflammatory processes should be composed of polyclonal cell populations.[7] In human medicine, various analytical systems are used for clonality testing, such as antigen receptor rearrangement or X-chromosome inactivation pattern (XCIP).[8] In veterinary medicine, polymerase chain reaction (PCR) for antigen receptor gene rearrangement (PARR, conforming clonality testing) is usually used to further characterize atypical, mixed, or mature lymphoid proliferation in small animal tissue fragments (e.g., intestinal biopsies). PARR can be used to evaluate fresh tissue aspirates (e.g., in stained or unstained cytology samples), peripheral blood, cell smears, fluid samples, and histopathological sections.[9] In regard to feline and canine chronic inflammatory enteropathies, PCR-based testing by evaluating antigen receptor genes is used to further differentiate chronic lymphocytic inflammation from neoplastic intestinal disease in intestinal biopsies in case of inconclusive microscopic evaluation.[10] This chapter gives an overview of the methods and clinical application of the PARR assay in regard to feline and canine chronic enteropathies. In addition, the chapter explains the possibilities, as well as the diagnostic limitations and pitfalls of lymphoid clonality testing for the differentiation of intestinal inflammation and lymphoma in dogs and cats.

##### General technical methods

Polymerase chain reaction for antigen receptor gene rearrangements (PARR) detects a clonal population of lympho-

| | Mutation | Mechanism | Reference(s) | Clinical symptoms |
|---|---|---|---|---|
| | *ATP7B* | Asada et al. (2020)[79] suggest a single-nucleotide variation in *ATP7B* causing primary copper-associated hepatopathy in cats. | Asada et al. 2020[79], Asada et al. 2019[80] | Liver failure due to copper accumulation |
| | *UGT1A6* | Shrestha et al. (2011)[81] reported a very likely candidate gene, for which all affected cats are homozygous (a mutated form of the *UGT1A6* gene that encodes UDP-glucuronosyltransferase 1A6). | Shrestha et al. 2011[81], Court and Greenblatt 2000[82] | Cyanosis, anemia, methemoglobinemia, icterus due to acetaminophen toxicity |
| | - | - | Hunt 2004[83], Berent and Tobias 2009[84] | Neurologic signs, ptyalism, anorexia, weakness, vomiting, inappetence, lethargy |
| | - | - | Struck et al. 2020[85], Niewold et al. 1999[86] | Liver as target organ: abdominal bleeding, liver failure |
| | - | - | Tremolada et al. 2013[87], Plesman et al. 2011[88] | Regurgitation, failure to thrive, nasal discharge |
| | - | - | Reimer et al. 2004[89] | Vomiting, diarrhea, abdominal pain, anorexia, and weight loss |
| | - | - | Osullivan 1996[90], Bredal et al. 1994[91] | Obstipation, failure to thrive, other gastrointestinal symptoms |
| | - | - | Cave et al. 2003[92] | Anorexia, vomiting, regurgitation, and obstipation |

cytes by amplification of gene rearrangements of the *T-cell receptor gamma-chain* (*TCRG*) gene and the *immunoglobulin heavy chain* (*IGH*) *V-J* gene (▶Fig. 1-14) The entire complementarity-determining region 3 (CDR3) and parts of the flanking V and J regions of the *TCRG* and the *IGH* genes are PCR amplified. The imprecise joining of the different genes, as well as the N region, are responsible for the variety in length and sequence in the CDR3 region of the *TCRG* among T cells and the *IGH* among B cells, resulting in amplicons of different lengths after triplicate PCR runs (▶Fig. 1-14). For the subsequent analysis of the gene rearrangement patterns present in a patient sample, use of genetic analyzers is superior to agarose or polyacrylamide gels.[10] For this analysis, the PCR products are subjected to multicapillary electrophoresis on a gene scanning device (e.g., QIAxcel® Advanced System Instrument; Qiagen, Venlo, Netherlands). Interpretation of the patterns should be based on the EuroClonality/BIOMED-2 guidelines for clonality testing in humans.[10,11]

## Diagnostic considerations for PARR

**Intestinal samples:** PARR testing of intestinal tissue is performed on genomic DNA isolated from intestinal lymphoid cells to differentiate neoplastic vs. inflammatory processes. PARR has been successfully used with formalin-fixed, paraffin-embedded (FFPE),[12] and snap-frozen biopsy samples collected both endoscopically and surgically (i.e., full-thickness biopsies).[13] However, the quantity and quality of the retrieved DNA can influence the laboratory results concerning background smearing and fragmentation of DNA. For this reason, every diagnostic laboratory performing PARR should report its diagnostic sensitivity and specificity data to avoid false conclusions by the clinician that are due to sample quality.[14] Also, storage time has an impact on the quality of DNA retrieval, as PARR performed on older samples is associated with more artifacts compared with using fresh samples.[14]

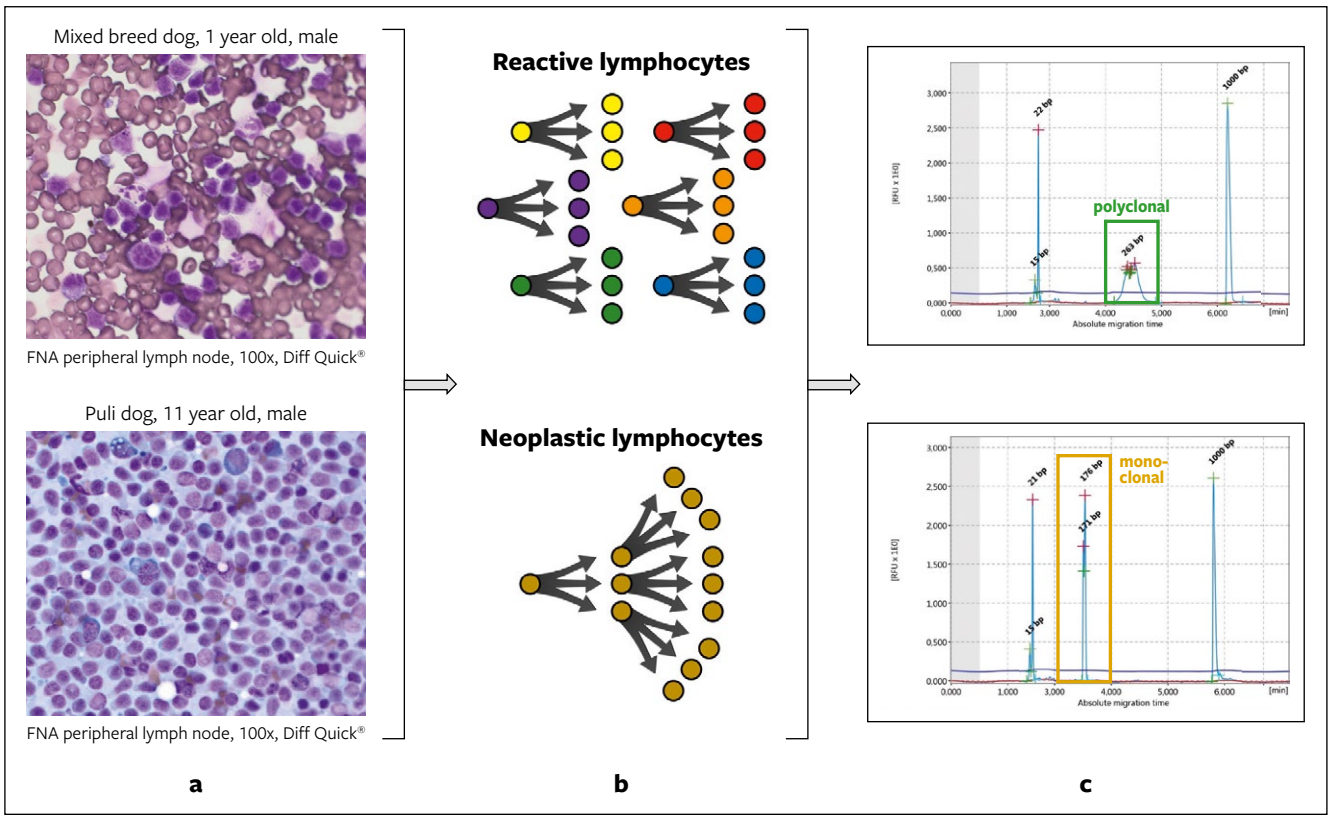



**Fig. 1-14** Characterization using antigen receptor gene rearrangements (B- and T-cell clonality) in two representative samples by PCR-based clonality testing

**a** Cytological samples showing an inconclusive morphology suggesting either a reactive hyperplastic lymph node or lymphoma.[33]

**b** Graphical representation of the principle of the origin of mono- or polyclonality.

**c** Electropherogram traces showing a polyclonal Gaussian curve (**green box**) or a monoclonal peak (**dark yellow box**). In reactive processes, lymphocytes are derived from multiple precursor cells that differ in the complementarity determining region 3 (CDR3) lengths, resulting in amplicons of variable sizes and a Gaussian distribution during multicapillary electrophoresis. In neoplastic processes, lymphocytes are derived from a single precursor cell and hence have an identical CDR3 length, resulting in amplicons of equal size and a single peak during multicapillary electrophoresis.

**Interpretation of electrophoresis profiles:** Although electrophoresis results should always be interpreted in conjunction with clinical, endoscopic morphological, histopathological, and immunohistochemical results, the clinician should be familiar with several electrophoresis curve patterns.

**Patterns of multicapillary electrophoresis:** A polyclonal result is characterized by numerous small peaks with a Gaussian distribution and signifies an inflammatory process (▶Fig. 1-15). However, alternative considerations (false negatives) in the context of clinical and histopathological data should also be considered, as there may be insufficient primer coverage, primer site mutations, an embedded clone obscured by a polyclonal background, or chromosomal aberrations.[10]

A monoclonal or biclonal pattern is characterized by one or more narrow reproducible peaks, 2–3 times the height of any background peaks, and signifies a neoplastic process derived from a single mutated cell (▶Fig. 1-16). However, clonal expansion can also occur in the absence of neoplasia or in response to antigenic stimulation.[10,15]

An oligoclonal profile is characterized by multiple peaks (3–6 peaks; ▶Fig. 1-17). This pattern signifies either a neoplastic or reactive/non-diagnostic sample depending on the criteria established by the laboratory performing the test.[10,15] Due to the different cassettes in the TCRG receptor, individual rearrangements of every cassette are possible. These are detected by multiplex primer setups, and no more than two peaks can be seen with neoplastic populations.

A pseudoclonal pattern is characterized by either one or more non-reproducible peaks (non-identical PCR replicates),

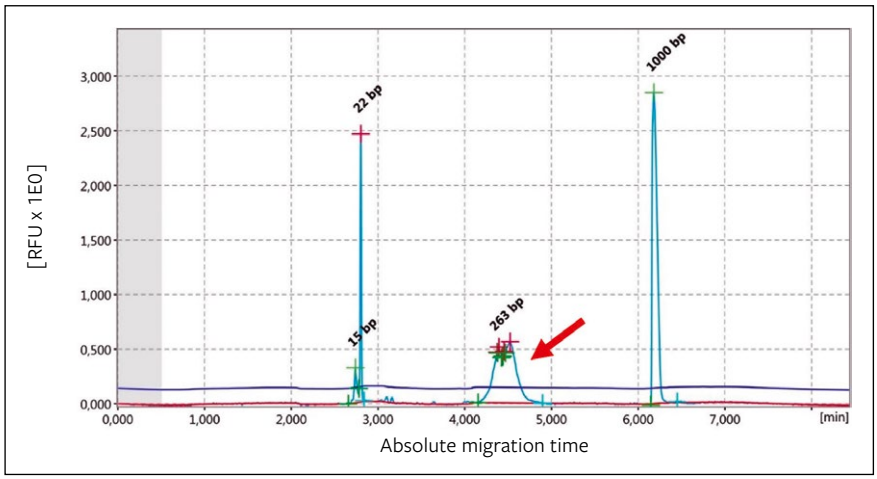



**Fig. 1-15** Exemplary electropherogram of a polyclonal result

The peak pattern shows a Gaussian distribution (**red arrow**) and therefore is addressed as polyclonal. The distinct 15 and 1000 bp peaks show the alignment markers, whereas the 22 bp peak represents leftover PCR primers.

**RFU** = relative fluorescent unit.

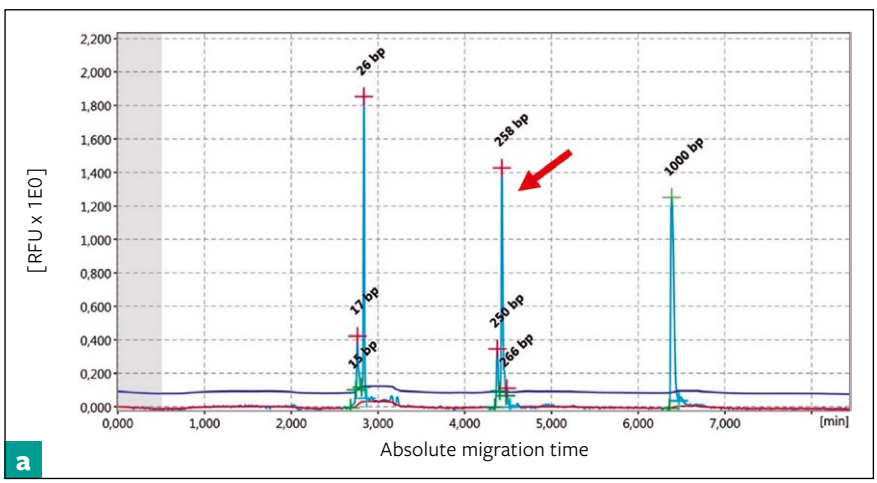
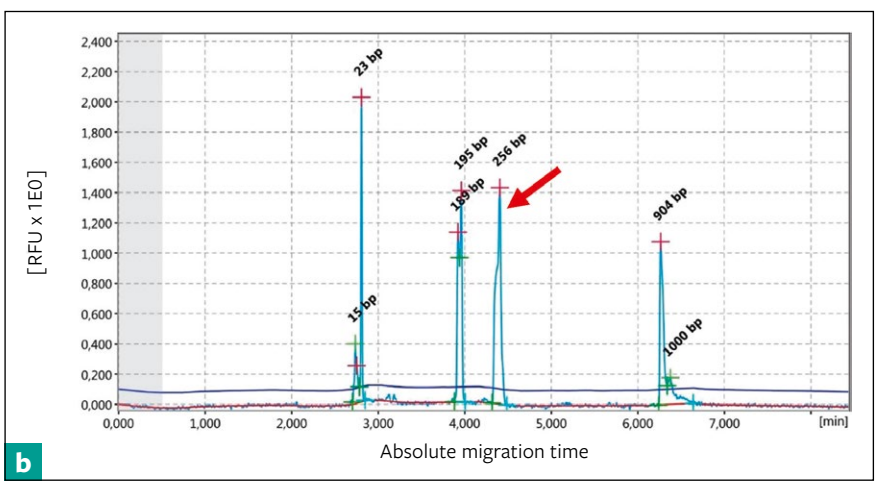



**Fig. 1-16** Exemplary electropherograms of monoclonal and biclonal results

**a** Monoclonal (**red arrow**) profile




**b** Biclonal (**red arrow**) profile

The distinct 15 (17) and 1000 (904) bp peaks show the alignment markers, whereas the 23 and 26 bp peaks represent leftover PCR primers.

**RFU** = relative fluorescent unit.

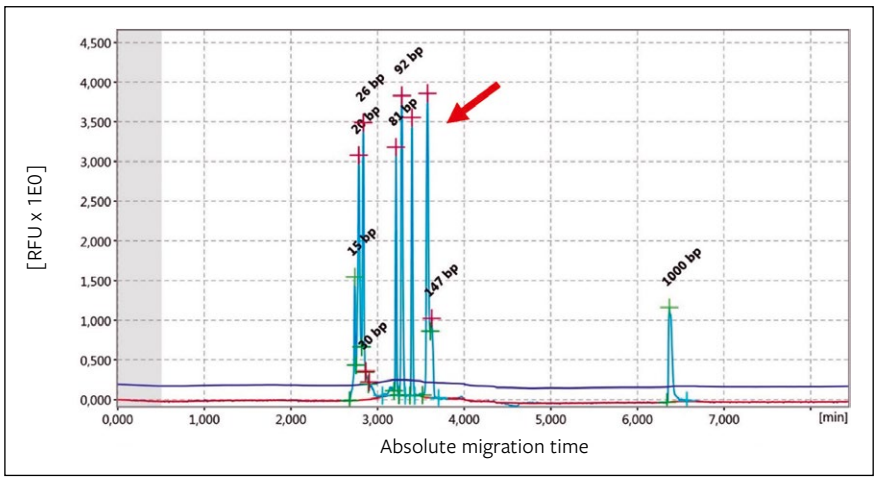



**Fig. 1-17** Exemplary electropherogram of an oligoclonal (**red arrow**) profile

The distinct 15 and 1000 bp peaks show the alignment markers, whereas the 20 and 26 bp peaks represent leftover PCR primers.

**RFU** = relative fluorescent unit.

no peak(s), or a Gaussian curve and signifies an insufficient or mutated target DNA. For this reason, all primer sets must be analyzed in duplicate or, even better, in triplicate fashion. The pseudoclonal result is most likely due to insufficient DNA quantity or integrity.[10]

## Considerations for interpreting lymphoid clonality

**Cats:** Low-grade alimentary lymphoma (LGAL, ▶Chap. 11.3) is the most common intestinal neoplastic disease in cats.[16] LGAL patients present with chronic gastrointestinal signs, overlapping with those in cats with chronic inflammatory enteropathy (CIE); also known as inflammatory bowel disease or IBD (▶Chap. 11.2). Although it has been hypothesized that chronic intestinal inflammation in cats could lead to the development of LGAL, no scientific evidence has been demonstrated.[16] Some investigators have proposed that intestinal lymphoma and feline chronic inflammatory enteropathies should no longer be considered two distinct disease processes but may belong to the same disease spectrum.[17] As definitive differentiation of LGAL and IBD is often not possible, the clinician is left with a stepwise therapeutic approach – food elimination, immunosuppressive therapy, or even chemotherapeutics.

PARR was investigated to help in the differentiation of these two conditions. Moore et al. reported 22 monoclonal and 3 oligoclonal expression results in 28 samples from cats with intestinal lymphoma.[18] In contrast, polyclonal expression was shown in IBD patients (n=9) or healthy cats (n=3). In 2011, Kiupel et al. described a diagnostic algorithm for feline intestinal samples to differentiate lymphoma from inflammation.[19] This study also suggested that full-thickness biopsies are superior to endoscopically collected biopsies. However, other authors were unable to confirm these findings. In addition, the combination of different modalities, such as immunohistochemistry (IHC) combined with flow cytometric immunophenotyping or PCR results for B- and/or T-cell clonality, may improve the ability for an accurate diagnosis. In a recent study, the authors integrated IHC and clonality testing for the differentiation of lymphoma and IBD, increasing the number of cases diagnosed with lymphoma.[20] Sabattini et al. studied 77 cats with chronic enteropathy in a multivariant survival study. Compared with other tests, such as cytology, histopathology, and IHC, only a clonality-based diagnosis of lymphoma was significantly associated with poor survival, with a risk of enteropathy-related death that was 2.8 times higher in cases of a monoclonal result.[21] This study reported a high specificity (87–97%) of clonality testing compared with the other testing modalities. However, a recent study reported on 12 of 20 healthy cats interpreted as having small-cell lymphoma and another as having emerging small-cell lymphoma.[22] These diagnoses were based on integrated results from histopathology, IHC, and clonality testing. Only three cats eventually developed gastrointestinal signs, two of which were euthanized 295 days and 654 days post-endoscopy. The remaining 17 cats did not show clinical signs of CE after a median of 709 days (range: 219–869 days). Huber et al. examined 34 cats with lymphocytic-plasmacytic enteritis concerning clonality and found that 67.5% of the examined intestinal tissue samples (26/34 cats) showed a T-cell clonality and were therefore suspicious for T-cell lymphoma or false positives in case of intestinal inflammatory enteropathy.[23] Unterkreuter et al. studied clonality in 42 non-domestic felines, identifying a monoclonal pattern in only 3 out of 8 cases diagnosed with lymphoma, which could be interpreted as false negative PARR results or false positive test results of the other diagnostic tests utilized.[24] These studies show that clonality testing must be interpreted in light

of the clinical examination and in combination with other test results, such as IHC and flow cytometry. In addition, the age of the cats seems to play a major role, as older cats tend to show monoclonal results with a higher frequency.[22] A regrouping from chronic enteropathy to LGAL based on the clonality results alone is thus not advised.[16]

In contrast to cats, canine alimentary lymphoma is a rare disease with a generally poor prognosis.[25] This circumstance makes it even more important to differentiate alimentary lymphoma and inflammatory bowel disease correctly.

**Dogs:** Differentiation is further complicated by both disease processes potentially overlapping. In human medicine, intestinal T-cell lymphoma can be considered a sequel of chronic irritation due to chronic inflammatory gastrointestinal diseases.[26] Also, in veterinary medicine, it has been hypothesized that a progression from canine CIE to intestinal lymphoma, especially enteropathy-associated T-cell lymphoma (EATL), is a subtle process.[27,28] However, as in cats, proof for this hypothesis is also lacking in dogs. This chapter should make the clinician aware of the possibilities and possible pitfalls of clonality testing concerning the differentiation of CIE and intestinal lymphoma in dogs. The consequences of monoclonal test results in dogs that have a histopathological diagnosis of inflammatory enteropathy are controversial. In one study, the sensitivity of PARR for intestinal lymphoma based on endoscopically retrieved biopsies was reported to be 66%.[12] Another study reported a significantly worse prognosis for Shiba Inu dogs diagnosed with CIE and a monoclonal PARR result than Shiba Inu dogs diagnosed with CIE and a polyclonal PARR result.[28] The authors of this study concluded that the dogs were falsely diagnosed with IBD and should have been regrouped as lymphoma. However, several authors suggest the opposite. Luckschander-Zeller et al. studied the clonality of snap-frozen intestinal biopsy samples from 35 dogs diagnosed with CIE with histopathological lymphocytic-plasmacytic enteropathy.[13] Four of these patients had monoclonal or oligoclonal results. Intestinal biopsies of all control dogs (healthy beagles) showed polyclonal patterns for B- and T-cell primers. All samples from dogs with CIE showed a polyclonal pattern for B-cell primers. Targeting TCRG, four patients showed a monoclonal or oligoclonal pattern. Nevertheless, clinical improvement was observed in all dogs. This study showed that a false positive result, probably derived from canonical amplifications in CIE dogs, is possible. Also, Carrasco et al. reported that 2 of 8 cases diagnosed as intestinal lymphoma, based on histology and IHC, were polyclonal. In all IBD cases, a polyclonal result was observed as well.[29] This study showed that false negative results might also occur. These false negative results should be interpreted in light of other factors, such as dependency on the recognition spectrum of the primers used in the assay and the number of neoplastic cells within a sample.[15] In summary, a stepwise approach for the diagnosis of CIE or intestinal lymphoma, including PARR as a diagnostic tool, seems wise. Regrouping a diagnosis based on PARR alone and in contrast to all other evaluated patient diagnostic data is considered controversial.

#### 1.3.5.2.2 Histology-guided mass spectrometry

Histology-guided mass spectrometry (HGMS) profiling is a technique where targeted intestinal tissue is probed by mass spectrometry on histological staining to analyze endogenous molecules from specific cell types.[30] In human medicine, this technique is used to differentiate benign and malignant lesions.[31] In a recent retrospective study, HGMS of paraffin-embedded duodenal tissue was used to differentiate feline lymphocytic-plasmacytic enteritis and intestinal small-cell lymphoma.[32] The results showed similar sensitivity and accuracy but higher specificity than seen with clonality testing.[32]

**KEY FACTS**

- Clonality testing can serve as a complementary tool for the differentiation of chronic inflammatory enteropathy and intestinal lymphoma.
- Preanalytical aspects, such as DNA quality and age of the sample, must be considered when interpreting test validity.
- Diagnostic sensitivity and specificity of the PARR (polymerase chain reaction for antigen receptor gene rearrangements) result are highly dependent on the primer sets used and should be provided by every diagnostic lab offering the test.
- A regrouping of the diagnosis based on PARR results alone is not advisable.
- The interpretation of a PARR result considers all clinical and morphological data available.

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
svg.to/9842-01-03-05

## 1.4 Diagnostic imaging

Lorrie Gaschen

### 1.4.1 Introduction

The variety of diagnostic imaging modalities that have become available to veterinarians has led to a need for expanded expertise in ultrasound, computed tomography (CT), nuclear scintigraphy, and magnetic resonance imaging (MRI). However, conventional radiography and ultrasonography remain essential, cost-effective, and readily available methods for diagnosing many gastrointestinal disorders in dogs and cats. In fact, ultrasonography has become an invaluable diagnostic tool and has diminished the need for barium contrast studies in animals presenting for vomiting and/or diarrhea.

Radiography and ultrasonography of the abdomen should be performed together since they provide complementary information. Survey radiographs provide a global view of the abdomen that cannot be obtained with sectional imaging, such as ultrasonography. Survey radiographs may also allow an immediate diagnosis, as is the case of some animals with intestinal obstruction. Indications for plain **radiography** include dysphagia, regurgitation, vomiting, acute abdomen, constipation, abdominal pain, abdominal distension, weight loss, anorexia, certain biochemical abnormalities (e.g., icterus), or a palpable mass. In animals with chronic diarrhea or marked abdominal effusion, abdominal radiographs are less beneficial.[1]

The spectrum of gastrointestinal diseases that can be better identified by **ultrasonography** includes intussusceptions, pancreatitis, peritoneal infiltrative disease, gastrointestinal wall infiltrations, abdominal neoplasia, and hepatobiliary disease. Ultrasonography also provides functional information regarding intestinal motility and hemodynamics. Furthermore, ultrasound-guided, percutaneous tissue biopsy can be performed to collect samples for cytological or histological examination. However, the clinical usefulness of ultrasonography is highly operator dependent, and the detection and interpretation of abnormalities rely heavily on the sonographer's expertise.

**Barium contrast studies** of the GI tract are generally only indicated when the combination of clinical information, survey radiography, and ultrasonography do not lead to a diagnosis or if ultrasound is unavailable.[2] Indications for a positive contrast upper gastrointestinal study include determining the location of structures of the GI tract, assessing wall thickness, determining transit time, and diagnosing luminal, mural, and extramural obstructive disease. Contraindications to performing barium contrast studies include survey radiographic evidence of obstructive disease or free peritoneal gas or effusion. Although iodinated contrast agents may be used, they should be avoided in debilitated or dehydrated patients since they can worsen the patient's condition or lead to a hypovolemic state.[3]

**Contrast-enhanced ultrasonography (CEUS)** uses gas-containing stabilized microbubbles that remain intact in the vascular space for several minutes after intravenous (IV) injection and increase the intensity of the backscattered ultrasound.[4] CEUS can be useful in dogs and cats to differentiate malignant vs. benign focal liver lesions and to diagnose portosystemic shunts and hepatic fibrosis.[5–11] CEUS has also been shown to be 100% accurate in diagnosing gallbladder rupture in the dog as it identifies discontinuity of the gallbladder wall.[12] CEUS has also been described for the assessment of perfusion in the liver, kidneys, pancreas, small intestines, and regional lymph nodes of healthy dogs and cats.[13–16] Finally, in affected animals, CEUS has been used to diagnose intestinal wall ischemia in cats and duodenal perforation in dogs.[17,18]

**CT, MRI**, and **nuclear scintigraphy** are alternative methods used to investigate the GI tract, hepatobiliary system, and pancreas in cats and dogs.[19–22] CT may be performed to detect abdominal neoplasia and portosystemic shunts or for imaging the pancreas.[23–34] Dual-phase CT can also be used to improve the conspicuity of the gastrointestinal wall, especially that of the small intestine.[24] MRI is not frequently used for GI tract examinations, although it has been described for investigations of hepatobiliary and pancreatic disease.[35,36]

Nuclear scintigraphy provides functional information about the GI tract and has been well-established in veterinary medicine. In the hands of an experienced user, per-rectal or splenic scintigraphy has significantly improved the rapid diagnosis of portosystemic shunts and allows for the quantification of the shunting fraction both pre- and postoperatively.[37,38] Nuclear scintigraphy has also been used to diagnose hepatobiliary disease and assess gastric emptying time.[19,39] CEUS can also detect portosystemic shunts.[40] Portal venous hypoperfusion due to a portosystemic shunt alters the microvasculature of the liver, which can be detected with CEUS, and a number of quantitative measurements can be used to diagnose shunts due to altered hepatic arterial and portal venous time-activity curves, and hepatic parenchymal enhancement.[40]

This chapter provides guidelines for the diagnostic imaging approach in dogs and cats with gastrointestinal disorders. Each section discusses the imaging of different anatomic regions according to specific clinical signs. Imaging for the diagnosis of hepatobiliary and/or pancreatic disorders is described in a separate section. Although radiography and ultrasonography are emphasized, indications for alternative imaging modalities are also described.

### 1.4.2 Oropharynx

Patients with dysphagia, regurgitation, or vomiting are approached differently depending on which sign predominates. Dysphagia and regurgitation can often be differentiated from vomiting by a thorough history and physical examination. Regurgitation can occur with both oropharyngeal and esophageal disorders. However, patients with exaggerated swallowing attempts, gagging, or pain when drinking or swallowing food often have oropharyngeal dysphagia. Regurgitation is characterized by the passive retrograde expulsion of undigested food, whereas animals with vomiting show a forceful ejection of partially digested food with a marked abdominal effort.

Survey radiographs of the pharynx and cervical regions should always be performed to rule out structural abnormalities, such as fractures of the hyoid apparatus or radiopaque foreign bodies. Both lateral and ventrodorsal views should include the pharyngeal and laryngeal regions and the entire cervical and thoracic esophagus. Thoracic radiographs in three planes (left, right, and *ventrodorsal* [VD] or *dorsoventral* [DV]) are always indicated in animals with dysphagia to rule out the presence of aspiration pneumonia.

#### 1.4.2.1 Structural abnormalities

**Survey radiographs** should be evaluated for increased soft tissue opacities in the oropharyngeal, retropharyngeal, or cervical regions, which may impinge upon or displace the airways of the oropharynx, nasopharynx, larynx, or trachea (▶Fig. 1-18). Soft tissue space-occupying lesions may be due to lymphadenomegaly, abscesses, polyps, neoplasms, or foreign body granulomas. Radiopaque foreign bodies may be immediately evident; however, radiolucent ones may not be visible or appear as space-occupying soft tissue lesions. The presence of gas within soft tissues can be seen with abscesses or foreign body penetration.

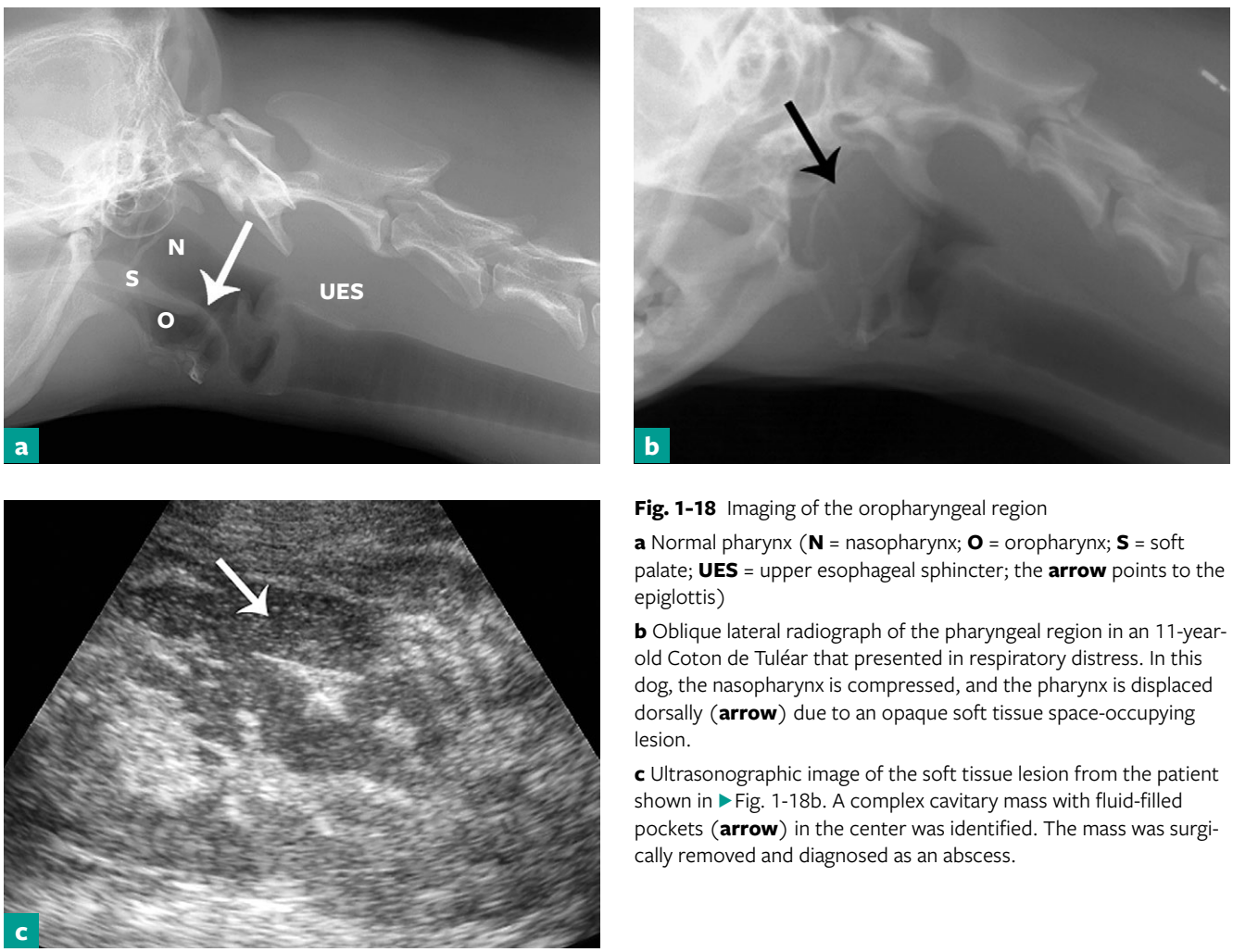



**Fig. 1-18** Imaging of the oropharyngeal region

**a** Normal pharynx (**N** = nasopharynx; **O** = oropharynx; **S** = soft palate; **UES** = upper esophageal sphincter; the **arrow** points to the epiglottis)

**b** Oblique lateral radiograph of the pharyngeal region in an 11-year-old Coton de Tuléar that presented in respiratory distress. In this dog, the nasopharynx is compressed, and the pharynx is displaced dorsally (**arrow**) due to an opaque soft tissue space-occupying lesion.

**c** Ultrasonographic image of the soft tissue lesion from the patient shown in ▶Fig. 1-18b. A complex cavitary mass with fluid-filled pockets (**arrow**) in the center was identified. The mass was surgically removed and diagnosed as an abscess.

**Ultrasonography** can be used to determine the origin and character of soft tissue swellings of the neck and retropharyngeal region. High-frequency linear array transducers are best suited for examining the cervical region since most structures are very superficial. However, curved-linear array transducers are also adequate.[41] The thyroid and salivary glands and the retropharyngeal or mandibular lymph nodes can become enlarged due to inflammation, abscessation, or primary or metastatic neoplasia. Perforating foreign bodies can be recognized as hyperechogenic structures of varying size with acoustic shadowing (▶Fig. 1-19).[42] Pinpoint hyperechogenic structures with reverberation echoes signal the presence of air and should not be mistaken for foreign material. Lingual foreign bodies and abscesses can also be diagnosed by ultrasound using a ventral, inter-mandibular approach (▶Fig. 1-20).[43]

**MRI and CT** are advanced modalities for examining the cervical region, screening for foreign bodies, and determining the origin and character of masses.



**Fig. 1-19** Foreign body in the cervical region

Ultrasound image of the cervical region of a dog with a chronic draining wound. A 3 mm long, hyperechoic, linear structure (**arrow**) with distinct acoustic shadowing (**two smaller arrows**) was detected in the soft tissue. Diagnosis: wood splinter with abscess.

### 1.4.2.2 Functional disorders

Functional swallowing disorders may result in oral, pharyngeal, cricopharyngeal, esophageal, and gastroesophageal dysphagia.[44] **Survey radiographs** of animals with functional disease are generally unremarkable. Thoracic radiographs are indicated to rule out the presence of aspiration pneumonia and megaesophagus, which can occur with functional disorders. Lateral radiographs of the oropharyngeal and cervical regions are required to rule out structural abnormalities. Focal gas accumulations may be detected in the proximal esophagus due to either esophagitis or functional disorders. The presence of an open, air-filled upper esophageal sphincter and an air-filled esophagus can be seen with cricopharyngeal achalasia since the sphincter cannot maintain a positive resting pressure (▶Fig. 1-21). However, the findings of air in the esophagus in panting, sedated, or anesthetized animals are not uncommon and should be interpreted with caution

A **contrast study** performed with fluoroscopy or static radiographic images is indicated when survey radiographic examination is unremarkable. However, without the possibility of fluoroscopy and dynamic acquisition of images at 30 frames per second, the details about bolus formation and passage are usually not observed with static radiographic images alone. Videofluoroscopic swallowing studies (VFSS) allow quantification of the phases of swallowing and are assessed by analyzing the video frames for the pharyngeal

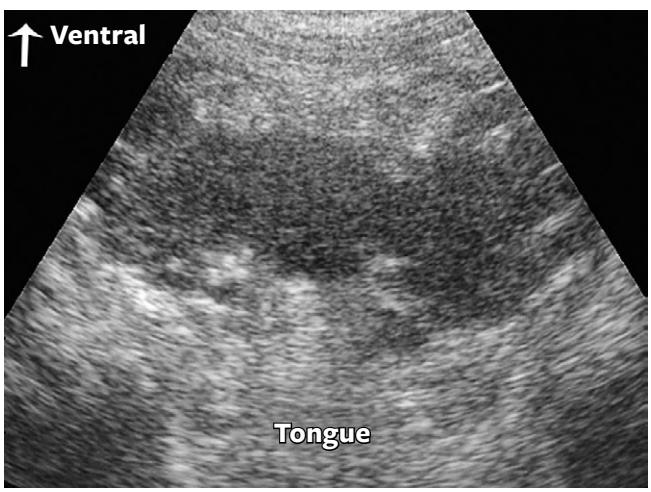



**Fig. 1-20** Lingual foreign body

Ventral transverse ultrasound image of the caudal oral cavity at the level of the angular processes of the mandible in a dog with acute dyspnea, cyanosis, and pharyngeal swelling. A space-occupying lesion with a complex echotexture at the base of the tongue was identified. The mandibular rami can be seen as anechoic structures on either side of the tongue. The lesion was explored surgically and found to be an abscess, most likely due to a perforated foreign body.

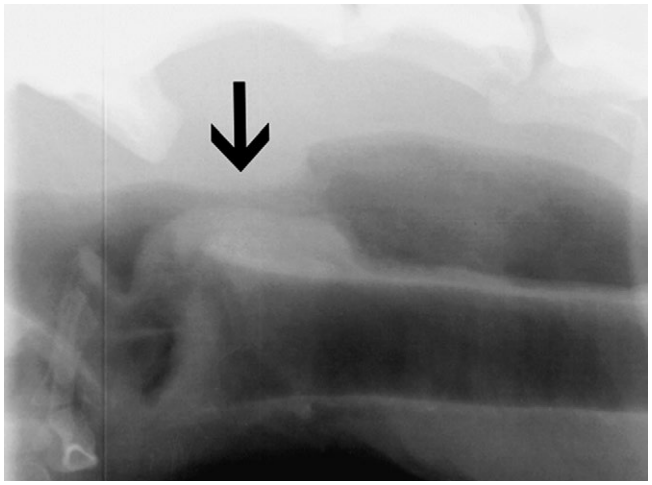


**Fig. 1-21** Megaesophagus

Lateral radiograph of the pharynx in a 4-year-old German shepherd with regurgitation due to megaesophagus. The upper esophageal sphincter is open and air-filled (**arrow**). The cervical esophagus is dilated and air-filled. The presence of air in these structures indicates the possibility of either a functional or structural disorder. The final diagnosis in this dog was achalasia due to myasthenia gravis. (Courtesy of Dr. Johann Lang, Division of Radiology, Vetsuisse, University of Bern, Switzerland.)

constriction ratio, timing of swallowing events (maximal pharyngeal contraction, opening of the upper esophageal sphincter, closing of the upper esophageal sphincter, and reopening of the epiglottis), type of esophageal peristalsis, and esophageal transit time.[45]

**Swallowing studies** are generally performed in conscious animals as sedation may inhibit swallowing or increase the risk of aspiration. Initially, a liquid contrast agent should be administered into the oral cavity. Liquid barium sulfate suspensions (45–85% w/w) are preferred for barium swallows with 5–20 mL of the suspension being administered, depending on the size of the animal. A medium-sized dog typically receives 15 mL liquid suspension for a swallow study.[44] Ideally, the study should be repeated using barium-coated kibble. With the animal in lateral recumbency, the act of swallowing should be observed immediately by video fluoroscopy at 30 frames/second and recorded in a digital format for future review (▶ Fig. 1-22). VFSS may also be performed in the standing position using a horizontal beam. Esophageal transit times have been shown to be delayed in patients in lateral recumbency, and if this region is of concern, a standing horizontal beam study may be preferred.[46] A recumbent vs. sternal or standing position should not affect objective parameters of pharyngeal or cricopharyngeal function.[46]

In an animal with normal swallowing, once the bolus of liquid or food is prehended, it is propelled to the pharynx, the pharynx contracts, and swallowing continues as a reflex. The bolus is pushed through the cranial esophageal sphincter. The epiglottis simultaneously flips upward to cover the larynx. The cranial esophageal sphincter relaxes to allow passage of the bolus into the esophagus. Then the sphincter closes to prevent retrograde movement of the bolus. The esophagus transports the bolus via primary and secondary waves to the caudal esophageal sphincter and into the stomach.[44]

In a study of 216 dogs with dysphagia, 28% of the VFSS procedures were unremarkable, 13% showed pharyngeal dysphagia, 8% showed cricopharyngeal dysphagia, 45% showed esophageal dysmotility, and 45% showed evidence of dysfunction of the lower esophageal sphincter (gastrointestinal reflux and hiatal hernia).[45]

Retention of contrast medium in the oral cavity and its absence in the pharynx and esophagus can be observed in animals with oral dysphagia. When mechanical obstruction can be ruled out, idiopathic neuromuscular dysfunction is usually the cause. If direct damage to the tongue can be ruled out, a brain stem lesion (hypoglossal nerve) may be suspected as the underlying cause. Retention of substantial amounts of contrast medium in the pharynx following swallowing of the

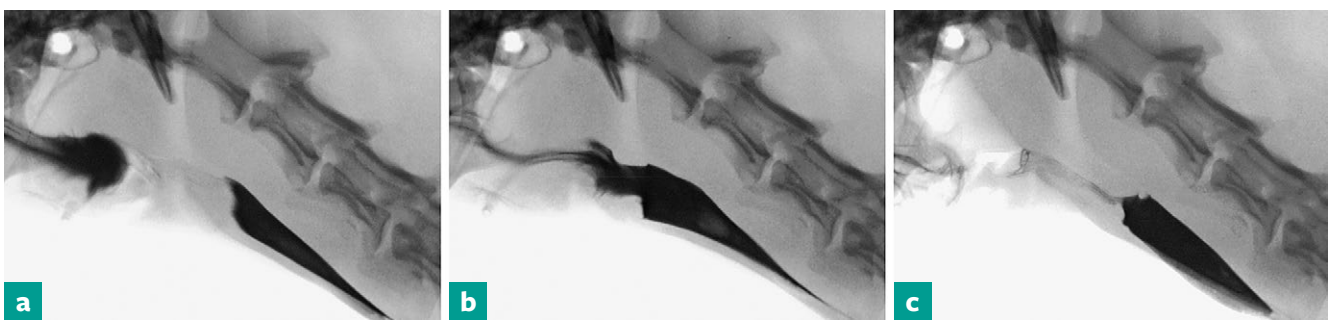



**Fig. 1-22** Barium swallow in a normal dog

Static digital fluoroscopic images of a barium swallow in a healthy dog. The pharyngeal (**a**), cricopharyngeal (**b**), and esophageal (**c**) phases are shown. (Courtesy of Dr. Johann Lang, Division of Radiology, Vetsuisse, University of Bern, Switzerland.)

bolus is observed during pharyngeal phase dysphagia. Aerodigestive disorders due to swallowing disorders may also be observed on VFSS and can be seen in dogs that present with coughing but without signs of alimentary disease.[47] Aerodigestive disease spans a range of diseases with defects in respiratory-swallow coordination.[47] In one study, VFSS features of aerodigestive disease included aspiration of food or fluid into the larynx or trachea, pharyngeal dysfunction (hypomotility or spasticity), reflux, and epiglottic retroversion.[47]

**Cricopharyngeal dysphagia** is characterized by retention of contrast medium in the pharynx with reflux of the contrast medium into the oro- or nasopharynx, aspiration into the larynx, retention in the cervical esophagus, and hypertrophy or distortion of the cranial esophageal sphincter. Dogs will have an increased pharyngeal constriction ratio and delayed opening of the upper esophageal sphincter.[45] Often, very small amounts of contrast medium are observed passing through the sphincter, and multiple attempts to swallow occur before the bolus passes through the cranial esophageal sphincter is also seen.[44] This disease is often seen in young dogs and is called cricopharyngeal achalasia (▶Fig. 1-23). In contrast, in patients with cricopharyngeal achalasia, the upper esophageal sphincter remains open, and contrast can be observed moving freely between the esophagus and pharynx through an open sphincter (▶Fig. 1-24). This should alert the clinician to a neuromuscular disorder, such as myasthenia gravis.

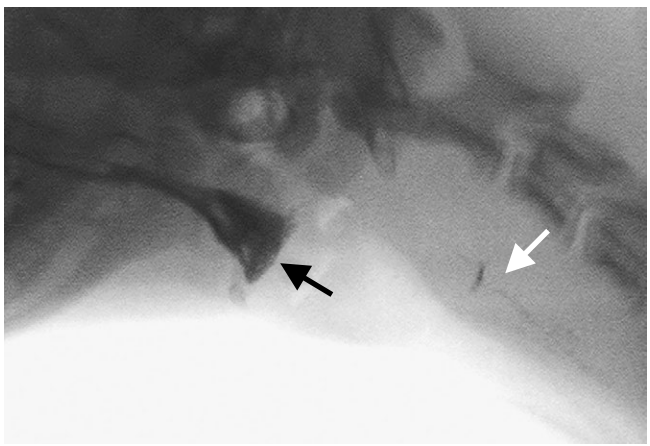


**Fig. 1-23** Cricopharyngeal achalasia

Static digital fluoroscopic image of a barium swallow in a 5-month-old American Staffordshire terrier with dysphagia and failure to thrive. The puppy showed clinical signs of cricopharyngeal dysphagia and could only swallow food intermittently. There is retention of contrast in the pharynx. Fluoroscopically, pharyngeal contractions were evident, and the contrast bolus was repeatedly advanced towards a closed upper esophageal sphincter (**black arrow**). Occasionally, some contrast material passed through the sphincter and was visible in the esophagus (**white arrow**). Diagnosis: cricopharyngeal achalasia.

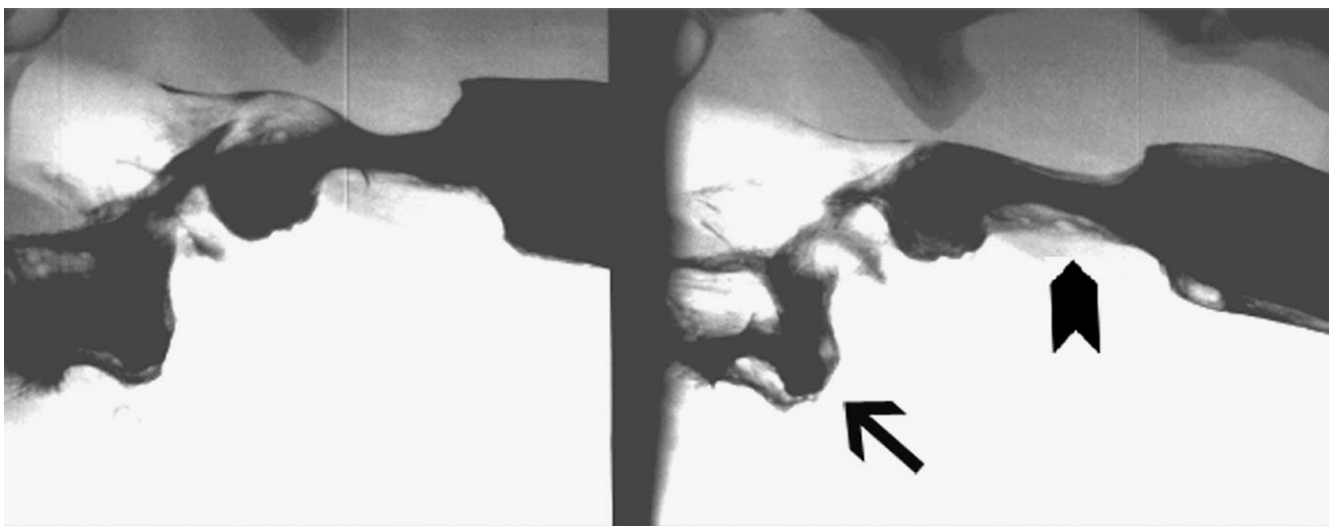


**Fig. 1-24** Cricopharyngeal achalasia

Barium swallow in a dog with myasthenia gravis. This figure shows a barium swallow in the same dog, as shown in ▶Fig. 1-23. Note that there is retention of contrast in the pharynx (**arrow**), and the upper esophageal sphincter remains open (**arrowhead**) and filled with contrast. (Courtesy of Dr. Johann Lang, Division of Radiology, Vetsuisse, University of Bern, Switzerland.)

### 1.4.3 Esophagus

The radiographic features associated with esophageal disease are listed in the box below. Radiography is central to the diagnosis of megaesophagus. It allows rapid identification of the affected segments and assessment of the degree of esophageal dilation. A small amount of air in the esophageal lumen can be expected in dogs that are panting or nervous during the radiographic procedure or those under sedation or general anesthesia (▶ Fig. 1-25). The presence of ventral pulmonary consolidations and pleural fluid on thoracic radiographs should raise the suspicion of mediastinitis, esophageal rupture, and/or aspiration pneumonia (▶ Fig. 1-26).

**Radiographic signs of esophageal diseases**

- Increased visibility
- Tracheal stripe sign
- Dilation with air, fluid, or food
- Pneumomediastinum
- Mediastinal space-occupying lesion
- Ventral displacement of the trachea and heart
- Increased lucency of the dorsal thoracic region
- Ill-defined pulmonary consolidations located ventrally
- Pleural fluid
- Midline caudal thoracic soft tissue opacity cranial to the diaphragm

Esophagography with barium sulfate creams or suspensions is indicated when esophageal disease is suspected, and survey thoracic radiographs are unremarkable. VFSS is the gold standard for the assessment of esophageal motility disorders.[45,48] VFSS allows real-time and post-acquisition evaluation (frame by frame), increasing the diagnostic accuracy.

**NOTE**

In the presence of a pneumomediastinum or mediastinitis, aqueous iodine agents may be used orally, but if aspirated, they may induce life-threatening pulmonary edema due to their hypertonic nature.

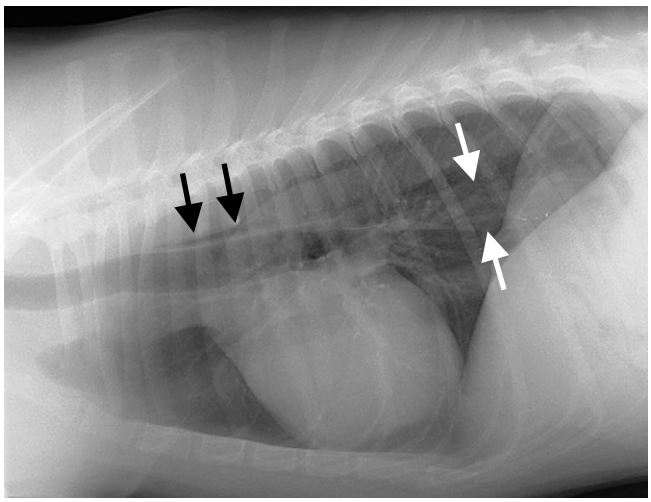


**Fig. 1-25** Lateral thoracic radiograph of a healthy dog

Dogs and cats that are nervous or panting when radiographs are taken may have small amounts of air or fluid in the esophagus. Air is typically seen just cranial to the base of the heart (**black arrows**). The caudal esophagus may appear as a soft tissue opaque band (**between white arrows**) between the aorta and caudal vena cava.

The goal of the esophagram should be to determine the location and type of esophageal abnormality. However, the esophagram may only provide limited information since it can only differentiate intraluminal lesions from extramural lesions and cannot determine the exact cause. If evaluation using a liquid barium suspension is equivocal, a barium-coated food bolus should be fed. Gravity-assisted esophageal transit studies using a Bailey chair in dogs with megaesophagus and lower esophageal sphincter disease, such as achalasia, provide improved diagnostic efficacy and better management strategies.[49]

Extramural or intramural lesions that do not alter the esophageal mucosa may go unnoticed during conventional endoscopy of the esophagus. In contrast, echoendoscopy allows for the detection of intramural neoplasms and extramural space-occupying lesions of the mediastinum that may compress the esophagus, but this modality has limited availability (▶ Fig. 1-27). CT is more widely available and is considered the best modality to examine the entire thorax, including the mediastinum, and to assess mural and extramural lesions.

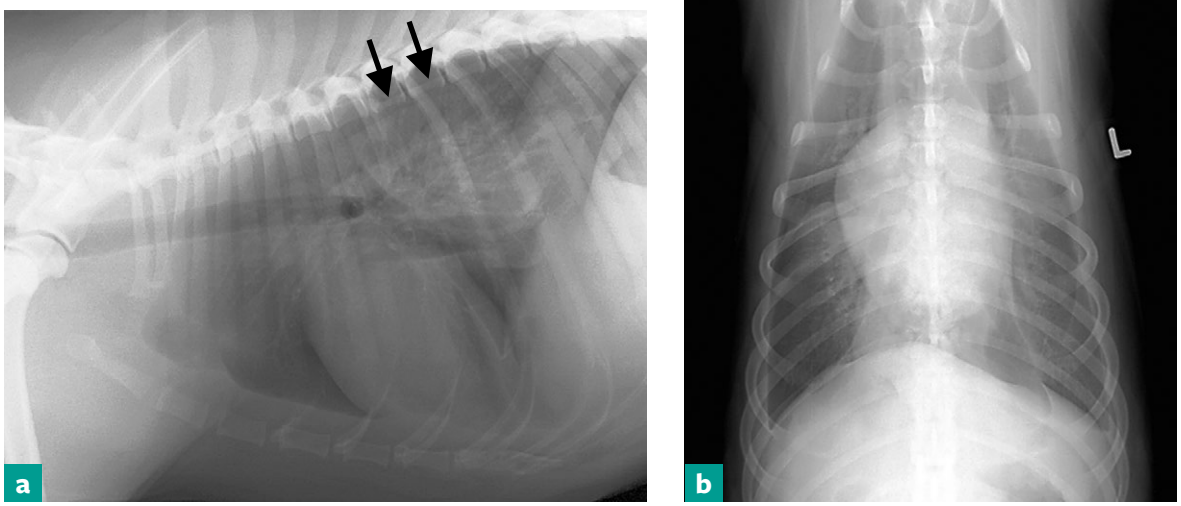



**Fig. 1-26** Perforating esophageal foreign body

Lateral (**a**) and ventrodorsal (**b**) thoracic radiographs of a 2-year-old American Staffordshire terrier that presented in lateral recumbency and shock with severe abdominal pain. A mixed radiopacity in the region of the caudal esophagus is present. Additional findings include the presence of pleural fluid and pneumothorax. Note the retracted border of the caudal lung lobe (**arrows**) with free air surrounding it dorsally. Differential diagnoses include trauma, pulmonary disease, and mediastinitis. A piece of rawhide was removed surgically from the esophagus, which had perforated the esophagus.

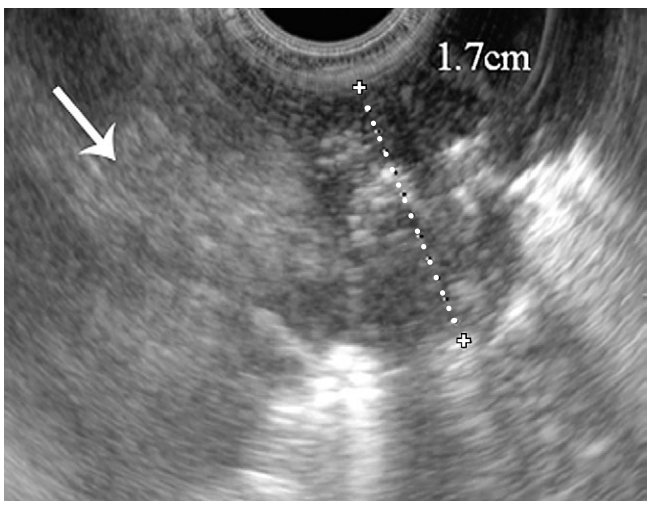



**Fig. 1-27** Esophageal endoscopy of an esophageal mass

Esophageal echoendoscopy shows a nodular infiltration with disruption of the esophageal wall layering in a diameter of 1.7 cm (**distance shown: dotted line**). The lesion has a complex echostructure that includes hyperechoic foci with reverberation echoes (i.e., gas bubbles in the mass). A separate portion of the lesion (**arrow**) was 2 cm in diameter, homogenous, and had invaded through the esophageal wall to invade the peri-esophageal region. The presence of multiple intralesional vessels with arterial flow was demonstrated on Doppler ultrasound. Histological diagnosis: esophageal carcinoma.

### 1.4.3.1 Generalized esophageal dilation

Generalized megaesophagus can be visualized by the presence of a dilated, gas-filled lumen along the entire length of the esophagus on survey radiographs. The tracheal stripe sign is present due to superimposition of the esophageal and tracheal walls and the longus colli muscle ventral to the 5th and 6th thoracic vertebrae (▶Fig. 1-28). The caudodorsal thorax may also appear hyperlucent due to the presence of air in the esophagus. Differential diagnoses for generalized dilation of the esophagus are numerous. In young animals, megaesophagus is most commonly idiopathic. In adults, central nervous system and neuromuscular disorders, such as myasthenia gravis, feline dysautonomia, polyneuritis, or polymyositis are more likely to be the cause.[44,50]

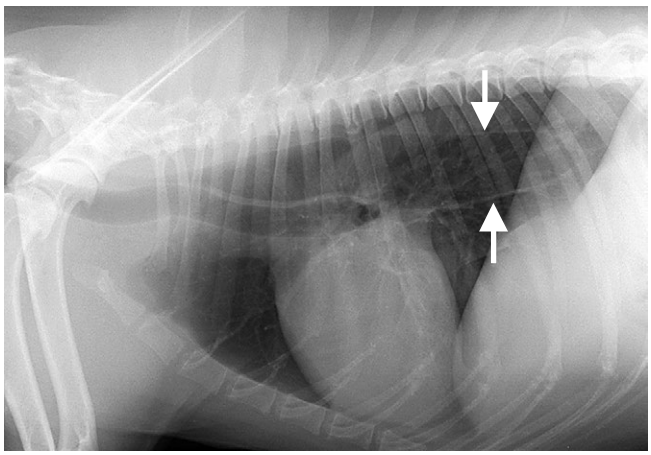


**Fig. 1-28** Megaesophagus
Lateral thoracic radiograph showing generalized megaesophagus. The esophagus is air-filled, the dorsal thorax appears hyperlucent, and the thin walls of the esophagus can be identified (**arrows**).

**Lower esophageal sphincter achalasia (LES-AS)** is another cause. LES-AS in people is due to a primary esophageal motility disorder resulting from a selective loss of inhibitory myenteric neurons, leading to failure of the LES to relax in response to a pharyngeal swallow and impaired esophageal peristalsis.[51] LES-AS may be overlooked in a subpopulation of dogs with esophageal dysphagia, and its recognition is crucial for creating therapeutic strategies, such as injection of botulinum toxin A, dilation procedures, or myotomy.[52] It is recommended to perform VFSS in dogs in the standing position using a radiolucent positioning device and three boluses of positive contrast agents in liquid, puree, and kibble consistency.[53] The VFSS features of LES-AS include failure of the LES to open during pharyngeal swallowing, abnormal LES relaxation of >50% of swallow attempts, passage of ingesta from the esophagus to the stomach only due to hydrostatic pressure, the presence of a baseline fluid line, and a "bird beak" sign at the LES.[54]

**Endocrinopathies**, such as hypothyroidism or hypoadrenocorticism and toxicities, trauma, tetanus, and thymoma, are additional differential diagnoses for generalized megaesophagus. Dilation can also be seen with hiatal hernias (▶Chap. 5.3.9) and gastric volvulus. Furthermore, an air-filled megaesophagus can be seen in cats with lower airway disease due to dyspnea and aerophagia. Mechanical causes of generalized dilation can be due to foreign bodies and strictures located either intraluminally, murally, or peri-esophageally.

**Idiopathic esophageal dysmotility (IED)** is increasingly recognized in young brachycephalic dogs. VFSS features include prolonged esophageal transit time, decreased propagation of secondary peristaltic waves, and gastroesophageal reflux and is described as secondary to congenital or acquired luminal obstruction, esophagitis, hiatal hernia, diverticula, or fistulas.[54] Brachycephalic dogs, especially the French bulldog, are at increased risk for hiatal hernia, prolonged esophageal transit time, and gastroesophageal reflux compared with non-brachiocephalic breeds.[54,55] The diagnosis is made by VFSS when primary esophageal peristaltic waves propagate the liquid bolus <5 cm into the proximal esophagus or if contrast material from more than two swallowed boluses accumulates in a portion of the esophagus and cause focal dilation before secondary peristalsis is stimulated.[54] Additional features of IED include retrograde contractions, prolonged esophageal transit time, gastroesophageal reflux more than once per swallowed bolus, and if a hiatal hernia occurred during the study. Esophageal transit time is considered abnormal if a bolus takes more than 5 seconds to reach the lower esophageal sphincter. Hiatal hernia is diagnosed during a swallow study when the lower esophageal sphincter is displaced cranially to the diaphragmatic contour in the thoracic cavity.

VFSS assessment of dysphagic cats can be used as in dogs to diagnose hiatal hernia, esophageal strictures, and esophageal dysmotility.[56] In a study of eleven cats, esophageal stricture and hiatal hernia were common causes of esophageal and gastroesophageal dysphagia. Using VFSS, cats were given 3–5 mL doses of liquid barium suspension, and 3–5 swallows were recorded. Barium-soaked kibble should be given if the cat is amenable to eating it.[56] This study also showed that pharyngeal and cricopharyngeal disorders are very rare in cats.

### 1.4.3.2 Segmental esophageal dilation

Localized or segmental esophageal dilations may be located anywhere along the esophagus (▶Fig. 1-29). Potential causes include foreign bodies, segmental hypomotility, esophagitis, diverticula, hernias, acquired strictures, congenital ring anomalies, and mural or extramural lesions due to inflammation or neoplasia. Foreign bodies and strictures may also present radiographically as mediastinal soft tissue opacities rather than focal dilations. Common sites of esophageal strictures are the thoracic inlet, the base of the heart, and the gastroesophageal junction. In young dogs and cats, esophageal strictures are often due to vascular ring anomalies, such as a persistent right aortic arch (▶Chap. 5.3.11).[57] These are recognized by a ventral displacement of the trachea in the cranial thorax and varying degrees of esophageal dilation cranial to the base of the heart. Barium esophagrams are contraindicated in the presence of large fluid- or food-filled esophageal dilations or in the presence of pleural effusion. Angiography should be performed to definitively rule out a vascular ring anomaly in any puppy or kitten where this condition is suspected. Adult onset clinical signs of a congenital ring anomaly can also be found in dogs and cats and usually represents an atypical vascular defect and incomplete ring that only partially constricts the esophagus.[58,59]

## 1.4.4 Stomach

Following the clinical history, physical examination, and laboratory database, survey radiographs and ultrasound imaging are important diagnostic tools in dogs and cats with vomiting. Radiography is a rapid modality used to assess extra-abdominal structures, the abdominal wall, diaphragm, and vertebrae, and to detect obstructive lesions and radiopaque foreign bodies. The significance of the presence of radiopaque material in the GI tract must be correlated to the type of foreign body, its size, and the clinical signs observed in the animal. Regardless of inherent diagnostic limitations, lateral and ventrodorsal

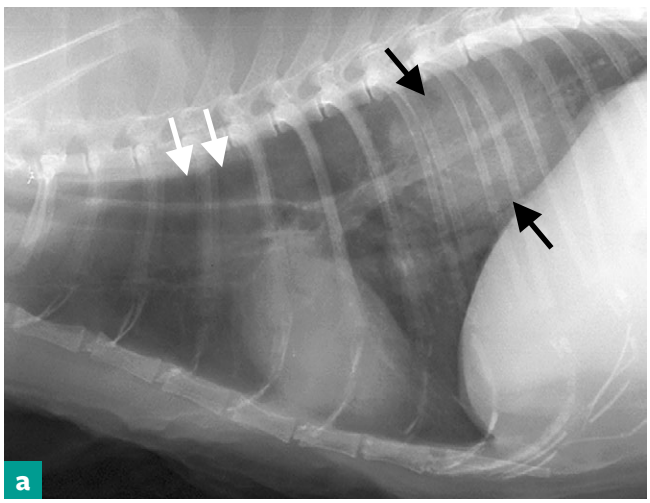






**Fig. 1-29** Esophageal mass

Lateral (**a**) and ventrodorsal (**b**) thoracic radiographs of a 16-year-old European shorthair that presented with chronic dyspnea, anorexia, and weight loss. A round soft tissue opacity in the region of the caudal mediastinum can be seen (**black arrows**). Note the segmental dilation of the esophagus cranial to the lesion (**white arrows**). Additional pulmonary nodules are seen in the right caudal lung lobe. Possible origins of the mass are esophageal, intraluminal or mural, peri-esophageal, or pulmonary. Differential diagnoses include neoplasia, granuloma, abscess, or an esophageal foreign body. See ▶Fig. 1-27 for echoendoscopic evaluation of this mass. Histological diagnosis: esophageal carcinoma.

survey radiographs should always be performed prior to contrast studies, ultrasonography, or endoscopy.

Prior to both radiography and ultrasonography, animals should be fasted for a minimum of 12 hours, though this may not be possible in emergency situations. Dependent upon the radiographic findings, a combination of ultrasonography and endoscopy may be deemed necessary. Ultrasonography should always be performed prior to endoscopy or barium studies since the presence of excessive intestinal gas or barium sulfate will create ultrasound artifacts that prohibit thorough examination of the abdomen.

For ultrasonographic evaluation of the GI tract, high-frequency curved and linear array transducers are recommended. High-frequency transducers have the best resolution for evaluation of gastrointestinal wall layering. Moreover, linear transducers allow for the best resolution of small intestinal layering and echogenicity (▶Fig. 1-30). A 5–7.5 MHz transducer is adequate for large dogs whereas frequencies of >7.5 MHz are best for smaller dogs and cats. Ultrasound examination of the stomach and small bowel should include an assessment of the peritoneum, mesentery, and lymph nodes.

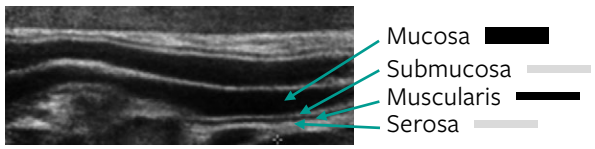



**Fig. 1-30** Intestinal wall layering

This ultrasound image of a normal jejunal segment in a dog showing normal wall layering was generated using a 7.5 MHz linear array transducer.

Gastrointestinal contents, especially gas or barium, may hinder the ultrasonographic examination. Even under ideal conditions, it is difficult to examine the entire stomach during abdominal ultrasound, especially in large dogs or when the stomach is greatly dilated. To improve imaging of the stomach, it can be filled with small amounts of water by either allowing the animal to drink or by administering it by stomach tube. This may facilitate the examination of the gastric wall, which can be difficult when the stomach is contracted.

An ultrasonographic evaluation of the GI tract should include an assessment of wall thickness, layering, and symmetry, localization and distribution of thickening, motility, and luminal content.

#### 1.4.4.1 Gastric dilatation and volvulus

Severe gastric distension may be caused by excessive quantities of food, gas, and/or fluid in the stomach. If the stomach is dilated and food-filled but positioned normally, dilatation is probably the most likely diagnosis (▶Fig. 1-31a). Severe dilatation, together with displacement of the stomach, is a sign of gastric volvulus. In dogs with gastric volvulus, the stomach appears compartmentalized or segmented with band-like soft tissue opacities apparent between the gas-filled segments (▶Fig. 1-31b–d). The radiographic localization of the pylorus is key to the diagnosis. The pylorus is usually displaced dorsally and to the left. A right lateral radiograph is usually sufficient to diagnose gastric volvulus, showing the pylorus to be gas-filled and located dorsally. The spleen is also often enlarged due to circulatory compromise and may also be displaced. The esophagus and small intestines often appear dilated and gas-filled. Gastric volvulus without severe distension may also occur. Therefore, it is always important to interpret the radiographic findings in light of the clinical findings. Dogs with a previous gastropexy that present with recurrent vomiting may have some degree of gastric distension and displacement radiographically. Although rare, compared with dogs, cats may also develop gastric dilatation-volvulus.[60]

#### 1.4.4.2 Gastric causes of chronic vomiting

Primary gastric causes of chronic vomiting include diffuse inflammatory infiltration, neoplasia, foreign body, polyps, ulcers, pyloric hypertrophy, and delayed gastric emptying. However, the diagnosis of these conditions can be challenging and often requires a combination of radiography, ultrasound, and endoscopy. Thickening of the stomach wall is commonly associated with chronic vomiting and is probably one of the most commonly over-interpreted findings on survey radiographs. The superimposition of fluid with the stomach wall may lead to the impression that the wall is thickened due to silhouetting artifacts. The same is true for fluid within the small intestines. Thickening of the rugal folds in dogs or cats with chronic gastritis is difficult to appreciate on survey radiographs for the same reason. Liquid barium contrast studies or, preferably, ultrasonography, are required to confirm a radiographic suspicion of wall thickening. Negative contrast studies can be obtained by filling the stomach with gas and taking radiographs in various positions.[2] This technique may allow detection of focal wall infiltrations. However, because both negative and positive contrast radiographic studies of the stomach are very time-consuming and can be difficult to interpret, ultrasound is generally the method of choice for imaging the stomach wall.

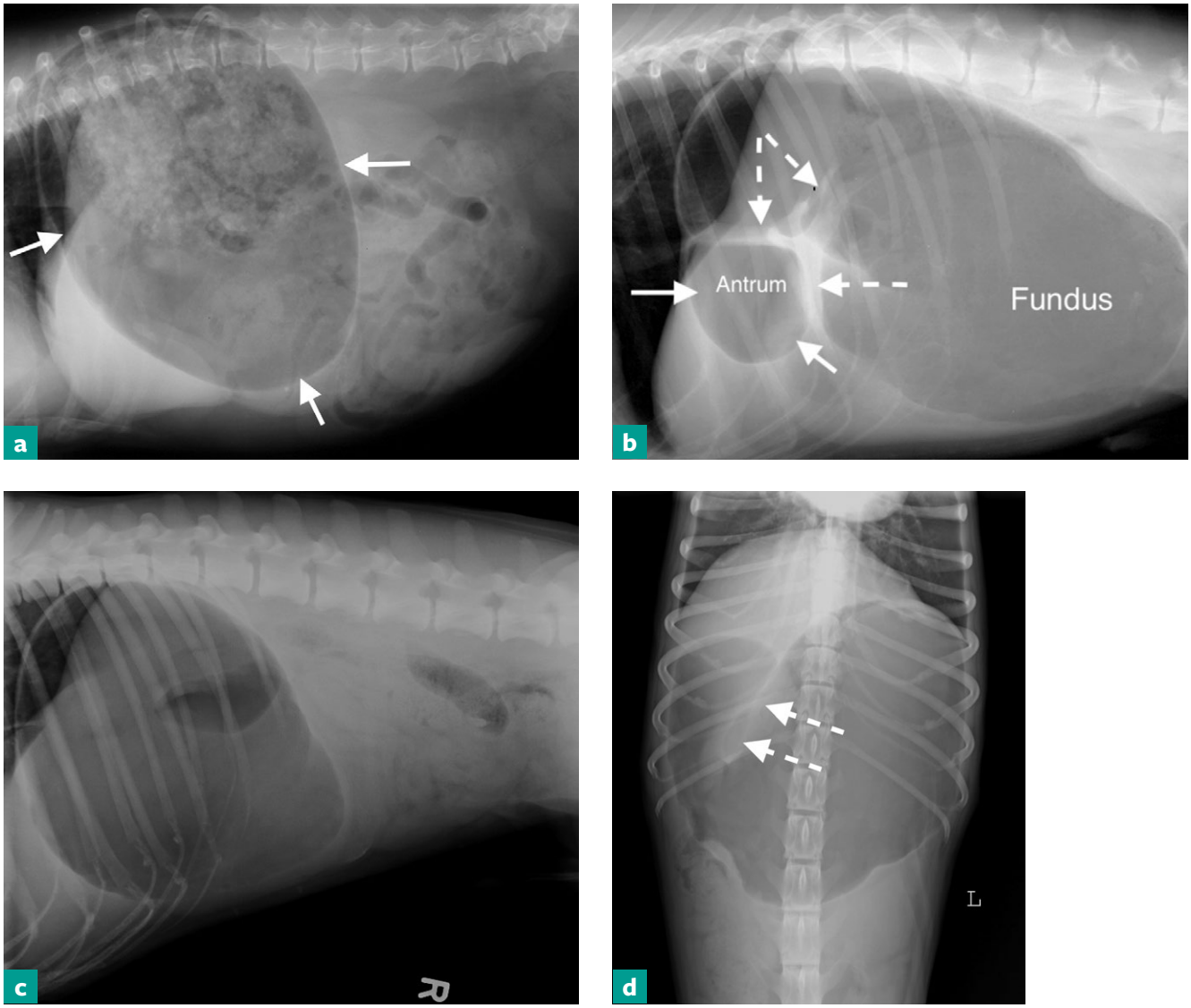



**Fig. 1-31** Gastric dilatation and gastric dilatation and volvulus

**a** Gastric dilatation without volvulus. The gastric fundus is still located craniodorsally (**arrows outline the distended fundus filled with gas**).

**b** Gastric dilatation and volvulus. The gastric fundus is located caudoventrally, the pyloric antrum craniodorsally (**arrows show the antrum**). Compartmentalization of the stomach is seen as soft tissue bands in the radiographic image that are created between the fundus and antrum when a volvulus occurs (**dashed arrows show the soft tissue bands**).

**c, d** 360°gastric torsion. The fundus appears to be in its normal position. Note the soft tissue band (**arrows**) between the body and the pylorus in the ventrodorsal image. A stomach tube could not be passed in this dog, and the 360°nature of the torsion was confirmed during surgery.

Ultrasonographically, **thickening of the stomach wall** can be characterized as focal or diffuse, concentric, or asymmetric. Attention to technique is necessary since oblique scanning of the stomach wall may lead to an artificially increased thickness and disruption of wall layering.[61] Therefore, scanning in multiple planes perpendicular to the stomach wall is necessary to avoid this error. Focal thickening with disrupted wall layering may be caused by neoplasia, granulomas, or ulcers. Generalized thickening is more commonly seen with inflammatory disease but can also occur with diffuse neoplastic infiltration. Thickening of the gastric wall is considered to be present when the wall thickness is >5 mm in dogs or >3 mm in cats.

**Radiopaque gastric foreign bodies**, such as bone fragments, are the most frequent incidental finding. If the object is still located in the stomach 1–2 days after the initial examination, its presence should be further investigated. Radiolucent foreign bodies can be identified by endoscopy, ultrasound, or contrast studies (▶Fig. 1-32). Only a small amount of barium should be administered, or a double-contrast gastrogram should be performed since large volumes of barium can obscure both wall infiltrates and foreign material. Alternatively, a negative contrast gastrogram can be performed.

**Chronic pyloric obstruction** can occur either due to narrowing of the lumen because of wall infiltration or mechanical blockage of the orifice. Survey radiographs usually show some degree of gastric distension. In a dog with clinical signs of vomiting, a 3-view abdominal radiographic series is strongly advised.[62] Anatomically, the outflow tract (antrum, pylorus, and duodenum) is located on the right side of the abdomen. For example, in the left lateral position, gas in the stomach rises up to the non-dependent side (right side in a left recumbent dog), and obstructions in the outflow tract are easier to detect vs. in a right lateral image since they will be highlighted by gas surrounding them (▶Fig. 1-32b). In cats, however, obtaining both right and left lateral images is not helpful for assessing the gastric outflow tract unless there is moderate to severe gastric dilatation present.[63] Barium studies may also help to identify obstructive pyloric disease. However, differentiating hypertrophic pyloric stenosis from inflammatory infiltrates, or neoplasia is often difficult since they all lead to a narrowing of the pyloric orifice due to annular thickening, and they all have a similar appearance radiographically. Detecting intraluminal filling defects in the area of the pylorus is also possible. These may be due to foreign bodies, polyps, severe inflammatory infiltrates, or neoplasms.

The gastroduodenal junction can be examined ultrasonographically in dogs. Congenital hypertrophic pyloric stenosis and chronic hypertrophic gastropathy have a similar ultrasonographic appearance. Circumferential thickening (>3 mm) of the muscularis layer can be recognized by a hypoechoic layer that appears like a ring in a cross-section. In chronic hypertrophic gastritis, the mucosa can also be thickened. Strong peristaltic contractions against the thickened pylorus can also be observed. These contractions fail to propel food through the pylorus, and a reflux movement of gastric contents can be seen and recorded on videotape.

**Gastric ulcers** will lead to disruption of the mucosal surface, and they cannot be diagnosed using survey radiography. Their diagnosis requires a barium contrast study, ultrasound, or endoscopy. It is important to remember that ulceration of the stomach wall has various causes and that the stomach wall should be thoroughly investigated, preferably with ultrasound, for evidence of underlying infiltrative disease. Ultrasonographically, benign ulcers appear as a localized wall thickening.[64] Mucosal craters with an irregular surface and the adherence of gas bubbles may also be seen. Unfortunately, the presence of luminal gas, food, or lack of ultrasound beam penetration in large or obese dogs may make the detection of gastric ulcers more difficult. Benign ulcers may appear similar to those associated with neoplasms. When the thickened stomach wall shows a loss of wall layering, gastric neoplasia should be suspected.

**Gastric wall edema** can lead to wall thickening >5 mm and has been observed in dogs with vomiting secondary to pancreatitis and in dogs with hypoalbuminemia.[65] Ultrasonographic features of gastric wall edema due to pancreatitis in dogs include some or all of the following: a thickened wall, complete loss of wall layering, thickening of the submucosa, and muscularis thickening.[65] In dogs with pancreatitis, the thickening may be focal and adjacent to the affected pancreas. In dogs with hypoalbuminemia, 21.4% showed gastric wall thickening with a mean of 10.0 mm +/- 2.0 mm, preserved mucosal layering, thickening of the submucosa, and alterations in the regular wall layering.[65] Gastric wall thickening in dogs with vomiting, pancreatitis, or hypoalbuminemia should be monitored for sonographic resolution once clinical signs have ceased to rule out neoplastic infiltration.

**Gastric neoplasia** is uncommon in dogs and cats. Carcinoma is the most common type of gastric neoplasia in dogs with lymphoma being the most common in cats (▶Chap. 6.3.4). Gastric neoplasia is generally only diagnosed on survey radiographs when it is large enough and when the proliferative tissue projects into the gas-filled lumen. Lack of gas in the stomach may cause mural lesions to be overlooked. Diffuse stomach wall infiltrations are even more difficult to diagnose radiographically. Focal gastric wall masses are typical with carcinoma, leiomyoma, and leiomyosarcoma, while generalized wall thickening may be seen with a number of other conditions, including chronic hypertrophic gastritis,

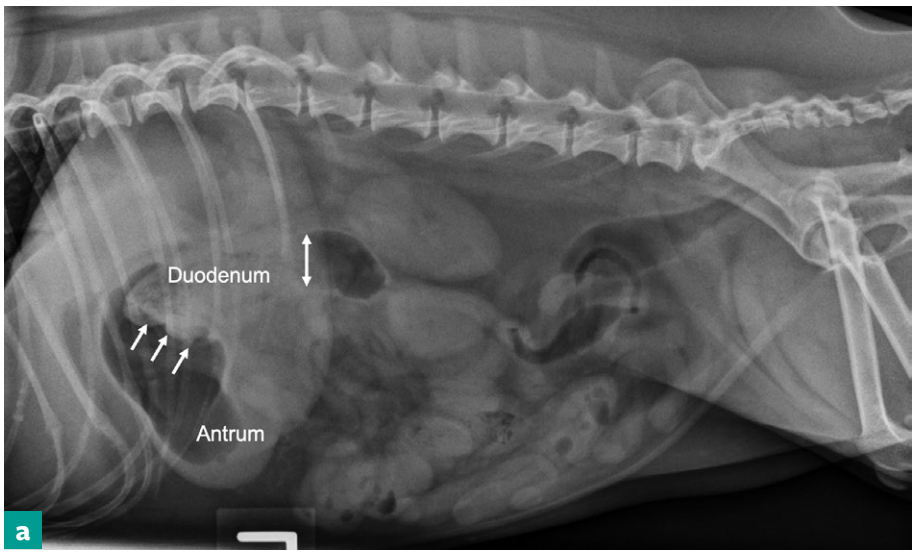
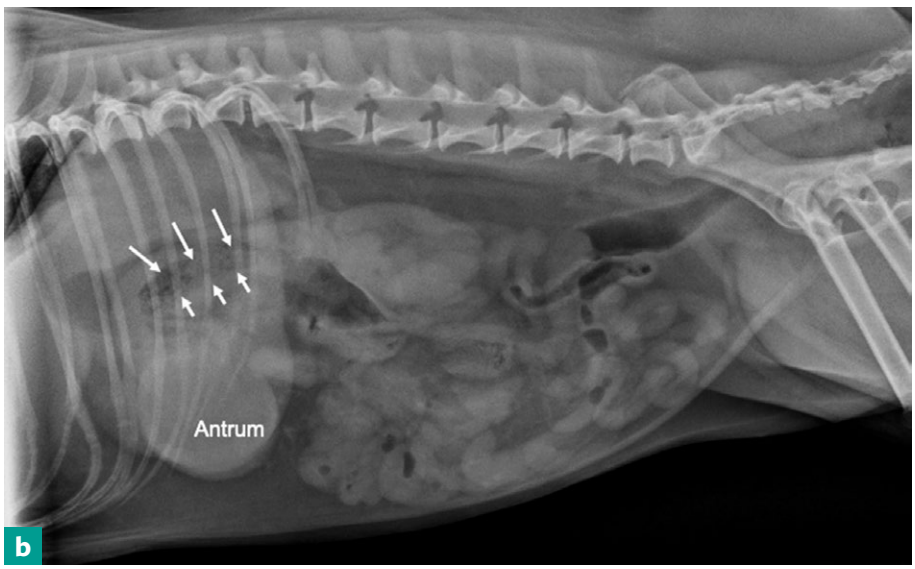



**Fig. 1-32** Gastric foreign body

**a** Left lateral abdominal radiograph of a dog with a foreign body located in the pyloric antrum and proximal duodenum. The left lateral recumbency allows gas to rise into the right sided pyloric antrum and duodenum, highlighting opaque foreign material in that location (**arrows**).




**b** Right lateral radiograph of the same dog as shown in panel a. With the right side dependent in right lateral recumbency, the antrum fills with fluid and the foreign body is more difficult to detect in the duodenum (**arrows** show heterogeneous foreign material).

gastric wall edema, eosinophilic gastritis, fungal infiltrations, and neoplasms, such as lymphoma or histiocytic sarcoma. Diffuse and localized gastric wall infiltrations and masses are better imaged with ultrasound, which often eliminates the need for gastrointestinal contrast studies. Neoplasms can be recognized during abdominal ultrasound by observing wall thickening and a disruption of the normal wall layering. The neoplastic lesion usually shows a decreased echogenicity and may create the appearance of pseudolayering.[66] Also, regional lymph nodes are often enlarged (▶Fig. 1-33). Gastric lymphoma occurs in both dogs and cats and causes a generalized, hypoechoic thickening of the gastric wall with loss of wall layering.[67]

Ultrasound-guided percutaneous fine-needle aspiration (FNA) or biopsy of the gastric wall can be performed to differentiate neoplastic and inflammatory infiltrates. FNA can be performed with a 20-gauge needle, or biopsies can be taken with an 18-gauge spring-loaded biopsy device. When the gastric wall is >2 cm, a tru-cut spring-loaded biopsy is feasible.

Contrast-enhanced computed tomography (CT) has been shown to be helpful in staging canine gastric tumors.[31] CT features of lymphoma, carcinoma, leiomyoma, and inflammatory polyps overlap. However, CT is advantageous for diagnosing local invasion and distant metastasis for staging purposes, in addition to characterization of the origin and extent of the lesion.[31]

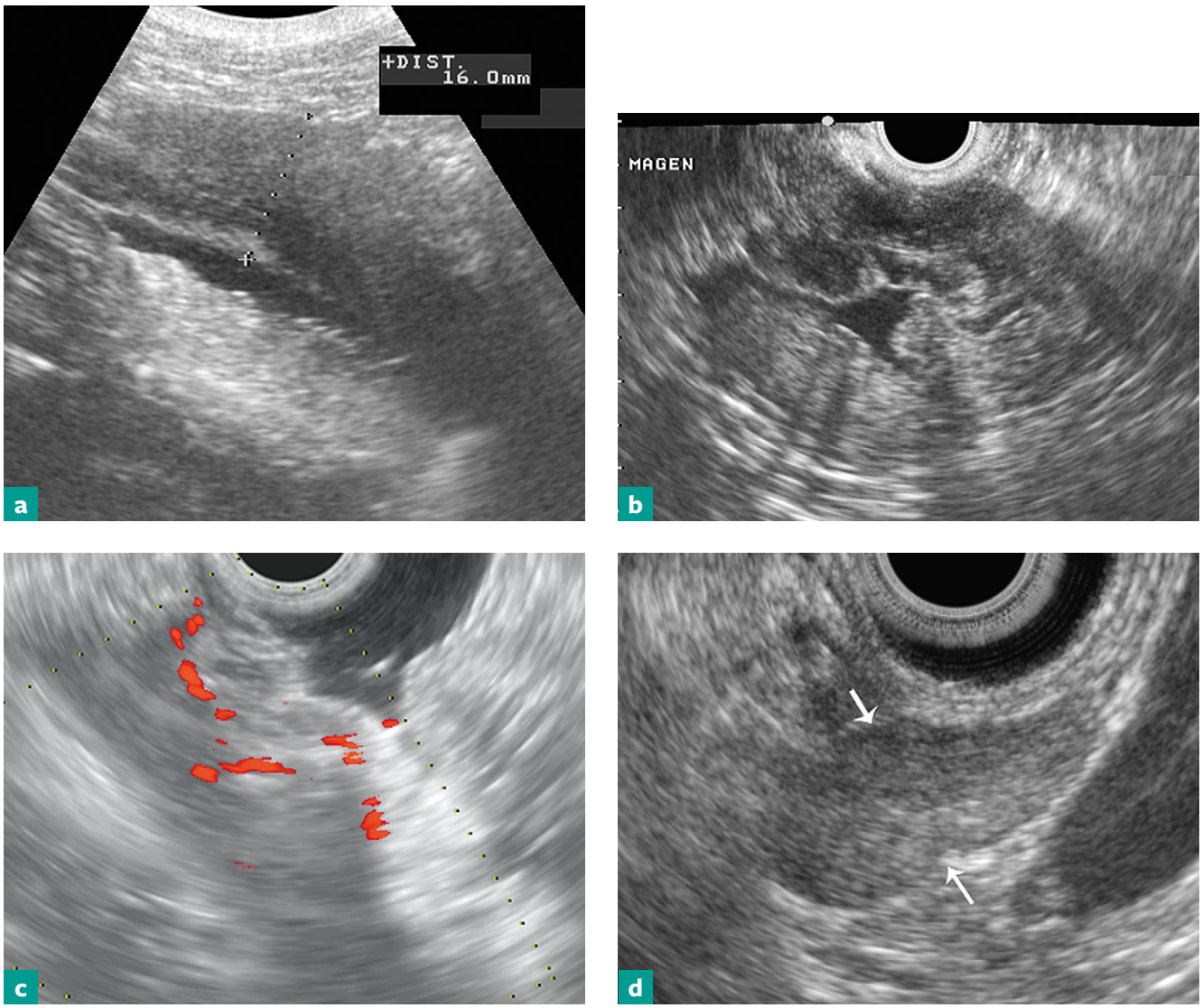



**Fig. 1-33** Gastric carcinoma

**a** Transabdominal ultrasound image using a 7.5 MHz curved array transducer in a 45 kg Leonberger dog with chronic vomiting and weight loss. Localized thickening (16 mm) of the gastric wall with disruption of wall layering was identified.

**b** The dog underwent anesthesia for gastroscopy, and an endoscopic ultrasound examination of the stomach was performed. The infiltration could be better localized to the lesser curvature of the stomach.

**c** Doppler ultrasound showed the lesion to be well-vascularized.

**d** The gastric lymph nodes were found to be enlarged and rounded (**between arrows**). Intraoperatively, the mass was non-resectable. Diagnosis: gastric carcinoma.

#### 1.4.4.3 Diagnosis of delayed gastric emptying

Mechanical obstruction due to a pyloric foreign body, gastric neoplasia, pyloric hypertrophy, antral mucosal hypertrophy, or antral polyps can generally be ruled out with a combination of radiography, ultrasound, and endoscopy. The diagnosis of other causes of delayed gastric emptying can be more difficult to diagnose. Radiographic techniques employ either indigestible radiopaque markers, barium meals, or liquid contrast agents (barium or iodine-containing).[39,68–70] However, radioscintigraphy is now considered the technique of choice for the detection of delayed gastric emptying.[39,68]

It has been shown that water intake, meal size, food type (dry vs. canned), and kibble shape can influence the rate of gastric emptying in cats.[71,72] The rate of gastric emptying in normal animals depends mainly on the state of filling of the stomach and the type of contrast medium used, as well as stress and sedation. Animals should be kept in a quiet environment during the study and, if possible, should not be sedated. Iodine-containing contrast media show a much more rapid passage time than barium sulfate.

**NOTE**

Even a low dose of contrast medium may lead to longer emptying times. The standard dose for barium suspensions is 6 ml/kg in dogs and 10 ml/kg in cats and should be administered when the stomach is empty. Barium sulfate should be present in the duodenum by 15 minutes after administration in the dog and 5 minutes in the cat. The stomach should be free of barium after 1–4 hours in the dog and after 20 minutes in the cat. The presence of food in the stomach prior to the examination will delay gastric emptying for up to 15 hours or even more (longer for dry than moist food).

Ultrasonographic techniques for determining gastric emptying and motility rely upon measuring the cross-sectional area of the gastric antrum in the relaxed and contracted state before and 0, 15, 30, and 60 minutes after a meal. Motility is assessed by a motility index (MI), which is calculated by multiplying the amplitude with the frequency of contractions counted over a 2-minute period.[73,74] Amplitude is the difference between the gastric antrum cross-sectional area in the relaxed state and the contracted state divided by the cross-sectional area in the relaxed state. Ultrasonographic assessment of gastric emptying and motility have also been shown to correlate to measurements made by radioscintigraphy.[73,75]

### 1.4.5 Small intestines

#### 1.4.5.1 Ileus

Ileus is a failure of the intestinal contents to be transported aborally and is recognized radiographically by the presence of dilated bowel segments. Survey abdominal radiographs should always be performed in animals suspected of having ileus. Ultrasound alone in such instances does not allow a global view of the abdomen, is much more time-consuming, and non-gastrointestinal causes of the patient's clinical signs, as well as any secondary abnormalities may be overlooked. The radiographic appearance of ileus is dependent on its duration, location, and type. Acute or very proximal obstructions may be associated with little intestinal dilation radiographically, whereas chronic or more distally located obstructions will be associated with more severely dilated bowel segments. The two major types of ileus are obstructive (mechanical) and functional. Obstructive ileus may be partial or complete and can be due to foreign bodies, torsion, volvulus, herniation, intussusception, adhesions, granulomas, or neoplasms.

Barium passage through the small intestines can be used to identify intraluminal, mural, or extramural obstructive, as well as non-obstructive or partially obstructive lesions. An upper GI study is a good option for vomiting dogs and cats with equivocal radiographs or for those with chronic weight loss when ultrasound is not available. Another benefit is that the study can be reviewed by a teleradiologist.

**NOTE**

Barium is contraindicated prior to endoscopy or ultrasound, as endoscopic images can be obscured, and barium causes significant attenuation of sound and acoustic shadowing.

##### 1.4.5.1.1 Partial obstruction

Anorectic animals or animals held off food (>12 hours) should not have small bowel segments containing granular material resembling that of food. Granular or more opaque small bowel contents may be detected in patients with a partial obstruction. The intestines in such animals may be mildly dilated (1–1.5 times the mid-height of the fifth lumbar vertebral body [L5]) proximal to the obstruction or may be of normal diameter (▶Fig. 1-34). Because fluid passes through the narrowed lumen, the contents remaining proximal to the partial obstruction become denser and, therefore, radiographically more opaque and lead to a gravel sign (▶Fig. 1-35).

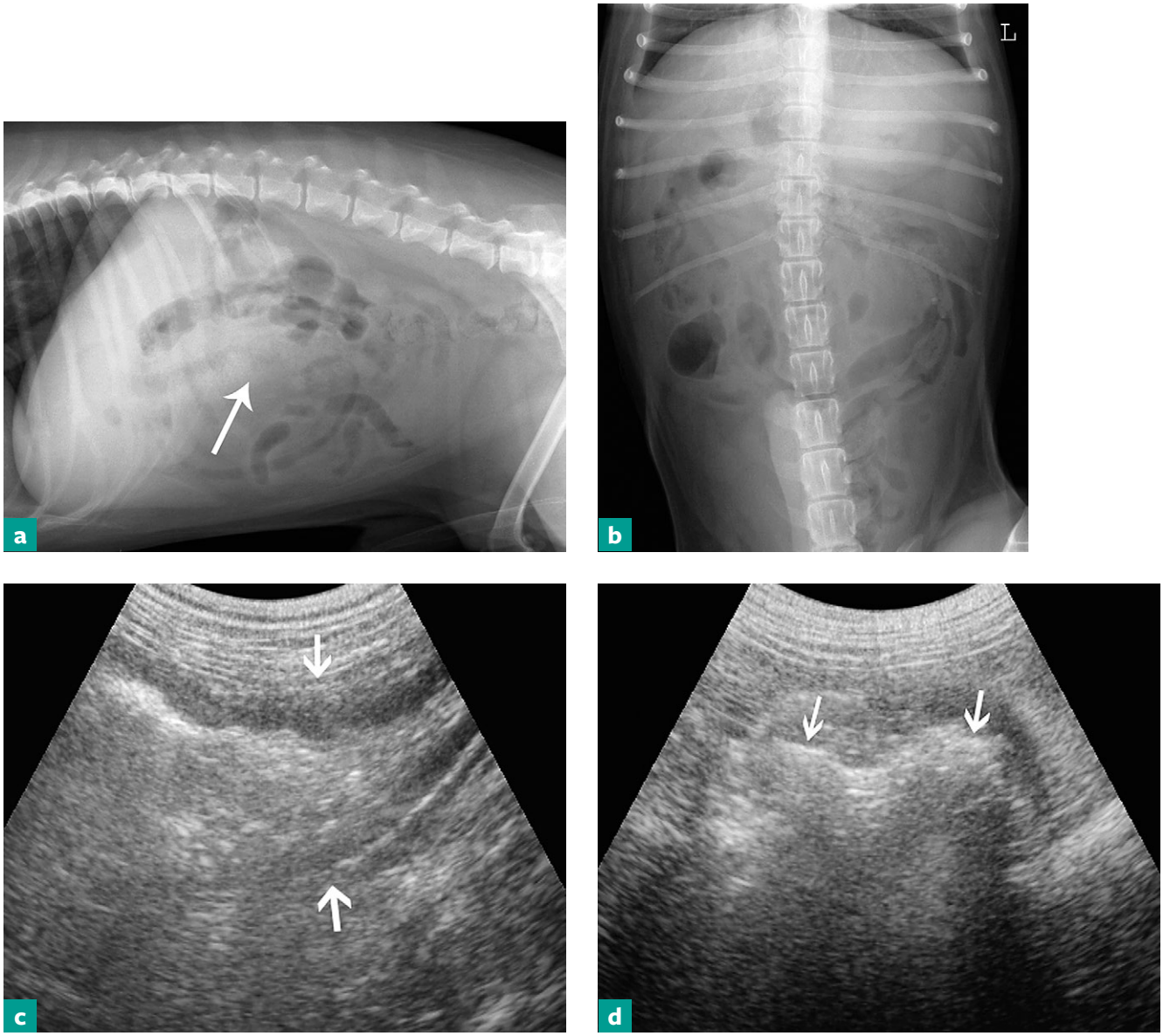



**Fig. 1-34** Small intestinal foreign body

Radiographic (**a + b**) and ultrasonographic (**c + d**) investigation of a 6-year-old West Highland white terrier with a 1-month history of vomiting and weight loss. On clinical examination, the dog's abdomen was painful.

Lateral (**a**) and ventrodorsal (**b**) abdominal digital radiographs. There is a loss of mid-abdominal detail (**arrow**) with mildly dilated small intestines. Although the dog was held off food for over 12 hours, some of the small intestines have a granular content (also known as gravel sign; **arrow**), which is difficult to differentiate from feces in the colon in this dog.

**c, d** An ultrasound examination showed dilated and fluid-filled jejunal segments proximal to an intraluminal structure with a hyperechoic wavy surface (**arrows**) and acoustic shadowing. An unidentifiable foreign body was removed from the site surgically.

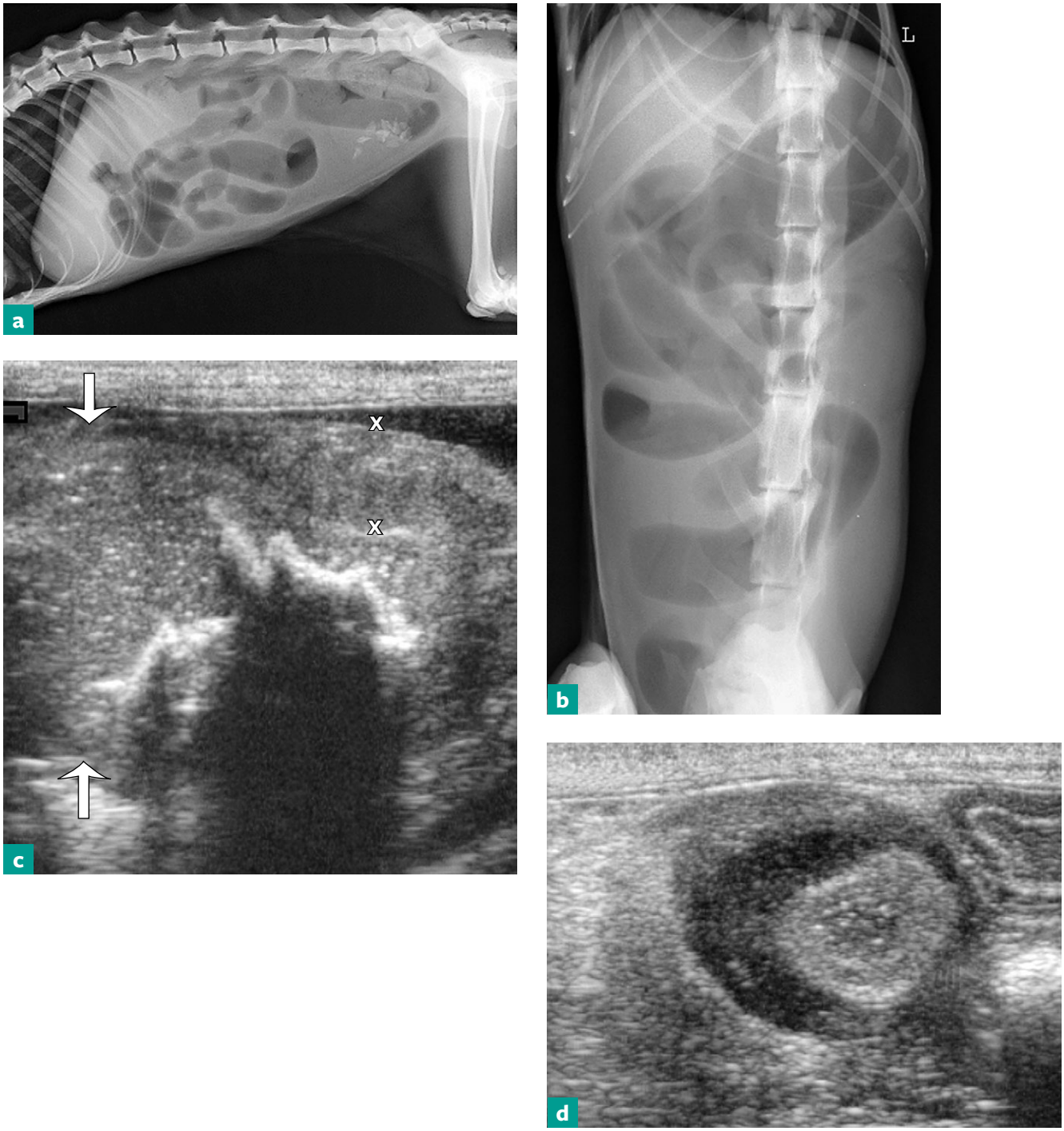



**Fig. 1-35** Small intestinal neoplasia

Lateral (**a**) and ventrodorsal (**b**) abdominal radiographs of the abdomen of a 9-year-old, castrated male European short-haired cat with a 5-month history of anorexia and weight loss. The cat's condition worsened 3 days prior to admission. The radiographs show cachexia with loss of abdominal detail. Most of the small intestinal segments are severely dilated and air-filled. In the caudoventral abdomen, there are multiple mineral opaque structures that are clumped together. Note that the descending colon is visible and filled with feces.

**c** Dilated and fluid-filled distal jejunal segment (**between arrows**). The wall is thickened (**between x–x**) with disrupted wall layering. The irregular hyperechoic structures with clean distal shadowing are concretions that have collected proximal to the long-standing obstruction.

**d** The site of stenosis shows that the wall is thickened with an outer hypoechoic and inner hyperechoic wall layering. The regional lymph nodes (not shown) were enlarged and inhomogeneous. Histological diagnosis: adenocarcinoma.

#### 1.4.5.1.2 Complete obstruction

More severe dilations, usually with gas, are seen in animals with complete obstructions (▶Fig. 1-36). Dilation (1.5–2 times the height of the body of L5) is seen proximal to the site of obstruction, and the segments distal to it usually appear empty and contracted. Due to this, the jejunal segments appear to have highly variable diameters. This is due to the continued peristaltic activity in those distal segments. Feces may still be present in the colon, depending on the duration of the obstruction. Proximal duodenal or pyloric obstructions may show no radiographic abnormalities. Distal jejunal obstructions may cause generalized dilation and resemble a functional ileus radiographically. Using a small intestine to L5 ratio of 1.7, the diagnosis of intestinal obstruction has a 66% sensitivity and specificity.[76] The low sensitivity and specificity of comparing the small intestinal diameter to vertebral body height underscore that this method should be used as an initial indicator and that other methods, such as repeat radiographs or ultrasonographic examination, are required when the initial radiographs are equivocal.

#### 1.4.5.1.3 Functional ileus

Another form of ileus can be characterized by uniformly normal to mildly dilated intestinal loops due to a lack of peristaltic activity (▶Fig. 1-37). This is known as adynamic, functional, or paralytic ileus. Functional ileus results in obstruction since the intestinal contents pool in the GI tract. It may affect the stomach, small intestines, or large intestines. Radiographically, the bowel segments may have a homogeneous soft tissue opacity when fluid-filled, or a mixed pattern of gas and fluid may also be present. Such an adynamic intestinal pattern can be due to the administration of pharmaceutical agents, such as parasympatholytics or sedatives. Other causes are peritonitis, blunt abdominal trauma, electrolyte imbalance, or enteritis of various causes. Dysautonomia is a disorder of the autonomic nervous system that can also lead to generalized dilation of the GI tract in both dogs and cats.[77] A complete obstruction in the distal jejunum or at the ileocecal level may also lead to the same radiographic appearance. Decreased peristalsis may be limited to the duodenum in patients with pancreatitis (▶Chap. 10.3.1).

#### 1.4.5.1.4 Detecting ileus with ultrasound

Generally, the clinical state of the animal, in conjunction with radiographic findings, provides adequate information to determine if there is obstructive disease requiring surgery or not. However, when abdominal radiographic findings are unclear, an obstruction cannot be ruled out, or the radiographic findings do not explain the severity of the clinical signs, further diagnostic procedures are warranted.

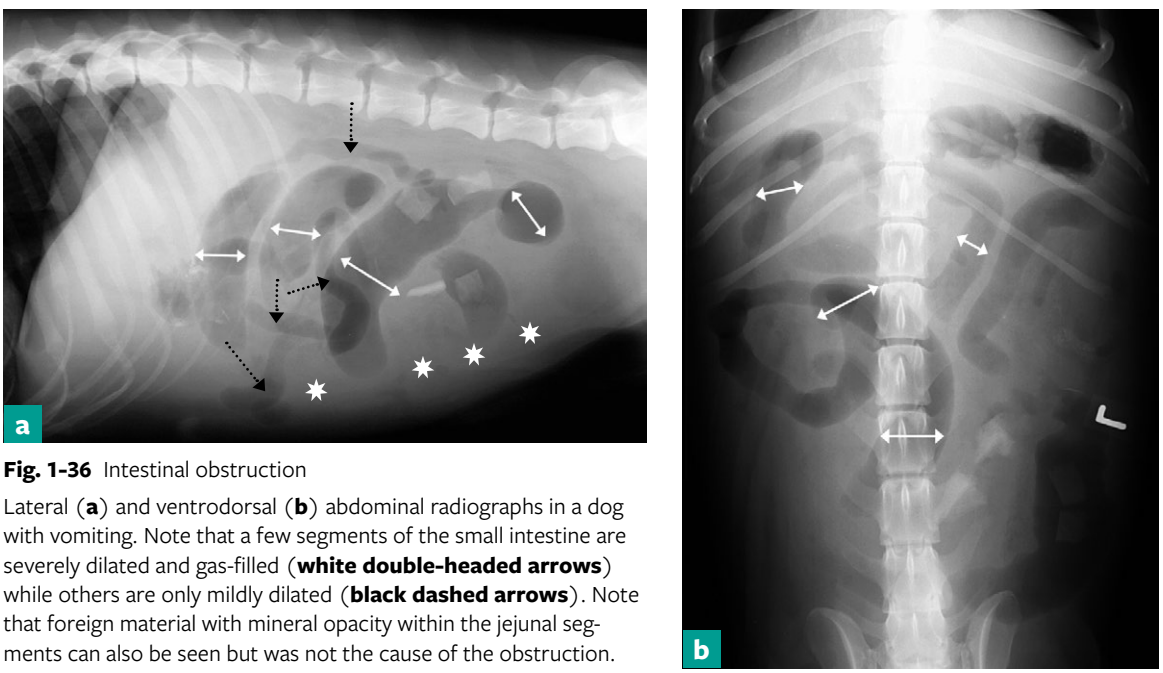



**Fig. 1-36** Intestinal obstruction

Lateral (**a**) and ventrodorsal (**b**) abdominal radiographs in a dog with vomiting. Note that a few segments of the small intestine are severely dilated and gas-filled (**white double-headed arrows**) while others are only mildly dilated (**black dashed arrows**). Note that foreign material with mineral opacity within the jejunal segments can also be seen but was not the cause of the obstruction. There is loss of serosal detail (✶) due to peritoneal effusion. Diagnosis: mid-jejunal mechanical ileus due to a radiolucent foreign body.

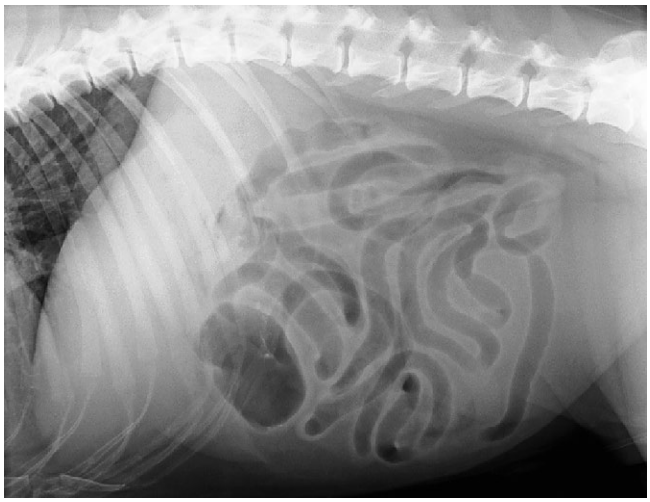


**Fig. 1-37** Functional ileus

Lateral abdominal radiograph of a dog with vomiting and diarrhea for 2 days. The small intestines are moderately dilated but of uniform diameter and air-filled. Diagnosis: functional ileus.

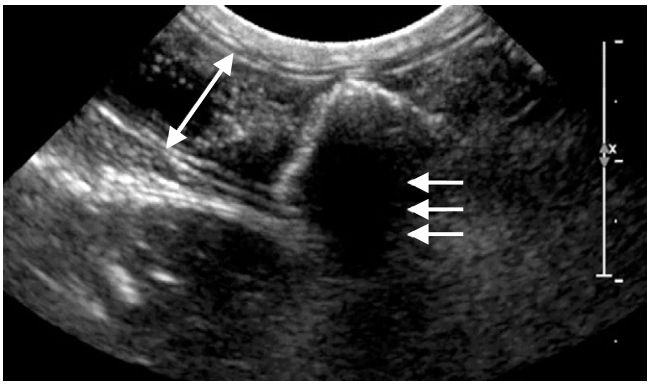


**Fig. 1-38** Ultrasound image of a vomiting cat

The cat's stomach was distended radiographically. Ultrasonographically there was a hyperechoic, triangular-shaped intraluminal foreign body with distal acoustic shadowing (**arrows**) in the duodenum with dilation orad to the obstruction (**double-headed arrow**).

Ultrasonography has the advantage that it does not require ionizing radiation and can be used to inspect the small intestines for wall layering, thickness, dilation, and peristalsis as well as for intraluminal, intramural, and extraluminal causes of obstruction. Functional ileus can show a lack of peristalsis and generalized dilation of the small intestines.[78] Contractions can be observed with two-dimensional real-time imaging, and approximately five contractions per minute are considered normal for the stomach, and one to three are considered normal for the small intestine.

**Radiolucent intestinal foreign bodies** may be detected by ultrasound, especially when they cause mechanical obstruction. Solid material generally appears as a hyperechoic interface, which casts an acoustic shadow from the intestinal lumen.[79] Balls will have a round or curvilinear surface, peach pits are irregular, and bones generally have a smooth regular surface. Linear foreign bodies (FBs) can sometimes be identified in plicated segments of small bowel. FBs tend to remain fixed in the same position and a repeat examination a short time later shows that they have not moved. The finding of severe dilation of one or more segments of the jejunum and the stomach, together with empty, contracted bowel segments distally may indicate a complete or partial obstruction. Care should be taken not to misinterpret a gas-liquid interface in a dilated bowel segment as an obstruction. FBs appear as linear, hyperechoic intraluminal structures with acoustic shadowing (▶ Fig. 1-38). Obstructive luminal material will also lead to dilation of the bowel lumen orad to the obstruction while the bowel on the aborad side will be empty or normal in size. This is helpful when determining if the content is obstructive or not. Hyperechoic gas bubbles in the intestinal lumen can be misinterpreted as solid content. However, the bowel on either side of the luminal gas pocket will be of similar diameter orad and aborad to this hyperechoic gas artifact.

**Localized mural infiltrations** due to inflammation or neoplasia can slowly narrow the intestinal lumen. Some degree of intestinal dilation is present, and solid foreign material, such as small stones can collect proximal to the stricture. Ultrasonographically, neoplastic infiltrates produce intestinal wall thickening, often with a loss of wall layering.[80] Lymphoma is the most common intestinal tumor in cats but also occurs frequently in dogs. It commonly leads to either a symmetrical or asymmetrical, transmural, circumferential thickening. The wall layers are difficult to identify, and the entire wall appears hypo- to anechoic. The infiltration of the intestinal wall may be solitary, diffuse, or multifocal, and regional lymph nodes may be enlarged. However, complete intestinal obstruction often does not occur. Intestinal carcinoma often produces a solitary intestinal mass, as can polyps, leiomyomas, or leiomyosarcomas. Carcinomas tend to be annular, irregular infiltrations that invade the lumen and cause obstructions.[81] Regional lymphadenopathy can also commonly be identified. Granulomatous infiltrations due to fungal infections may also cause diffuse or focal infiltrations of the bowel wall and are difficult to distinguish from neoplasia ultrasonographically.[82] Histoplasmosis, for example, can produce localized and severe wall infiltrations that resemble

lymphoma. Jejunal smooth muscle hypertrophy has been described in the cat and can also cause focal wall thickening, but wall layering is maintained.[83] Feline gastrointestinal eosinophilic sclerosing fibroplasia is an inflammatory disease that causes wall thickening and loss of layering in the stomach, duodenum, jejunum, and colon and has been described as having similar sonographic features to neoplasia or fungal infiltration.[84] Because the ultrasonographic appearance of the bowel wall alone is not sufficient for a definitive diagnosis, either full-thickness biopsies, ultrasound-guided percutaneous biopsies, or fine-needle aspirates of the bowel wall are required for a definitive diagnosis of wall infiltrative diseases that thicken the wall or disrupt wall layering.

#### 1.4.5.1.5 Complicated ileus

Complicated forms of ileus include bowel perforation with peritonitis, free air in the abdominal cavity, and bowel ischemia due to thromboembolism, intussusception, or volvulus at the root of the mesentery. Linear FB can also lead to a complicated form of ileus. The presence of pneumoperitoneum together with abdominal effusion on an abdominal radiograph should alert the clinician to the fact that bowel perforation has occurred. Detecting free intra-abdominal air may require ventrodorsal horizontal beam radiography with the patient in left lateral recumbency. Free air can be detected just under the right abdominal wall and lateral to the duodenum. Volvulus or mesenteric thromboembolism can be recognized by the presence of generalized, severely dilated, and air-filled jejunal segments. Linear FBs produce characteristic changes on abdominal radiographs in dogs and cats (▶Fig. 1-39). The small intestinal loops appear convoluted and gathered or clumped together at one site (usually in the mid-right abdomen), and intraluminal gas bubbles appear asymmetrical and irregularly shaped. Ultrasonographically, the small intestinal segments will appear




**Fig. 1-39** Linear foreign body

Lateral (**a**) and ventrodorsal (**b**) abdominal radiographs of a dog presented for vomiting. Note the plicated appearance of the dilated and gas-filled small intestinal segments. Irregularly shaped gas opacities can be seen in adjacent intestinal segments.

**c** Ultrasound image of a linear foreign body. The intestines appear plicated and pulled together. Although not always visible, in this case, a string was identified sonographically (**arrow**).

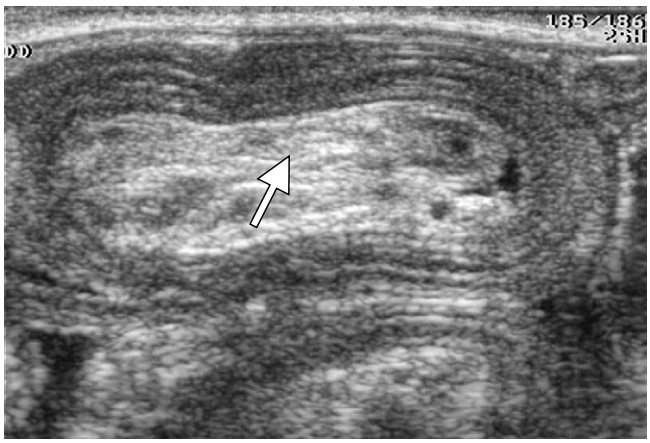


**Fig. 1-40** Intussusception

Ultrasound image of a jejunal intussusception in a young dog with diarrhea. Note the concentric intestinal layers. The hyperechoic center (**arrow**) represents invaginated fat.

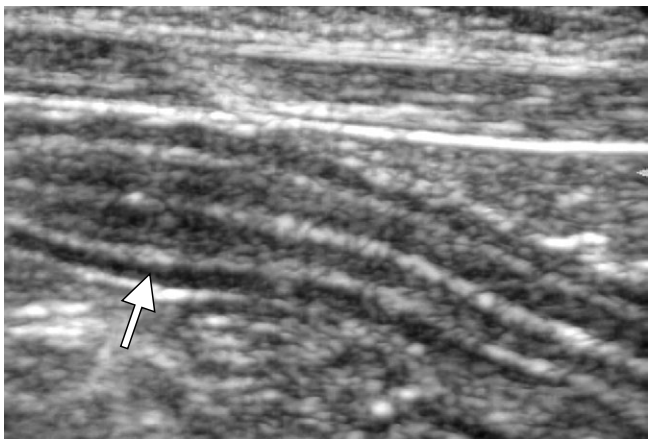


**Fig. 1-41** Eosinophilic enteritis

Ultrasound image of a jejunal segment in a cat with an eosinophilic inflammatory infiltrate of the small intestine. The muscularis layer (**arrow**) was found to be very prominent.

gathered up with the linear foreign material binding them together. The surrounding mesentery should be examined for increased echogenicity and free fluid, which could be indicative of rupture.

An intestinal intussusception can usually be quickly diagnosed with ultrasound. Multilayered, concentric rings of bowel can be identified (▶Fig. 1-40). The outer bowel segment is often thickened, edematous, and hypoechoic. More normal-appearing inner segments can also be identified. Hyperechoic tissue representing invaginated mesenteric fat may also be seen. In older animals, careful examination of the affected bowel for nodular infiltrations of the bowel wall and regional lymphadenomegaly is important since underlying neoplastic disease may be responsible for the intussusception.

### 1.4.5.2 Chronic diarrhea

Chronic diarrhea due to small intestinal disease is common in dogs and cats. Survey radiographs are often nonspecific, and gastrointestinal contrast studies are often unrewarding in patients with chronic diarrhea without vomiting. Ultrasound is superior to survey and contrast radiography for detecting intestinal wall infiltrates but has limitations in that it often does not help identify the underlying cause of diarrhea.[1] This being said, radiography and ultrasound remain screening tools to assess weight loss and detect gastrointestinal masses. Abdominal ultrasound allows for assessment of wall thickness and layering, localization of lesions, motility, and potential involvement of regional lymph nodes. Recently, investigators have tried to correlate intestinal wall thickness in healthy dogs with body weight.[85] In that report, the authors suggested normal duodenal wall thickness to be <5.1 mm for dogs up to 20 kg, <5.3 mm for dogs 20–29.9 kg, and <6.0 mm for dogs >30 kg, and normal values for jejunal wall thickness of <4.1 mm for dogs up to 20 kg, <4.4 mm for dogs 20–39.9 kg, and <4.7 mm for dogs over 40 kg.

### 1.4.5.3 Diffuse bowel wall infiltration

A number of gastrointestinal diseases lead to diffuse infiltration of the small intestinal wall. There are no known specific sonographic features that allow the differentiation of various infiltrative diseases. However, ultrasonography is important for localizing lesions within the GI tract and allowing further characterization of the degree of infiltration inferred by wall thickness and the appearance of wall layering. The mucosal, submucosal, and muscularis layers are most commonly affected (▶Fig. 1-41, ▶Fig. 1-42). The mucosa may also exhibit alterations in echogenicity varying in severity from diffuse pinpoint hyperechogenic foci to generalized hyperechogenicity. Severe mucosal thickening with increased echogenicity may be seen in animals with protein-losing enteropathy (PLE) and lymphangiectasia. In addition, the small intestine generally shows some dilation with fluid and gas and may have a decreased motility or a rigid appearance.

Thickening of the intestinal wall or a single layer due to inflammatory disease is difficult to differentiate from fungal or neoplastic infiltration. For example, a thickened muscularis layer alone can occur with either inflammatory or neoplastic infiltration or be due to smooth muscle hypertrophy. Lymph nodes may appear rounded and heterogeneous, and possibly

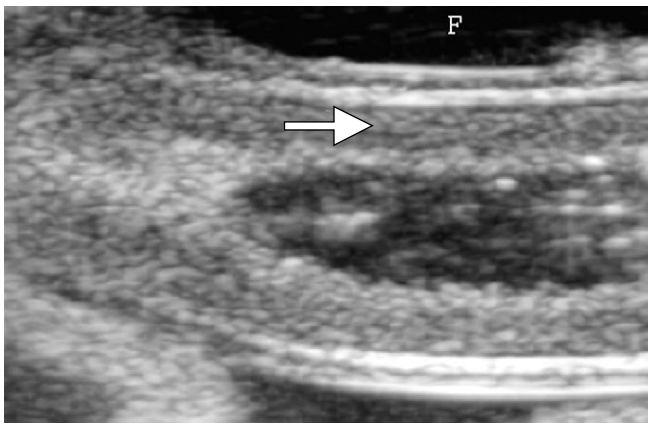



**Fig. 1-42** Protein-losing enteropathy (PLE)

Ultrasound image of a jejunal segment of a dog with PLE due to lymphangiectasia. The wall thickness was normal (3.8 mm), but the mucosa was hyperechoic (**arrow**), and there was free fluid (**F**) in the abdomen. The entire jejunum was affected. These sonographic findings are common in dogs with this syndrome.

show target lesions in patients with either disease process. Mycotic diseases, such as histoplasmosis, pythiosis, and cryptococcosis, can produce localized infiltrative disease that is sonographically similar to that of localized neoplasia.[82] However, neoplasia has been shown to produce more disruption of wall layering compared with inflammatory disease.[80] Sonographic abnormalities in animals with alimentary lymphoma may include thickening of the gastric or intestinal wall, loss of normal layering, a hypoechoic mass associated with the intestinal wall (▶Fig. 1-43), diffuse muscularis thickening, and abdominal lymphadenomegaly.[86,87]

A high percentage of cats with clinical signs of small bowel disease have small intestinal wall thickening >3 mm that corresponds to histopathological diseases such as inflammatory infiltrates, lymphoma, or a combination (▶Fig. 1-44).[88] Diffuse thickening of the muscularis of the small intestines in cats has two main differential diagnoses of idiopathic inflammatory bowel disease (IBD) and T-cell lymphoma.[89] In these two diseases, thickening of the muscularis contributes to the majority of the wall thickness. However, the degree of thickening of the muscularis is not statistically different between cats with idiopathic IBD and those with lymphoma. Therefore, thickening of the muscularis cannot be used to differentiate these two diseases.[89]

### 1.4.6 Large intestine

Lateral and ventrodorsal radiographs of the pelvic region can provide helpful information in dogs and cats with constipation, hematochezia, and/or painful defecation. Abnormalities of the colon, such as obstruction, megacolon, and obstipation, can usually be recognized radiographically. Since a large quantity of feces may be present in the colon prior to defecation in a normal animal, the finding of a radiographically distended colon must be evaluated relative to the patient's clinical signs.

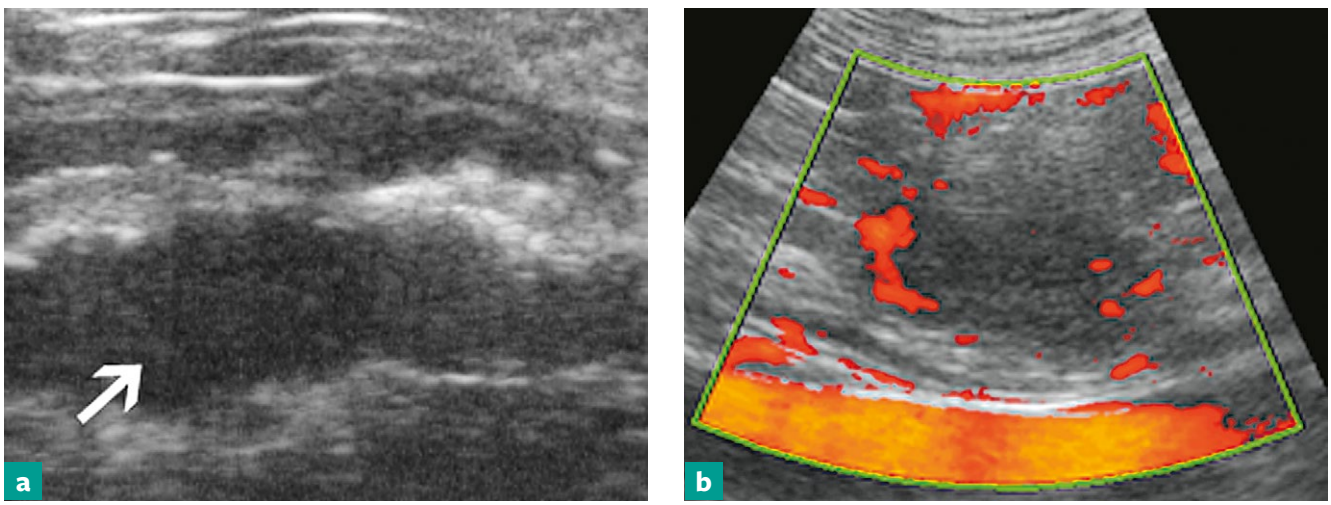



**Fig. 1-43** Intestinal lymphoma in a dog

**a** Ultrasound images of a 9-year-old mixed-breed dog with chronic diarrhea, anemia, and weakness. Multifocal, hypoechoic, 1.2 cm diameter intestinal wall infiltrations (**arrow**) were identified throughout the jejunum.

**b** Although Doppler examination initially showed no vascularity, following intravenous injection of 1 mL of Sonovue® (Bracco International, Amsterdam, NL) ultrasound contrast medium, numerous perilesional and intralesional vessels were identified. Percutaneous, ultrasound-guided fine needle aspiration of the intestinal wall was performed. Diagnosis: lymphoma.

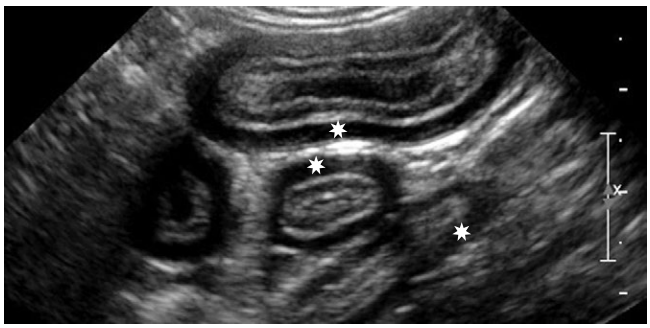


**Fig. 1-44** Intestinal lymphoma in a cat

Ultrasound image of a 5-year-old cat with vomiting, diarrhea, and weight loss ultimately diagnosed with lymphoma. The jejunum in this cat shows diffuse thickening of the muscularis (✱) and generalized wall thickening ranging from 3–3.5 mm.

#### 1.4.6.1 Colonic torsion

Although not common, colonic torsion is life-threatening and causes severe dilation and displacement of the colon from its normal location (▶Fig. 1-45). Radiographic features of colonic torsion include segmental distention, focal narrowing at the site of torsion, and displacement of the cecum and descending colon, with mild to no small intestinal distention.[90] CT can be used to confirm colonic torsion with the main CT feature being the "whirl sign" in addition to displacement and distension of the cecum and colon, focal narrowing of the colon, and distention of the mesenteric vasculature.[91] The whirl sign is created by the spiral path of the twisted tissue and associated blood vessels.[91] Additional CT features may include scant peritoneal effusion, pneumatosis coli, small intestinal distention, portal vein thrombosis, and reduced colonic wall contrast enhancement.[91]

#### 1.4.6.2 Other radiographic findings

Mechanical obstruction due to previous pelvic trauma or space-occupying lesions can be ruled out radiographically. Sublumbar lymph node enlargement, an extension of retroperitoneal masses, prostatomegaly in male dogs, uterine masses in female dogs, and perineal herniation, can also be detected radiographically. Dilation of the colon (to greater than the length of a lumbar vertebra) with impaction of feces with increased radiopacity can be due to constipation, obstipation, or megacolon. Increased soft tissue opacities or displacement or compression of the colon within the pelvic canal indicate the need for further imaging procedures such as ultrasonography.

#### 1.4.6.3 Sonographical findings

Ultrasonographically, the ileum, ileocecal junction, cecum, and ascending, transverse, and descending colon can be identified. When distended, the wall should have a three-layered appearance and a thickness of 1–2 mm. The empty colon will appear contracted, and many layers can be appreciated.

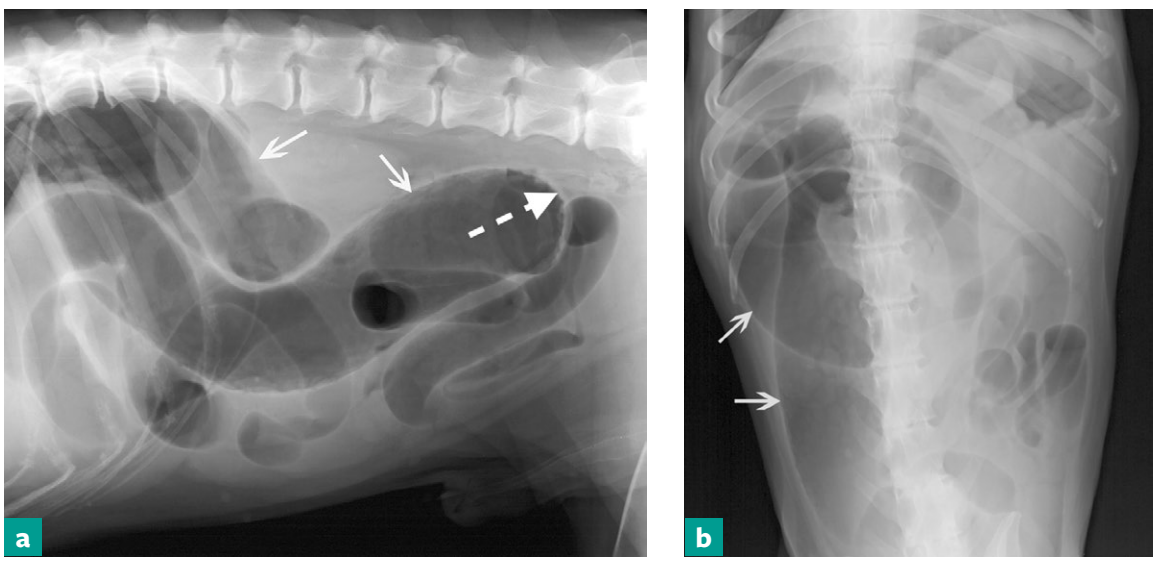



**Fig. 1-45** Colonic torsion

Lateral (**a**) and ventrodorsal (**b**) abdominal radiographs of a 13-year-old German shepherd dog with anorexia for 5 days and weakness in the hind limbs. Borborygmus and a tympanic abdomen were identified during physical examination. The entire colon (**arrows**) is severely dilated and air-filled. At the pelvic inlet, the gas pattern of the colon ends abruptly (**dashed arrow**). Diagnosis: colonic torsion.

This should not be misinterpreted as colonic wall thickening. Due to the presence of air and feces, it is often difficult to examine the entire colon by ultrasound. The pelvis also limits examination of the colon, but the rectum, as well as the perirectal and perineal regions, can be examined via a perineal approach. However, a certain length of the rectum within the pelvic canal cannot be examined in either dogs or cats. If the region of interest within the pelvic canal cannot be assessed due to overlying bone, radiographic contrast studies can be helpful in determining the origin of soft tissue masses causing displacement or compression of the colon. Negative and positive contrast studies of the colon may be performed, but they may be difficult to interpret due to the presence of fecal contents or lack of experience with this procedure. Barium enemas can be useful in the diagnosis of ileocolic intussusceptions, cecal inversions, strictures (▶Chap. 7.3.6), or wall infiltrations.

In dogs with diarrhea due to colitis, the colon may appear normal or irregular and may be air- or fluid-filled. Colitis due to diffuse, mild to moderate inflammatory infiltration will often show no radiographic or ultrasonographic changes, and colonoscopy is the diagnostic modality of choice in both dogs and cats (▶Chap. 1.5.2.3). Soft tissue lesions, such as neoplasia of the colon can be recognized radiographically as localized increased soft tissue opacities. However, they are not always evident on survey radiographs, and either a positive or negative contrast study of the colon may be required. Sonographically, focal infiltrations or intramural masses of the colonic wall may be detected and are associated with either neoplasms or granulomas (▶Fig. 1-46). Micronodular lesions in the colonic submucosa can be identified in dogs and cats with inflammatory disease, and these lesions likely represent reactive lymphoid follicles within the wall that resolve with resolution of clinical signs.[92] MRI and CT are alternative methods for examining the pelvic region or determining the involvement of the colon and surrounding tissues, especially when space-occupying lesions are present in that region.



**Fig. 1-46** Colonic neoplasia

Ultrasound image of the descending colon in a 12-year-old European short-haired cat with a history of tenesmus and hematochezia. Ultrasonographically, an irregular localized infiltration (4 mm) of the wall of the colon, just cranial to the pelvis, can be identified. The wall layering is disrupted, and the echotexture is complex. The regional lymph nodes were found to be enlarged and rounded. Histological diagnosis: mucinous carcinoma.



Hepatic causes of icterus, such as hepatic lipidosis, are more common than pre- or post-hepatic disease.

### 1.4.7 Liver and biliary tract

Clinical signs of hepatobiliary disease can be nonspecific and include anorexia, lethargy, and vomiting, as well as diarrhea, polyuria, polydipsia, and icterus in those animals with liver failure. The presence of icterus in the absence of anemia indicates hepatobiliary disease in both dogs and cats. Abdominal ultrasonography is the most useful non-invasive diagnostic tool for differentiating hepatic vs. post-hepatic causes of icterus.

The liver, gallbladder, biliary tract, duodenal papilla, and pancreas should be examined with a high-frequency transducer. Generally, curved array transducers with a small footprint are advantageous for examining these structures due to their location just behind and underneath the caudal border of the rib cage. Ultrasonographically, hepatic size can be estimated, and its internal architecture, including its portal, venous, arterial, and biliary vasculature in addition to its echogenicity and echotexture can be evaluated (▶Fig. 1-47). The size, wall thickness, and contents of the gallbladder as well as the size of the bile duct, can also be assessed. Normal wall thickness of the gall bladder in dogs is 1–2 mm, and in cats is 1 mm.[93,94] In addition, the proximal duodenal papilla can be assessed for signs of obstruction. Finally, the involvement of the pancreas in the disease process can also be assessed.

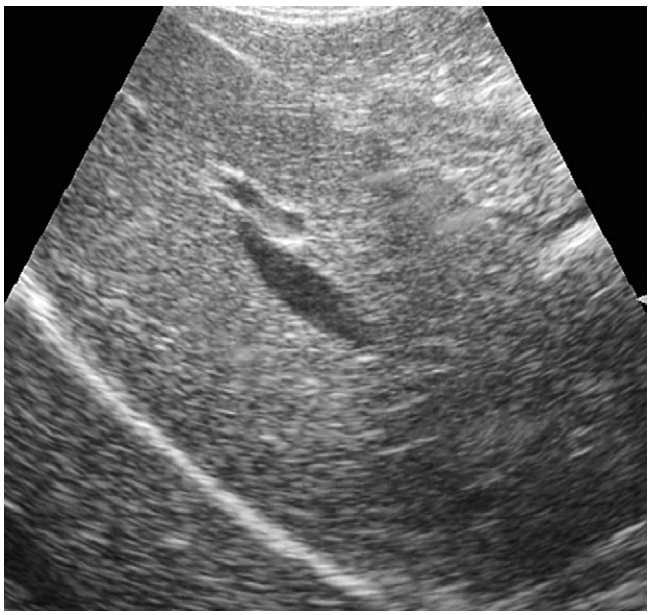


**Fig. 1-47** Normal canine liver

The liver has a medium echogenicity. Both portal veins (hyperechoic walls) and hepatic veins (no walls) are visible.

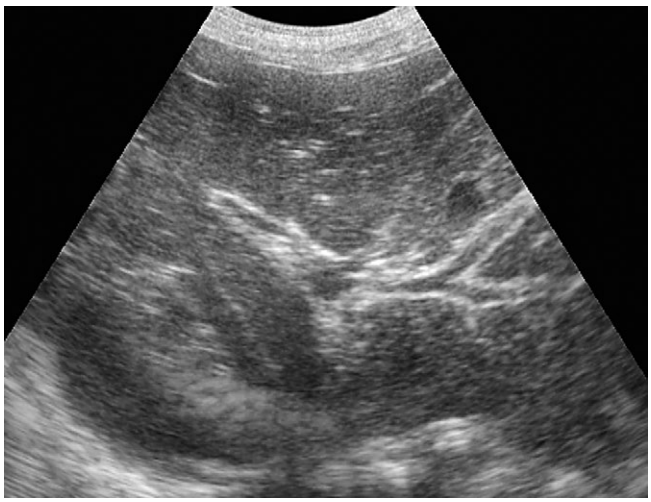


**Fig. 1-48** Cholangiohepatitis

Ultrasound image of a hypoechoic liver in a 2.5-year-old male cairn terrier with icterus and vomiting. The liver is enlarged, hypoechoic, and the portal veins are very prominent and hyperechoic throughout the entire liver. Histopathologic diagnosis: cholangiohepatitis.

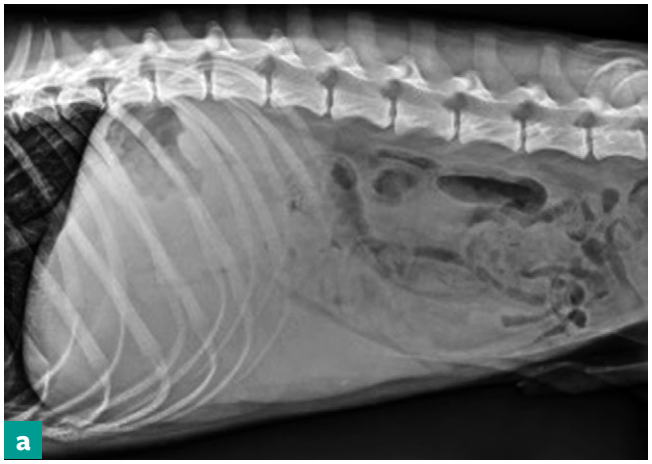
#### 1.4.7.1 Hepatic parenchymal disease

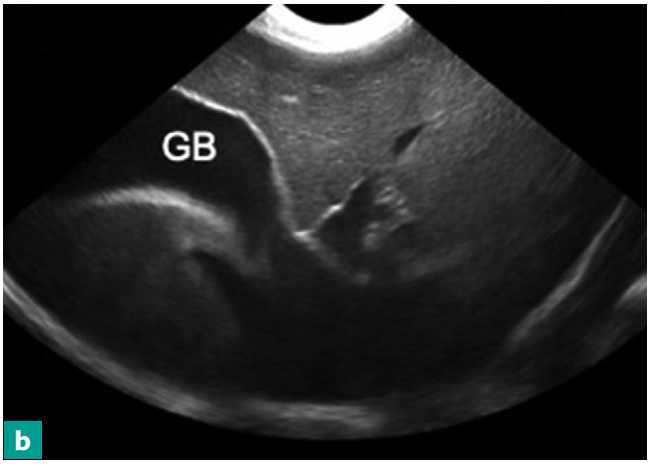
Abdominal radiography may show an enlarged liver in the cranial abdomen, but this finding is nonspecific, and differentiating generalized disease vs. a mass can be difficult. Ultrasonographic changes in patients with hepatic parenchymal disorders are generally focal or diffuse. Diffuse processes are more difficult to recognize than focal or multifocal processes, and a change in the echogenicity of the liver is the main ultrasonographic finding. The most common diffuse diseases in dogs and cats are inflammatory diseases, round-cell neoplasia, non-round-cell pre-nodular metastatic neoplasia, lipidosis, and vacuolar hepatopathy. Ultrasound criteria of echogenicity, diffuse or patchy hyperechoic or hypoechoic echotexture, uniform vs. coarse echotexture, portal venous clarity, and liver lobe geometry have not been found to be discriminatory for the various causes of diffuse liver disease and have a mean accuracy of only 36.5%.[95] This underscores the importance of obtaining samples for cytological or histological analysis in dogs and cats with diffuse liver disease.[96]

In patients with **acute liver injury**, ultrasonography is important for assessing the size and architecture of the liver. The liver may appear normal or enlarged with a generalized decrease in echogenicity. When the echogenicity is decreased, the portal veins appear much more visible, i.e., more hyperechoic than usual (▶ Fig. 1-48). This finding is nonspecific, and differential diagnoses may include toxic injury, infectious hepatitis, metabolic disease, trauma, vascular compromise, cholangiohepatitis, amyloidosis, lymphoma, and passive congestion.

Increased echogenicity of the liver can be detected in a number of conditions, including vacuolar hepatopathy (e.g., hepatic lipidosis in dogs or steroid hepatopathy in cats) and chronic hepatic diseases, such as cholangitis, hepatitis, cirrhosis, and neoplasia, such as histiocytic sarcoma, mast cell tumor, or lymphoma (▶ Fig. 1-49).[94,97–99]

**Feline hepatic lipidosis** is a common cause of intrahepatic cholestasis that can be recognized ultrasonographically (▶ Fig. 1-50). The liver of affected cats is enlarged, has rounded borders, and shows an increased echogenicity equal to or greater than that of the spleen. In addition, the liver may appear isoechoic or hyperechoic compared with omental fat and hyperechoic to falciform fat.[100] Beam attenuation may also occur, and the dorsal region of the liver may be difficult to visualize. The appearance of vascular structures is also diminished. It is important to remember that in obese cats, the liver will often be diffusely hyperechoic as an incidental finding.[101] CT has also been used to diagnose feline lipidosis.[102] Attenuation (as measured in Hounsfield units) in cats with induced lipidosis has been reported to be decreased compared with healthy controls.



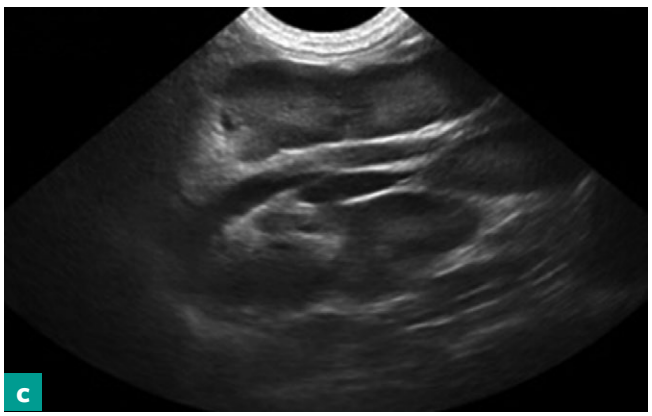




**Fig. 1-49** Lymphoma

**a** Lateral radiograph of the abdomen of a 1-year-old male Standard poodle that presented with lethargy and icterus. The liver and spleen are both enlarged.

**b** Ultrasound image of the liver. The liver is enlarged and diffusely hyperechoic such that the portal vein markings are not visible. **GB** = gallbladder

**c** Multiple enlarged jejunal lymph nodes

Diagnosis: intestinal lymphoma.

**Cirrhosis** and **end-stage chronic inflammatory disease** are less common in cats than in dogs, but hepatic fibrosis may be seen in cats. Ultrasonographic features of cholangitis (formerly termed cholangiohepatitis) range from normal, hyperechoic, hypoechoic, or heterogenous and shows a liver that is either normal in size or enlarged.[103] If portal hypertension is present, peritoneal effusion and splenomegaly can occur. Hepatic cirrhosis and chronic hepatitis are difficult to diagnose by ultrasound due to a large overlap of ultrasonographic features with those of other diseases and can have a similar appearance to those of neoplastic disease.[104] In dogs with idiopathic chronic hepatitis, the liver may be small or normal in size and may contain nodules. Ascites may or may not be present. Regenerative nodules tend to be round and distinct, and the surrounding liver may be of normal or increased echogenicity. Ultimately, a biopsy or fine needle aspiration is needed to arrive at a more definitive diagnosis.

In the **presence of ascites** without hepatic venous congestion, spectral Doppler evaluation of the portal vein can be used to rule out portal hypertension. The velocity of portal venous flow in patients with cirrhosis is generally reduced.[105] In the presence of portal hypertension and ascites, secondary

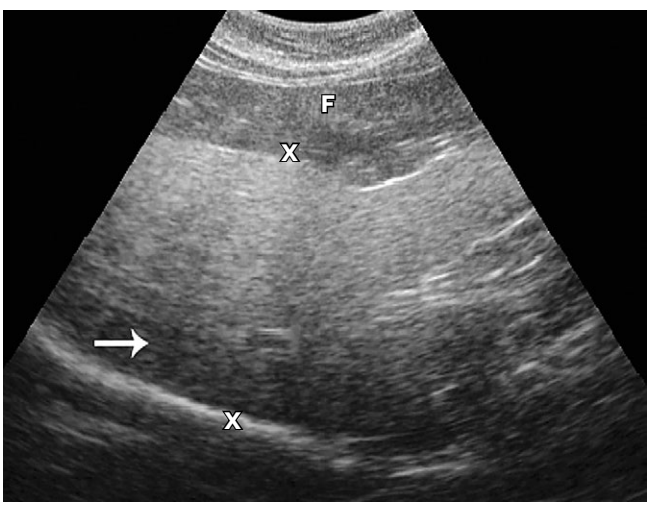



**Fig. 1-50** Hepatic lipidosis

Ultrasound image of a hyperechoic liver in a 16-year-old male European short-haired cat that presented with anorexia. The hyperechoic liver (**between x–x**) is homogenous, and few vessels are visible. The echogenicity is equal to or greater than that of the spleen and surrounding mesentery and falciform fat (**F**). Note the hypoechoic appearance of the liver dorsally (**arrow**) due to beam attenuation. Differential diagnoses include hepatic lipidosis, diabetes mellitus, and neoplasia. Cytologic diagnosis: hepatic lipidosis

portosystemic shunts may be detected. Secondary shunts can be recognized by the presence of many tortuous vessels in the abdomen. Doppler ultrasound will show the flow within these vessels to be monophasic and of low velocity, identifying them as portal in origin (▶ Fig. 1-51). Helical CT is an alternative diagnostic modality in veterinary patients with suspected portosystemic shunts.[106] Also, CEUS has been investigated in dogs for the detection of congenital portosystemic shunts.[11] Another screening method for extrahepatic portosystemic shunts involves measuring the portal vein/aorta ratio (PV/Ao ratio).[107] The ratio is calculated by measuring the diameter of the portal vein and the aorta in the transverse plane at the right dorsolateral abdomen, using an intercostal window. All dogs (n = 85) and cats (n = 17) with a ratio of <0.65 were later diagnosed with an extrahepatic shunt.[107] The PV/Ao ratio can also be calculated using CT and has been used to assess dogs with acquired portosystemic shunts. However, the ratio was similar for dogs with collateral vessels due to chronic hepatitis, primary hypoplasia of the portal vein, and dogs with congenital extrahepatic shunts.[108] No differences in the ratio between dogs with chronic hepatitis and healthy controls (1.05–2.01) were identified. However, the ratio differed significantly between dogs with chronic hepatitis and those with portal vein hypoplasia (0.24–0.67) and extrahepatic shunts (0.11–0.64).

**Diffuse hepatic changes** with the hepatic parenchyma displaying a heterogenous echotexture may be seen in some patients. Causes of a mottled, heterogenous liver with hyperechoic parenchyma and hypoechoic nodules include chronic hepatitis, vacuolar hepatopathy, nodular hyperplasia, fibrosis, toxic hepatopathy, storage diseases, hepatocutaneous syndrome, and neoplasia.[94] Neoplasia is the most common cause

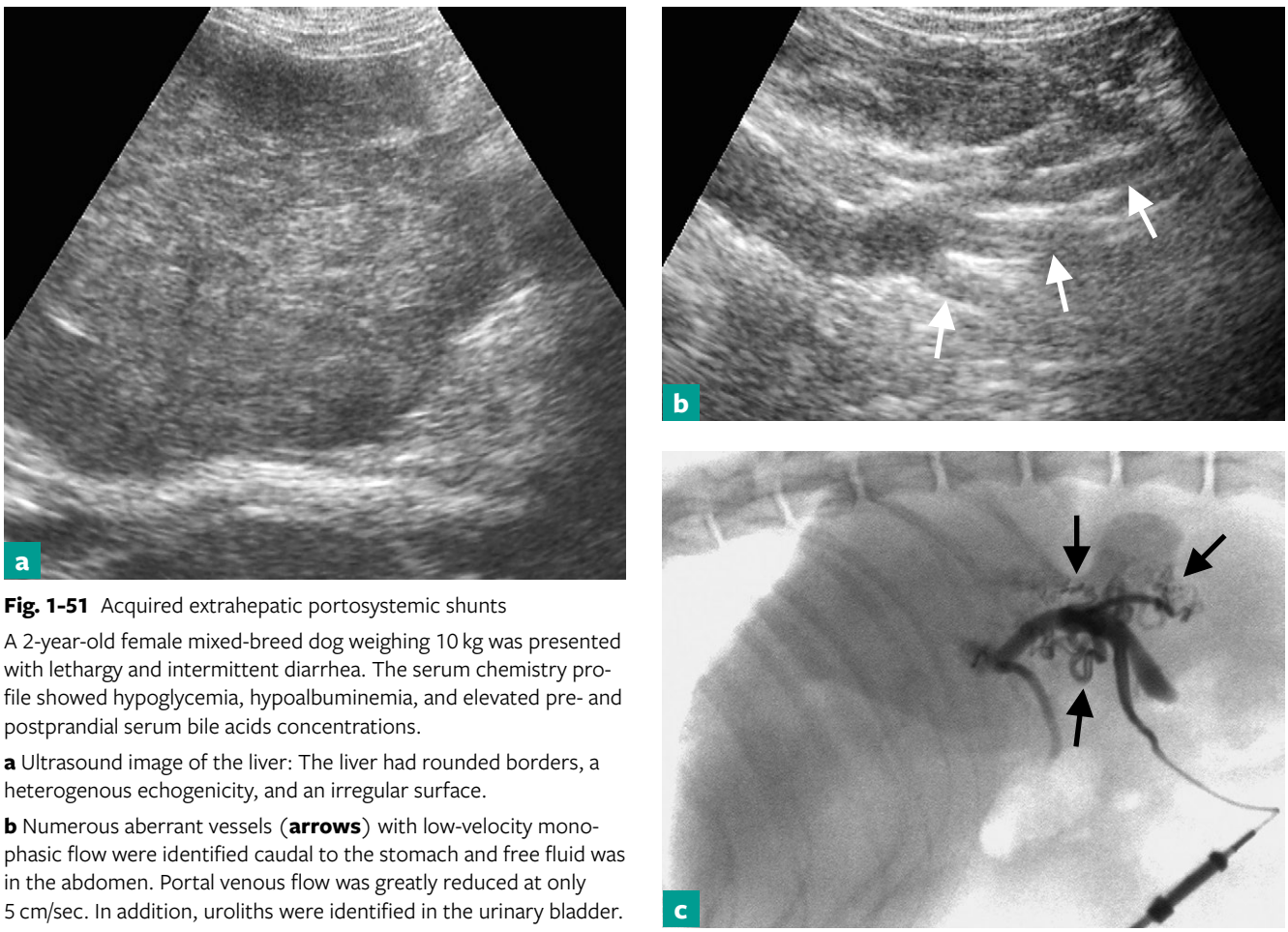



**Fig. 1-51** Acquired extrahepatic portosystemic shunts

A 2-year-old female mixed-breed dog weighing 10 kg was presented with lethargy and intermittent diarrhea. The serum chemistry profile showed hypoglycemia, hypoalbuminemia, and elevated pre- and postprandial serum bile acids concentrations.

**a** Ultrasound image of the liver: The liver had rounded borders, a heterogenous echogenicity, and an irregular surface.

**b** Numerous aberrant vessels (**arrows**) with low-velocity monophasic flow were identified caudal to the stomach and free fluid was in the abdomen. Portal venous flow was greatly reduced at only 5 cm/sec. In addition, uroliths were identified in the urinary bladder.

**c** Intraoperative mesenteric venous portogram: Multiple tortuous shunting vessels (**arrows**) are seen. A normal portal vasculature could not be demonstrated in this dog.

Diagnosis: Secondary extrahepatic portosystemic shunts due to chronic liver disease.

when the hepatic parenchyma appears diffusely complex or disrupted with poorly circumscribed areas of both increased and decreased echogenicity.

Contrast-enhanced ultrasonography has been found to be very useful for differentiating benign from malignant hepatic disease in humans.[109–111] This is similar in dogs where malignant nodules appear hypoechoic to the surrounding liver parenchyma during the peak portal and parenchymal phases of contrast perfusion. Benign nodules remain isoechoic to the liver parenchyma at peak enhancement. These features have been shown to have a 93.8% sensitivity and a 100% specificity leading to a positive predictive value of 100%.[112]

**Focal hepatic disease** is due to nodules or masses that may be isoechoic, hyperechoic, mixed echogenic, cavitated, gas containing, or cystic. Focal disease that has the features of a target lesion (focal nodule with a hyperechoic center and hypoechoic outer rim around it) are more often malignant (▶Fig. 1-52 and ▶Fig. 1-53).[113] Nodules and masses can be due to nodular hyperplasia, primary or metastatic neoplasia, or an abscess, hematoma, cyst, or cystadenoma.[94] CT and MRI are additional imaging modalities that can help to characterize liver masses, stage the disease, and plan the surgical approach.[114] One study compared CT and ultrasonographic features of hepatic masses in dogs and found that the presence of cavitations correlated with malignancy with an accuracy of 80.4% (▶Fig. 1-54).[115] On CT, cavitated regions had post-contrast features of low enhancement at <37 Hounsfield units on delayed phase scans and had an accuracy of 91.3% for malignancy.[115] Two CT studies have shown that hepatocellular carcinomas showed hypoattenuation in later phases of contrast enhancement and were heterogenous with marginal or central enhancement compared with benign lesions.[116,117] MRI has been shown to have good sensitivity for differentiating benign from malignant liver lesions in dogs.[118] MRI features in that study were more heterogenous and showed different enhancement patterns for malignant masses compared with normal liver and benign lesions. Newer MRI contrast agents that are more specific for hepatobiliary lesions have shown promising results in their ability to differentiate benign from malignant hepatic disease in dogs.[119,120] In one study, eleven lesions were diagnosed as malignant tumors, and all were hypointense to the surrounding normal liver parenchyma during the hepatobiliary phase using gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid.[119] Another study showed that late-phase imaging with gadobenate dimeglumine could detect liver metastases in dogs.[120] However, more studies need to be performed to assess the clinical utility of MRI for hepatobiliary imaging.

#### 1.4.7.2 Non-obstructive biliary tract disease

Cholangitis, cholangiohepatitis, and cholecystitis are inflammatory diseases of the biliary tract. Cholecystitis is a form of non-obstructive biliary disease that is usually seen with




**Fig. 1-52** Target lesion

Ultrasound image of the liver of a 13-year-old Bichon Frise that presented with a poor appetite and lethargy of one-week duration. The dog was ultimately diagnosed with hepatic carcinoma. Peripheral lymphadenopathy was also present. There is a focal targetoid lesion in the liver (**arrow**) with typical features of a central hyperechoic region surrounded by a hypoechoic halo.

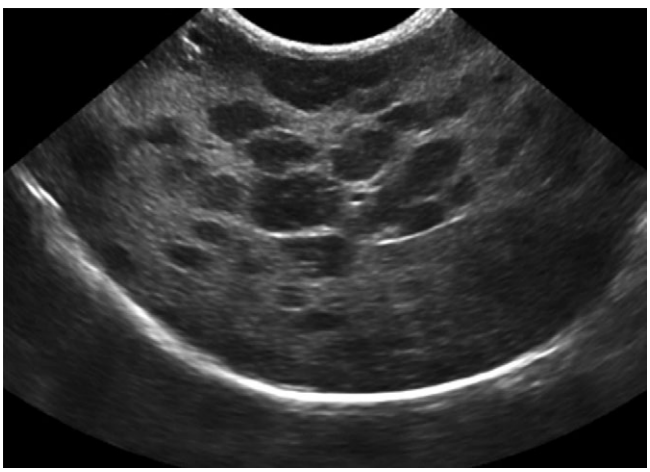


**Fig. 1-53** Hepatocutaneous syndrome

Ultrasound image of the liver of an 8-year-old female spayed Maltese with pruritic and ulcerative skin lesions ultimately diagnosed with hepatocutaneous syndrome. The liver is diffusely infiltrated with variably sized round-to-ovoid hypoechoic nodules.

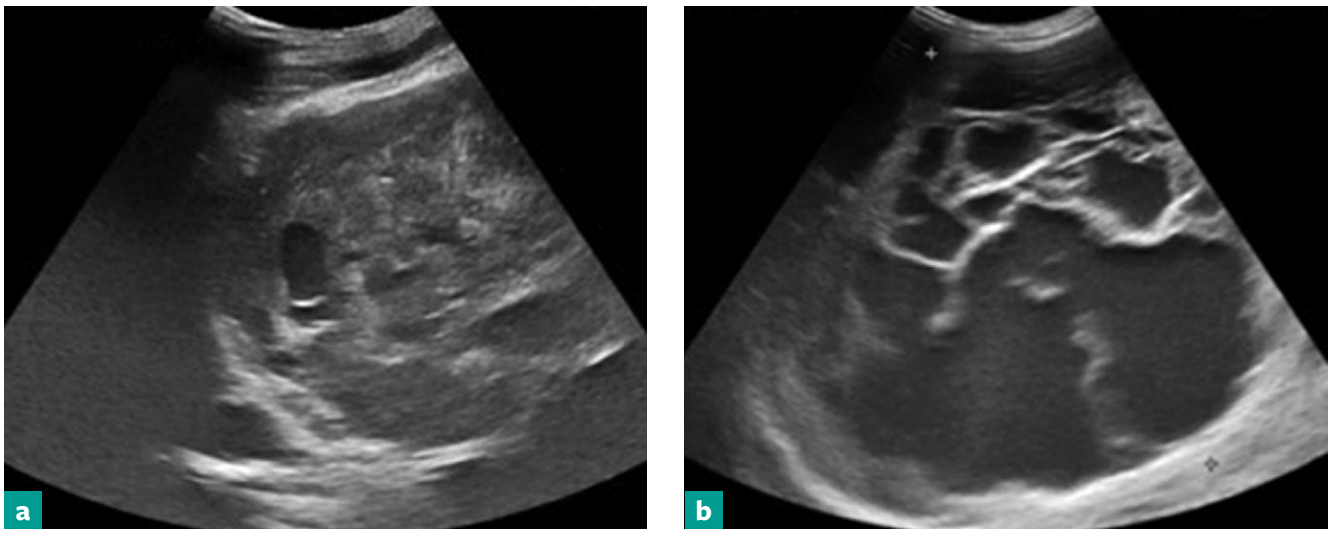



**Fig. 1-54** Ultrasound images of the liver of a 9-year-old German shepherd dog with an enlarged abdomen and a suspected liver mass, ultimately diagnosed with as hepatocellular carcinoma

**a** shows a severely enlarged liver that is focally heterogenous.

**b** shows that a large portion of the mass is cavitated with multiple internal septae and mildly echogenic fluid pockets.

inflammation due to bacterial infections. The infection may spread to the liver, causing cholangiohepatitis. If the cholecystitis is necrotizing, the infection may eventually lead to gallbladder rupture and bile peritonitis. In cats with cholangitis, neutrophilic forms of inflammation can be associated with sonographic features of gallbladder wall thickening, dilation, and tortuosity of the cystic and common bile ducts, diffuse hyperechogenicity of the parenchyma, hepatomegaly, hyperechoic gallbladder content, and choleliths. There is an overlap of ultrasonographic features with lymphocytic cholangitis as well.[103]

Cats with cholangitis can also have sonographic features associated with concurrent pancreatitis and/or inflammatory bowel disease.[121]

**Thickening of the gallbladder wall** is a common ultrasonographic finding in patients with cholecystitis and cholangiohepatitis.[93] Varying amounts of gallbladder sediment may be identified, but this finding is nonspecific. Cystic mucinous hyperplasia of the gallbladder wall is due to hyperplasia of the mucosa and shows sonographic features of small, wall-associated papillary projections into the gallbladder lumen.[94] The clinical significance of this finding is unknown, and its relationship to mucocele formation is unclear. Choleliths, choledocholiths (stones in the bile duct), and mineralization of the gallbladder wall may also be seen, but their significance is dependent on the clinical findings. All of these are hyperechoic structures with acoustic shadowing of variable size and location. Choleliths and choledocholiths have the potential to cause obstruction and the cystic and common bile duct should be traced to the major duodenal papilla to assess for luminal mineral structures. A thickened gallbladder wall is generally hyperechoic, possibly with an irregular inner surface. Polyps may occur in patients with chronic cholecystitis and appear as focal or multifocal wall infiltrations or nodules. Neoplasia, such as adenomas or adenocarcinomas, could have a similar appearance, but gallbladder tumors are rare.

The gallbladder may also appear to have two echogenic double rims with a hypoechoic space in between (▶Fig. 1-55). This double-walled appearance of the gallbladder can be seen with hypoalbuminemia, ascites, sepsis, acute inflammatory disease, or neoplasia. The presence of even small amounts of peritoneal fluid can create the appearance of a thickened gallbladder wall. Therefore, caution should be used in the interpretation of the gallbladder wall in patients with ascites.

**Emphysematous cholecystitis** may be detected radiographically as a zone of hyperlucency in the right craniоventral region of the liver. Ultrasonographically, reverberation echoes within the gallbladder lumen or wall may be recognized. This type of "dirty" shadowing can be differentiated from the "clean" shadowing seen with calculi within the gallbladder.

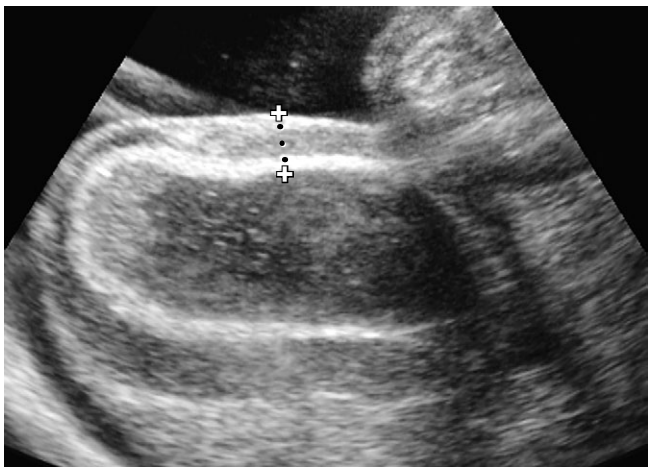


**Fig. 1-55** Gallbladder wall edema

Ultrasound image of the gallbladder in a 5-month-old mixed-breed dog that presented with weight loss and inappetence of 3 weeks duration. Serum hepatic enzyme activities and bilirubin concentration were elevated, and there was a clinical suspicion of hepatitis. Ultrasonographically, the liver was hypoechoic with prominent walls of the portal vein. The gallbladder wall was 8 mm thick (**+ • • • +**) and hypoechoic with an inner and outer hyperechoic rim (double-walled appearance). Ascites was also detected. Note that the double-walled appearance in this instance is not due to the presence of ascites since the thickened wall itself can be visualized. Diagnosis: gallbladder wall edema.



**Fig. 1-56** Gallbladder mucocele

Ultrasound image of the gallbladder in an 8-month-old male Rhodesian Ridgeback that presented for vomiting of 2 days duration and a painful abdomen. Radiographs of the abdomen showed signs of obstructive ileus, and an ultrasound examination was performed. An invagination was diagnosed. In addition, the liver and kidneys were enlarged, and the gallbladder contents showed a complex echostructure with a thickened wall. The dog was diagnosed with leptospirosis, cholangiohepatitis, and a biliary mucocele. (Courtesy of Dr. Johann Lang, Division of Radiology, Vetsuisse, University of Bern, Switzerland.)

**Biliary sludge** is gravity-dependent, homogenous, echogenic particulate matter and is a common finding in dogs that is usually incidental. In one study of 133 dogs, approximately half of the dogs had sludge, and those with >25% mobile sludge were typically older than those with none or minimal sludge.[122] Dogs with hyperadrenocorticism or hypothyroidism are more likely to have >25% sludge.[122] Gallbladder sludge is a less common finding in cats. Interestingly, in one study of 70 cats, the presence of one or more ultrasonographic abnormalities (i.e., thickened wall, mucosal hyperplasia, hyperechoic bile, or choleliths) was associated with a 21-times higher likelihood of a positive result on a bacterial culture of the bile compared with cats with a normal gallbladder ultrasound.[123] Also, a thickened wall or sludge had the highest odds of having bactibilia, but the finding of a combination of a thickened wall and sludge in cats did not increase these odds.[123] The sensitivity of gallbladder wall thickening on ultrasound was 96% for a positive bile culture, which has been shown to be pathologic in cats.[123,124] Percutaneous cholecystocentesis in cats is a safe modality for collecting bile for analysis, and in one study of 83 cats, only 14 had mild complications of focal peritoneal effusion (11), pneumoperitoneum (1), needle tip occlusion (1), and a failed first attempt (1).[125]

**Gallbladder mucoceles** are important findings in dogs with hepatobiliary disease and icterus and various sonographic patterns have been described (▶ Fig. 1-56).[126] Gallbladder mucoceles have the potential to rupture and may cause bile peritonitis. In general, the gallbladder wall is thickened, and its contents show a complex echostructure and echogenicity. Six ultrasound variations of mucoceles have been described.[127] These include type 1 with immobile content, type 2 with an incomplete stellate pattern, type 3 with a typical stellate pattern, type 4 with a kiwi-like pattern and stellate combination, type 5 with a kiwi-like pattern with residual central echogenic bile, and type 6 with a kiwi-like pattern (▶ Fig. 1-57). Neither clinical signs nor rupture has been correlated with a specific type of mucocele.[127] Ultrasonography has a low sensitivity for the identification of gallbladder rupture, and its pre-operative diagnosis is challenging.[128] Of 218 dog with confirmed gallbladder mucocele, 174 had a mucocele evident on ultrasound (79.8%), and 20.2% did not.[128] In the same study, 34 of the 174 mucoceles diagnosed sonographically also had features of rupture, which included a defect in or incongruity of the gallbladder wall, combined with pericholecystic effusion, or cranial abdominal effusion, and peritonitis with or without gallbladder visualization.[128] Of the 34 dogs diag-

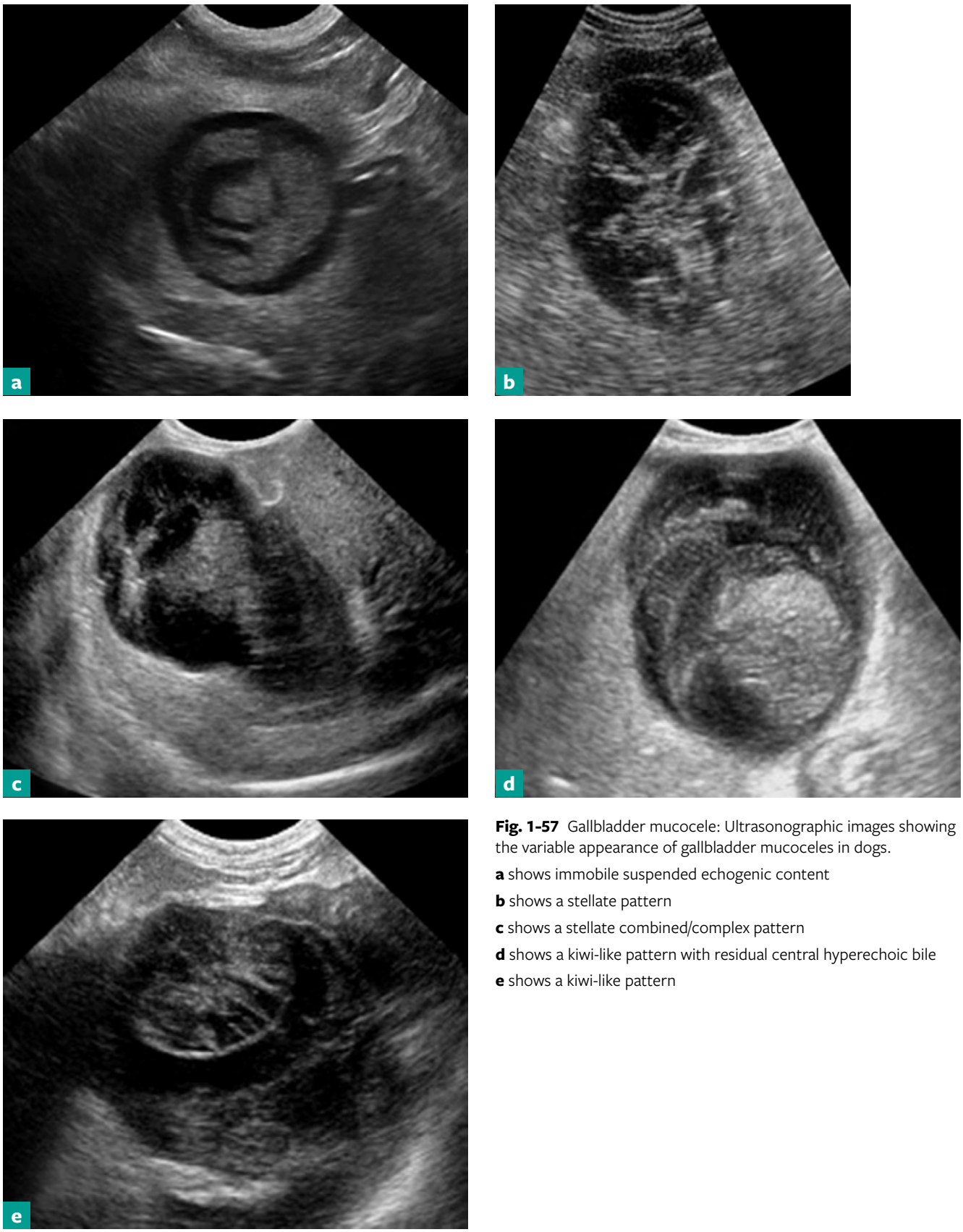



**Fig. 1-57** Gallbladder mucocele: Ultrasonographic images showing the variable appearance of gallbladder mucoceles in dogs.

**a** shows immobile suspended echogenic content

**b** shows a stellate pattern

**c** shows a stellate combined/complex pattern

**d** shows a kiwi-like pattern with residual central hyperechoic bile

**e** shows a kiwi-like pattern

nosed with rupture, 23 had a confirmed rupture at surgery, and the sensitivity and specificity of ultrasound for the diagnosis of rupture were 56.1% and 91.7%, respectively.[128] CT can also differentiate a subset of mucoceles in dogs with and without sludge, and a Hounsfield value of 48.6 is 52% sensitive and 96% specific for a gallbladder mucocele.[129] This study concluded that on pre-contrast scans, CT features of a hyperattenuating gallbladder with centrally distributed mineral content could be a mucocele.[129] Contrast-enhanced ultrasonography (CEUS) provides a more accurate diagnosis of a ruptured gallbladder than conventional ultrasonography. CEUS features of gallbladder rupture are a lack of enhancement of a portion of the wall at the rupture site. In one study, CEUS was reported to be 100% sensitive and specific for diagnosing wall necrosis and/or rupture in 24 dogs that were confirmed surgically.[130] In general, CEUS has also been shown to complement conventional ultrasonography by providing an improved diagnosis of wall necrosis, rupture, and cholecystitis and can differentiate gallbladder wall neoplasia from benign polyps.[130]

### 1.4.7.3 Obstructive biliary disease

Ultrasound can be used to detect dilated and tortuous common and hepatic bile ducts, choleliths, or biliary and peri-biliary obstructions. Biliary calculi, pancreatitis, neoplasia, granulomas, or abscesses are possible causes of biliary obstruction.[131] Liver flukes in cats are another cause in tropical and subtropical climates.

**CLINICAL PEARLS**

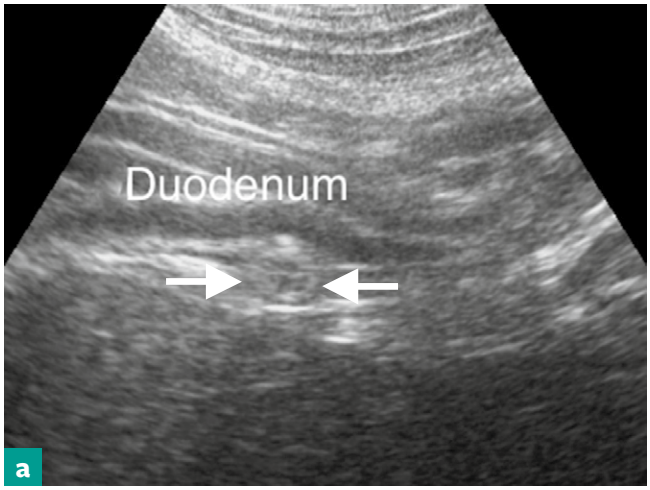
If the patient is anorectic or has been held off food prior to examination, the gallbladder can be very large, which should not be misinterpreted as biliary obstruction.

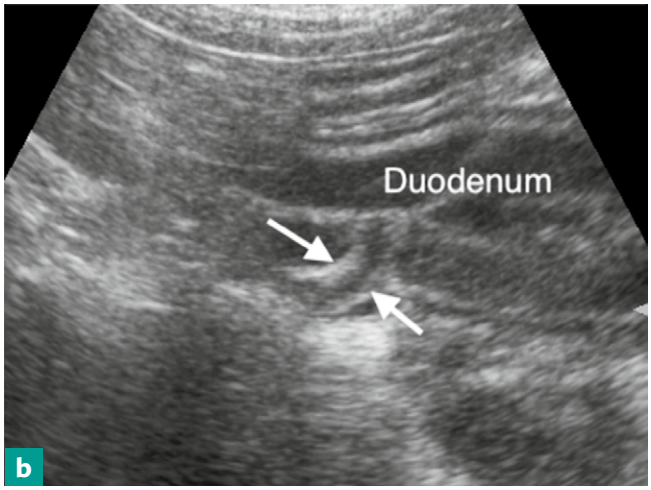
If obstructed, the gallbladder enlarges prior to the intrahepatic bile ducts, which may take days to weeks to dilate. Also, the common bile duct may take days to dilate following an obstruction.

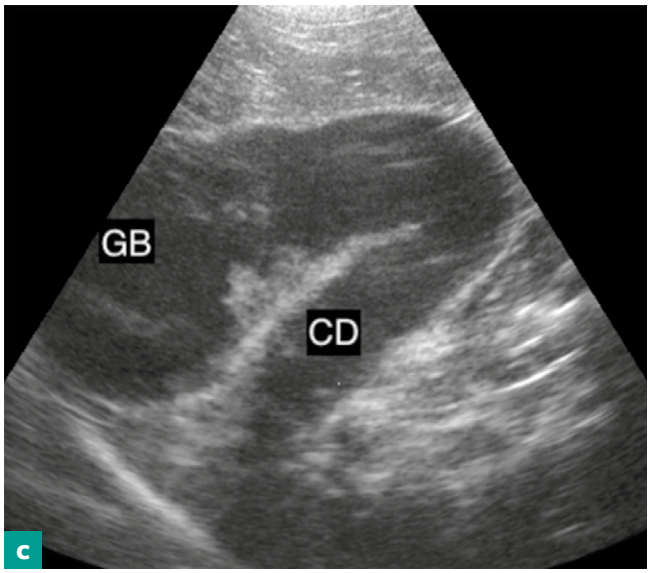
The porta hepatis and cranial duodenum can be challenging regions to examine with ultrasound. The presence of food and gas in the GI tract is one of the main barriers. With high-frequency transducers, however, the duodenal papilla and bile duct can even be seen in normal dogs and cats (▶Fig. 1-58a and b). Therefore, visualization of the bile duct should not be considered the sole criterion for biliary obstruction. The normal bile duct diameter should not be >4 mm in dogs and 3–4 mm in cats.[132]

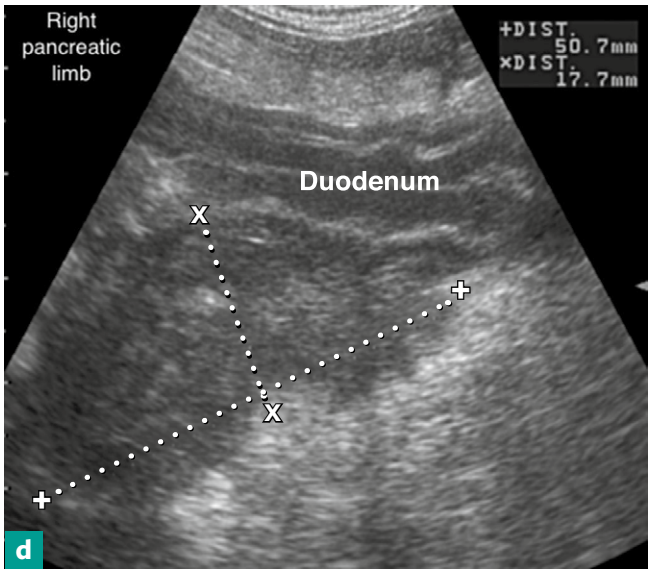
**Extrahepatic cholestasis** can be recognized by a distended gallbladder and bile duct (▶Fig. 1-58c). The pancreas and duodenal papilla can be sources of obstruction that can also be evaluated ultrasonographically (▶Fig. 1-58d). Choleliths, as well as pancreatitis, pancreatic abscesses, cysts, and neoplasia may cause mechanical obstruction of the bile duct (▶Fig. 1-58e). Bile duct carcinoma, pancreatic carcinoma, and lymphoma in cats are additional causes. Carcinosarcoma of the biliary system with ultrasound features of a multicystic hepatic mass has been reported in cats, which underscores that cystic structures or masses in the feline liver, while rare, may have benign or malignant etiologies.[133] Long-standing obstructions may lead to intrahepatic bile duct dilation (▶Fig. 1-58f). Ultrasonographically, a liver can be visualized as having "too many vessels," yet when examined with color Doppler, no blood flow is seen. Differential diagnoses for tubular fluid-filled structures in the liver are obstructions, biliary cysts, pseudocysts, biliary cystadenomas, and bile duct carcinoma.

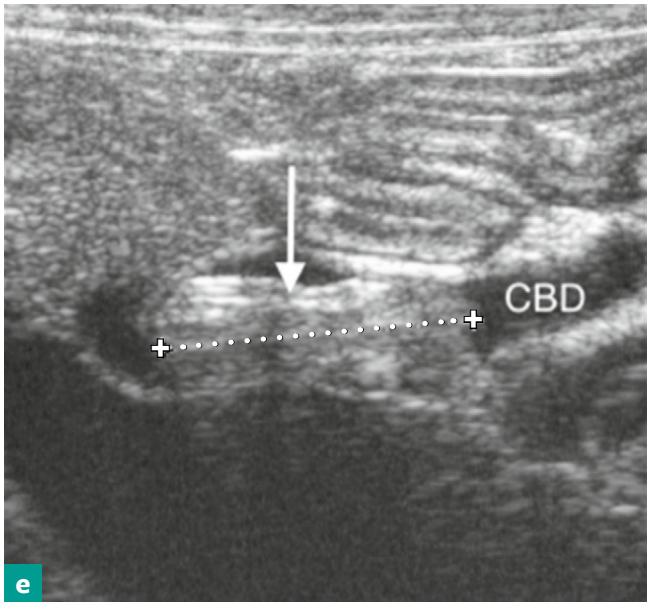
Nuclear scintigraphy and contrast radiography are not commonly performed to diagnose hepatobiliary disease in dogs and cats, but quantitative cholescintigraphy can be used to diagnose extrahepatic biliary obstruction.[134] Moreover, nuclear scintigraphy using Tc-99 m-mebrofenin shows promise in dogs for the quantification of hepatic function.[135] Endoscopic retrograde cholangio-pancreatography (ERCP) uses a combination of endoscopy and fluoroscopy for radiographic contrast imaging of the biliary and pancreatic ducts. Investigators experienced with this modality identified an enlarged common bile duct, intraductal filling defects, a deviated course of the common bile duct, and stenosis of the major duodenal papilla in some affected canine patients. This imaging modality requires specialized equipment and training but may be promising for the diagnosis of biliary and pancreatic diseases in dogs in the future.[136]


Duodenum
a


Duodenum
b


GB
CD
c


Right
pancreatic
limb
+DIST.
50.7mm
×DIST.
17.7mm
Duodenum
d


CBD
e

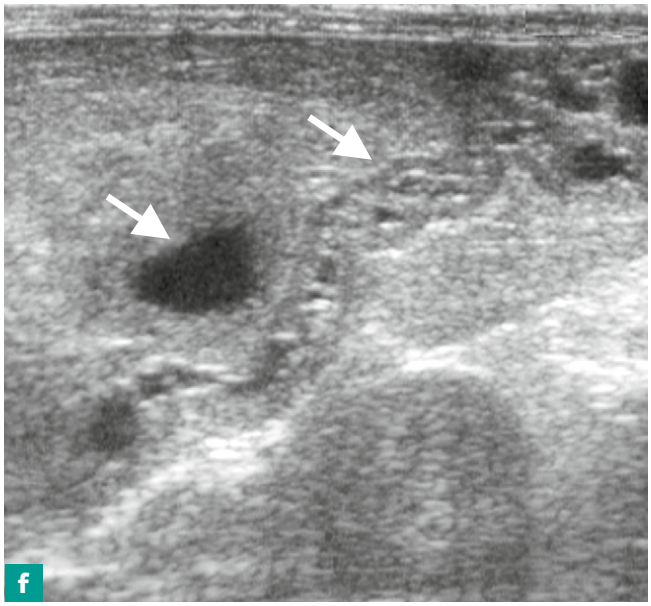

f

**Fig. 1-58** Ultrasonographic assessment of the bile duct

**a** Normal duodenal papilla in a cat (**between arrows**)

**b** Normal common bile duct entering the duodenal papilla in a dog (**between arrows**)

**c** Enlarged gallbladder (**GB**) and cystic duct (**CD**) in a dog with extrahepatic bile duct obstruction

**d** Pancreatitis in a dog causing obstruction of the bile duct at the duodenal papilla, resulting in cholestasis and icterus. The pancreas is enlarged, hypoechoic (**+ • • • +, x • • • x**), and adjacent to the duodenum.

**e** Intraluminal bile concrements (**+ • • • + shown with arrow**) obstructing the bile duct (**CBD**) in a dog with chronic cholecystitis and choleliths

**f** Cystic dilation of the intrahepatic bile ducts (**arrows**) in a cat with chronic cholestasis due to obstruction of the extrahepatic bile duct

#### 1.4.7.4 Interventional procedures of the liver and biliary system

Interventional procedures, such as FNA or biopsy of the liver and pancreas, can be performed using a 16- to 18-gauge biopsy needle, depending on the size of the animal. Both manual and spring-loaded instruments may be used. However, the sensitivity and specificity of cytology and histology from tissue samples collected by FNA have come under criticism.[137]

A coagulation profile should be performed prior to percutaneous true-cut biopsy, but it is not necessary prior to FNA unless there is a clinical suspicion of coagulopathy. Complications following liver biopsy are uncommon, reported in 1.9% of dogs in one study, but the same study found clinically silent major hemorrhage in 42.5% of dogs evaluated.[138] Percutaneous ultrasound-guided cholecystocentesis can be performed for cytologic and bacteriologic analysis with a high degree of safety in both dogs and cats. A 22-gauge, 1.5-inch (3.81 cm) needle with an attached 12 mL syringe is used via a right-sided transhepatic approach. Alternatively, a right ventral abdominal approach into the fundus of the gallbladder can be used.[139]

### 1.4.8 Pancreas

Abdominal radiography in dogs and cats suspected of pancreatic disease is typically of low yield yet is important to rule out other differential causes of vomiting, such as intestinal obstruction. Gastric and duodenal dilation due to focal peritonitis causing atony and mild dilation of the jejunum usually results in a nonspecific radiographic diagnosis of functional ileus. Ultrasonography is considered the standard imaging modality for the pancreas. The ultrasonographic examination of the pancreas is highly operator dependent and an excellent knowledge of anatomy, including vascular anatomy, as well as experience with ultrasonography, is required to locate the pancreas and interpret its appearance. High-resolution transducers are required to image the pancreas in healthy animals. Excessive gas in the GI tract as well as deep thoracic conformation, may inhibit visualization of the entire pancreas. Obese animals pose an additional barrier, even for experienced ultrasonographers. Furthermore, animals with pancreatic disease often have abdominal pain and resent transducer pressure in the region of the pancreas; analgesia may be necessary to perform a thorough examination in these animals.

The normal ultrasonographic features of the canine pancreas are an isoechoic to slightly hypoechoic parenchyma compared with the surrounding mesentery and a homogenous echotexture. The pancreatic size in the dog is up to 3 cm in thickness.[140] The pancreatic duct in dogs is small at 0.8 mm in diameter with a reported range of 0.1–1.2 mm.[140] In cats, the reported parenchymal thickness ranges from 0.3–10 mm, and the right limb is smaller than the left.[141] The feline pancreatic duct ranges from 0.7–2.5 mm in size, and there is a slight increase in size with increasing age.[142,143]

CT and MRI of the pancreas have been described in dogs and cats; however, improved diagnosis of pancreatic disease using advanced modalities has not yet been well established.[25,144–149]

#### 1.4.8.1 Pancreatitis

While ultrasound is generally considered a valuable tool for the diagnosis of canine pancreatitis, its sensitivity in cats with pancreatitis is variable.[150] In patients with acute pancreatitis, the pancreatic parenchyma becomes hypoechoic and enlarged. The surrounding mesentery of the pancreas is often diffusely hyperechoic and poorly circumscribed. However, these changes may be subtle in cats. When the mesentery is inflamed, and the bowel loops are distended with gas, the pancreatic tissue itself may be difficult to identify ultrasonographically (▶Fig. 1-59). Mild to moderate accumulations of free fluid may be detected in the cranial abdomen, which, when found with hyperechogenic mesentery, may indicate the presence of focal peritonitis. In such cases, the small intestinal loops, especially the duodenum, may be dilated due to functional ileus. This may contribute to a lack of visualization of the pancreas due to fluid and gas accumulation. In cats, multiple hypoechoic round foci of a few millimeters in diameter may be recognized if high-frequency (>7.5 MHz) transducers are used. These findings may represent either nodular hyperplasia or dilated pancreatic ducts.[151]

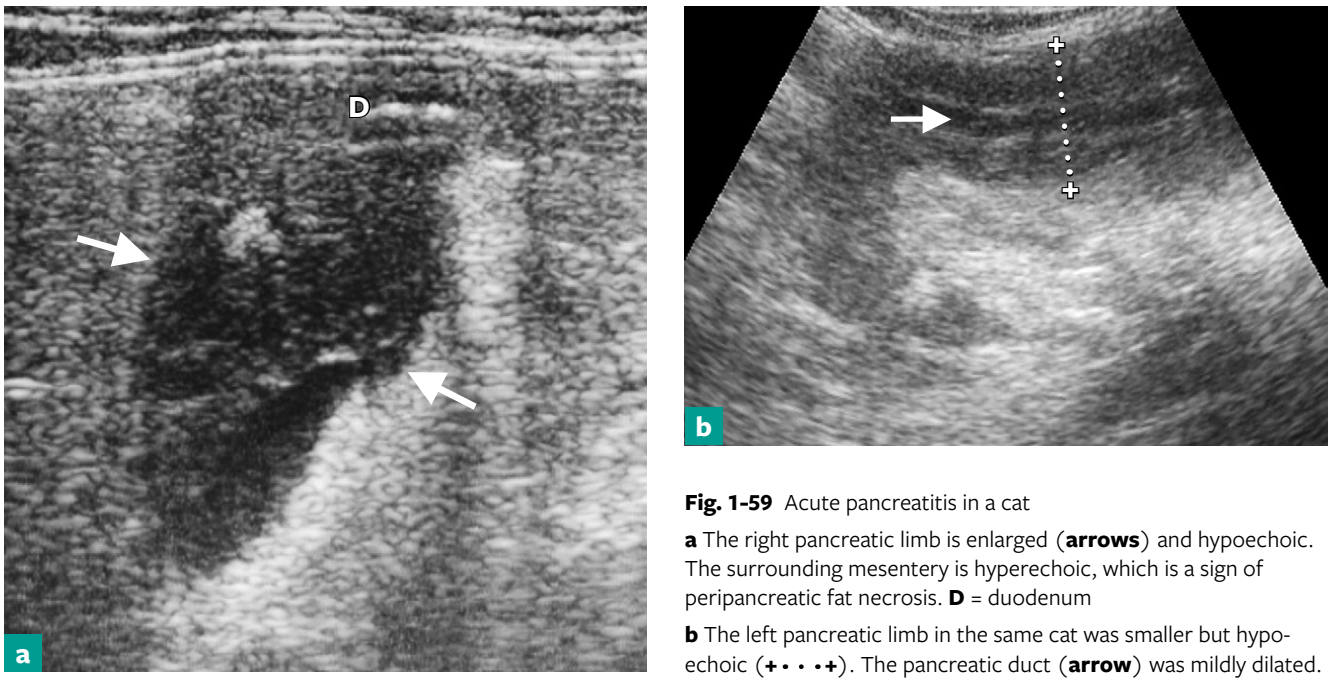



**Fig. 1-59** Acute pancreatitis in a cat

**a** The right pancreatic limb is enlarged (**arrows**) and hypoechoic. The surrounding mesentery is hyperechoic, which is a sign of peripancreatic fat necrosis. **D** = duodenum

**b** The left pancreatic limb in the same cat was smaller but hypoechoic (**+ • • • +**). The pancreatic duct (**arrow**) was mildly dilated.

CT has been used in dogs and cats to characterize and diagnose pancreatitis.[152] In dogs, an enlarged, homogenously to heterogeneously attenuating contrast enhancement of the pancreas with ill-defined borders can be identified. In cats with pancreatitis, MRI shows $T_1$W hypointensity and $T_2$W hyperintensity of the pancreatic parenchyma.[144]

Ultrasonography, CT, and MRI have been used to assess the feline pancreatic duct. Some studies have attempted to correlate the size of the pancreatic duct with increased serum feline pancreatic lipase (fPLI) concentrations and pancreatitis. Pancreatic duct dilation on contrast-enhanced CT has been identified in cats with increased serum fPLI concentrations compared with healthy controls.[146] Ultrasonographically, the presence of a thickened pancreatic limb, irregular pancreatic margins, and hyperechoic peripancreatic fat with clinical signs and an increased serum fPLI concentration are supportive of a diagnosis of pancreatitis.[153] CEUS of the pancreas in cats has been described, and significant differences between cats with exocrine pancreatic disease and healthy controls have been reported.[154,155] Diseases diagnosed in one study included neoplasia and pancreatitis, but nodular hyperplasia was also identified. Vascularity and blood volume were increased on CEUS in affected cats.

The ultrasonographic appearance of chronic pancreatitis in dogs and cats has not been well described. Recurrent episodes of pancreatitis may lead to chronic changes that can be identified ultrasonographically and mainly consist of fibrosis. The pancreas may be of normal size or enlarged with a heterogenous appearance or have a nodular architecture. Mineralizations may be present and may lead to acoustic shadowing.

Anechoic areas, suggesting fluid accumulation, can represent acute peripancreatic fluid accumulations, acute or chronic necrosis after the onset of acute pancreatitis, pseudocysts, or walled-off necrosis. Each of these may be sterile or infected with bacteria. These fluid accumulations have been previously described as phlegmons or abscesses in dogs and cats.

### 1.4.8.2 Pancreatic neoplasia

Pancreatic neoplasia is much less common than pancreatitis in dogs or cats.[156] Neuroendocrine tumors are the most common pancreatic neoplasms, followed by adenocarcinoma, and metastatic tumors (▶Chap. 10.3.3). Differentiation of pancreatitis and pancreatic neoplasia with ultrasound is not always easy due to the overlapping nature of their appearance.[156] Lymphadenomegaly can occur with either disease process, and surrounding tissues are often similarly altered. FNA or true-cut, laparoscopic, or surgical biopsy is often needed for conclusive differentiation. Involvement of multiple organs can occur in both severe suppurative pancreatitis or primary liver, pancreatic, or bile duct neoplasia.[156] Neo-

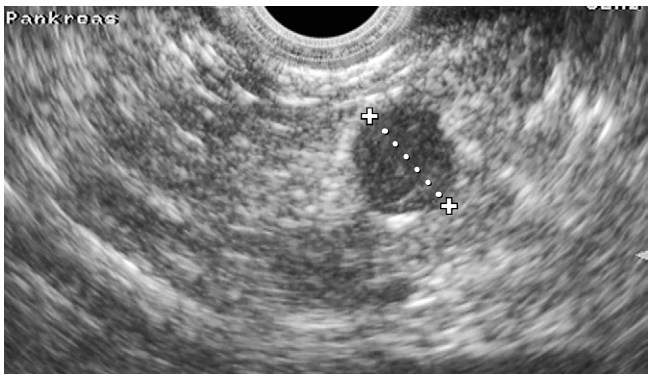



**Fig. 1-60** Canine insulinoma

Echoendoscopic image of the body of the pancreas in a 7-year-old female bearded collie with hypoglycemia. The pancreas was found to be unremarkable during a transabdominal ultrasound examination. An 8.6 mm diameter (**+ – +**), round, and hypoechoic nodule was identified echoendoscopically. The nodule was removed surgically and was diagnosed histologically as an insulinoma.

plasia of any one of these structures may invade adjacent organs and simulate inflammatory or granulomatous disease. In such cases, biopsy of both the liver and pancreas is warranted. Diffuse infiltrative diseases of the pancreas, liver, and other organs such as the stomach, duodenum, spleen, and lymph nodes may be seen in suppurative, granulomatous, and neoplastic disorders.

Depending on the size of a pancreatic nodule, the amount of gastrointestinal gas, and thoracic conformation of the patient, pancreatic neoplasms, such as insulinomas and adenocarcinomas, may be difficult to detect ultrasonographically. CT angiography may improve the diagnosis of insulinomas in dogs, and a case report showed a distinctly enhanced mass in the arterial phase.[157] Endosonography of the pancreas via a transgastric approach may allow a better assessment of the entire pancreas in dogs (▶ Fig. 1-60).[158]

Recently, CT and nuclear scintigraphy using radiolabeled leukocytes have been evaluated for assessing the canine and feline pancreas.[25,27] The MRI appearance of the normal feline pancreas has also been reported, but reports of its clinical use are sparse.[159] Such modalities may have future potential for diagnosing exocrine pancreatic disease, but more clinical data is needed before the routine use of these modalities.

Ultrasound-guided fine needle aspiration of the pancreas with a 20–22G needle has been shown to be a safe procedure in both diseased animals and healthy controls.[160]

## KEY FACTS

- Radiography and ultrasonography are two of the most valuable diagnostic tools for diagnosing gastrointestinal disease in dogs and cats.
- Thoracic radiography should be performed in every patient with regurgitation to assess the esophagus and rule out aspiration pneumonia. However, video fluoroscopic swallow studies are necessary to diagnose the cause of dysphagia.
- High-quality radiographs of the abdomen in three orthogonal planes (i.e., left lateral, right lateral, and VD) should be performed in patients presented for vomiting and are important for ruling out obstructive ileus. Abdominal ultrasound and/or barium studies may be indicated when survey radiography is equivocal.
- Ultrasonography is indicated in dogs and cats presenting with icterus. Hepatic vs. post-hepatic causes can be investigated, and ultrasound-guided fine-needle aspiration of the liver and/or pancreas can be performed.
- Abdominal ultrasound is clinically useful for the diagnosis of acute pancreatitis in both dogs and cats and should be used in conjunction with serum cPLI and fPLI concentration measurements to further support the diagnosis. Examination of the pancreas should also include assessments of the liver, gallbladder, mesentery, and regional lymph nodes to rule out multi-organ involvement or neoplasia.

## References

The complete list of references for this chapter can be downloaded from vetline.de:
svg.to/9842-01-04

## 1.5 Endoscopy

Michael D. Willard

### 1.5.1 Introduction

Endoscopy is the use of an instrument (i.e., the endoscope) to look into a cavity or orifice. Its main value to veterinary gastroenterology consists of allowing the collection of tissue samples without surgery. However, observation of morphological changes in the mucosal surface or removal of foreign bodies is also useful. Gastroduodenoscopy is the most common flexible endoscopy performed, but colonoileoscopy is also important.

#### 1.5.1.1 Indications

**Esophagogastroduodenoscopy** is primarily indicated

**a)** to biopsy the gastrointestinal mucosa in patients with clinical signs of gastrointestinal disease, such as vomiting, diarrhea, weight loss, anorexia, or hypoalbuminemia;
**b)** to detect and remove foreign bodies;
**c)** to identify a gastric outflow obstruction and determine the cause of such an outflow obstruction;
**d)** to look for sites of upper GI bleeding;
**e)** to inspect and/or biopsy the esophagus in patients suspected of having esophagitis or anatomic lesions of the esophagus;
**f)** to dilate benign esophageal strictures;
**g)** to help place gastrostomy tubes; and
**h)** to remove polyps.[1–3]

**Colonoileoscopy** is primarily indicated

**a)** to biopsy the ileum in patients with small bowel disease;
**b)** to biopsy the colon in patients with chronic colonic disease that is either non-responsive to therapeutic trials or that is characterized by concurrent hypoalbuminemia, weight loss, or systemic signs of illness;
**c)** to determine the cause of persistent hematochezia or dyschezia; and
**d)** to examine patients with known or suspected polyps or masses of the large bowel.[4]

Colonoscopy is done less frequently than gastroduodenoscopy because most large bowel diseases can be effectively diagnosed and treated using less invasive modalities.

Imaging is typically performed shortly before gastroduodenoscopy or colonoileoscopy. Radiographic imaging and especially abdominal ultrasonography may reveal evidence of infiltrative disease that is out of reach of the endoscope (e.g., mid-jejunum), free air or fluid (suggestive of a perforation), or widespread infiltrative disease (e.g., metastatic disease) that is amenable to less invasive means (e.g., ultrasound-guided fine-needle aspiration). Abdominal ultrasound is relatively specific but not as sensitive as desired for diagnosing infiltrative disease. Thus, it is often appropriate to endoscopically biopsy the GI tract even when there is no ultrasonographic evidence of infiltrative disease, which is the case in many patients with chronic enteropathy or intestinal lymphoma. Ultrasonography before colonoscopy is indicated if there is evidence of diffuse disease or systemic complications or if a tumor is suspected based upon rectal examination.

#### 1.5.1.2 Choice of endoscopes

Entering the duodenum and obtaining adequate tissue samples is often the most important but also the most challenging part of gastroduodenoscopy. An endoscope with a smaller outer diameter makes it easier to enter the duodenum. However, endoscopes with a smaller diameter usually have a smaller biopsy channel (e.g., 2.0–2.2 mm). Larger diameter biopsy channels (i.e., 2.8 mm) facilitate obtaining good quality tissue samples and the removal of foreign bodies. For cats and most dogs, a one-meter long insertion tube will allow visualization and biopsy of the duodenum and ileum, but some large dogs and those with long body conformations may require a 1.4–1.6-meter insertion tube. Unfortunately, the extra 0.4–0.6 meter in length can be challenging to navigate when scoping cats and medium- to small-sized dogs. Video endoscopes provide superior visualization compared with fiberoptic scopes, plus they allow two people to work together when removing complicated foreign bodies. However, fiberoptic scopes are less expensive and allow a competent endoscopist to accomplish almost everything possible with a video endoscope.

Having a selection of endoscopes is optimal (e.g., a pediatric gastroduodenoscope with a 7.9 mm outer diameter, a 1 meter long insertion tube, and a 2.2 mm biopsy channel; a standard gastroduodenoscope with a 8.5 mm outer diameter, a 1 meter long insertion tube, and a 2.8 mm biopsy channel; and a pediatric colonoscope with an outer diameter of 11 mm, a 1.4 meter long insertion tube, and a 2.8–3.0 mm biopsy channel). If only one endoscope is to be purchased, the dimensions should depend on the size of animals that most commonly undergo endoscopy (e.g., cats versus dogs, small dogs versus large dogs) and the number of endoscopies anticipated to be performed on a weekly basis. If only 2–3 gastroduodenoscopies will be done per month, it is probably

best to obtain a smaller diameter scope (e.g., 7.9 mm outer diameter) because it is doubtful that the endoscopist will achieve a high level of skill in passing the endoscope into the duodenum of cats and small dogs. If at least two endoscopies will be done weekly, one is likely to become proficient enough to maneuver slightly larger endoscopes (i.e., 8.5–9.0 mm outer diameter) with larger biopsy channels (i.e., 2.8 mm) into the duodenum of most adult cats.

## 1.5.2 Endoscopic procedures

### 1.5.2.1 Esophagogastroduodenoscopy

Patients with GI disease, especially those that are vomiting, sometimes have delayed gastric emptying. Therefore, food should be withheld for at least 24 hours before the procedure. One should not administer barium or sucralfate for at least one and preferably 2 days before the procedure. Various preanesthetic-anesthetic regimens may be used; glycopyrrolate plus either butorphanol or acetylpromazine is effective. However, narcotics (e.g., morphine, oxymorphone, or fentanyl) and prokinetic agents (e.g., metoclopramide) should be avoided.[5,6]

**CLINICAL PEARLS**

Ketamine may relax the feline pylorus and may thus facilitate entry into the duodenum. However, it also relaxes the lower esophageal sphincter, often making it necessary for someone to occlude the esophagus so that the stomach can be kept inflated during the procedure.

Induction of anesthesia with propofol and maintenance with isoflurane is effective. Sevoflurane is also useful, especially in very ill animals, but it is essential to assist respiration when using sevoflurane because the diminished tidal volume due to insufflation of the stomach with air may cause the patient to wake up in the middle of the procedure. The patient is placed in left lateral recumbency with the head slightly extended. A reliable mouth gag is always used, as a single bite on the endoscope may cause damage requiring expensive repairs.

The hollow viscus to be evaluated should be insufflated with enough air so that all of the mucosal surfaces can be inspected. Excessive insufflation of the stomach, which causes symptomatic gastric dilatation, should be avoided. Also, panoramic views are often more effective than getting too close. This is especially true when a "red out" (i.e., the endoscope is too close to the mucosa, and everything is out of focus) is experienced. The endoscope should only be advanced when the lumen can be visualized. Finally, while advancing the endoscope, it is often best to try to keep the tip of the scope aimed at the center of the lumen.

### 1.5.2.2 Gastroduodenoscopy

The insertion tube is lightly lubricated and gently inserted into the mouth, much like an orogastric tube. As the larynx is approached and one can see the endotracheal tube entering the trachea, the tip of the endoscope is directed slightly dorsally and gently advanced towards the cricopharyngeal sphincter. Immediately upon entering the cricopharyngeal sphincter, the operator should begin to insufflate so that there is moderate distension of the esophagus. Insufflation allows for mucosal inspections while advancing the endoscope towards the lower esophageal sphincter (LES) and the stomach. The lower esophageal sphincter (LES) usually appears as a "slit," although it sometimes is wide open. If the LES is closed, the operator should aim for the center of the sphincter and advance the endoscope gently rather than pushing hard and trying to force the tip into the stomach. The next step is determined by the size of the patient and the area(s) of interest. In small or medium-sized animals or in animals, where the stomach is the main focus of interest, one should first distend and examine the stomach. In large or very long dogs, in which examination and biopsy of the duodenum are important, it is typically better to enter and examine the duodenum before examining the stomach.[2,7]

It is critical to systematically examine all mucosal surfaces of the stomach because gastric lesions can be localized. After entering the stomach, the stomach is distended with air until the entire gastric mucosal surface can be examined. If the stomach cannot be distended because air escapes through an open LES, an assistant should gently apply pressure on both sides of the cervical trachea to occlude the cervical esophagus and trap air in the upper GI tract. However, insufflation must be limited to avoid excessive gastric distension. Even moderate overdistension impedes ventilation with both oxygen and inhalant anesthetics, and it may even become necessary to deflate the stomach so that the patient can be maintained under anesthesia. Excessive distension may also stimulate gastric peristalsis.

After the stomach is distended, a four-quadrant scan of the body of the stomach should be performed. Starting with the tip of the scope near the LES, the tip is moved in a square pattern going from 10 o'clock to 2 o'clock to 5 o'clock to 7 o'clock. Second, the tip of the scope is advanced and then maximally retroflexed so that the LES and fundus can be examined (i.e., one can see the insertion tube of the endoscope entering the stomach through the LES).

**CLINICAL PEARLS**

Insufficient examination of the fundic area is a common mistake of inexperienced operators, but this is where many foreign bodies and some infiltrative lesions can be found.

After a complete inspection of the gastric fundus, the tip of the endoscope is straightened and is advanced into the antrum by pushing the insertion tube into the patient. In this way, the tip of the scope will slide along the greater curvature, advancing into the antrum and toward the pylorus. The endoscopist may need to slightly deflect the tip of the endoscope upwards for it to enter the antrum without catching on a mucosal fold. Upon entering the antrum, one can see the pylorus at the back and to the left. The entire antral mucosa should be examined while advancing the tip of the endoscope towards the pylorus.

To enter the duodenum, the pylorus should be kept in the middle of the viewing field while advancing the tip.

**NOTE**

The tip of the endoscope is larger than the field seen by the endoscopist because the viewing port at the tip of the endoscope generally comprises approximately 20% of the endoscope diameter. Therefore, while the pylorus may appear as a "large hole" with plenty of room to admit the endoscope, it may be smaller than the diameter of the endoscope.

The endoscopist may advance the tip of the endoscope against the pylorus with modest pressure, as long as the pylorus can be seen in the middle of the viewing field. As the endoscope is advanced, the field of view often becomes blurred due to the endoscope being close to the mucosa. Insufflating air while pushing against the pylorus can help the endoscopist see the opening. If the pylorus cannot be kept in the center of the field of vision, even by rotating the endoscope, it sometimes helps to pass a biopsy forceps 5–10 mm into the pylorus and use it as a guidewire. This approach can cause erosions and hemorrhage but is sometimes useful. With practice, the endoscopist should be able to routinely enter the duodenum of cats as well as dogs weighing >3 kg with a 9.0 mm outer-diameter scope.

The mucosa just inside the pylorus can be challenging to examine, especially when disease-causing mucosal swelling (e.g., an ulcer) is present. After entering the pylorus, the duodenum immediately turns to the right (from the perspective of the image on the screen). To find the duodenal lumen, it sometimes helps to back up the tip of the scope by 1–2 mm while insufflating with air. Once the duodenal lumen is located, the operator should advance the endoscope as far as possible into the duodenum, keeping the lumen in the center of the field of vision. Due to the friable nature of the duodenum, it is especially important to visualize the entire circumference of the duodenal mucosa as the endoscope is being advanced. One should always remember that it is easy to create artifacts (i.e., linear erosions) by pushing the tip of the endoscope against the duodenal mucosa (▶Fig. 1-61).

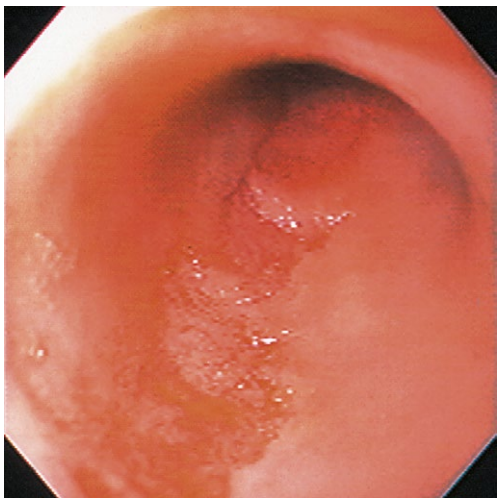


**Fig. 1-61** Abrasions of the duodenal mucosa

Endoscopic view of duodenal mucosa with a linear abrasion caused by the endoscope. Such iatrogenic lesions must be distinguished from spontaneous lesions.

As the stomach is distended with air, the distance the tip of the endoscope must travel as it slides along the greater curvature towards the pylorus becomes greater. In small or medium-sized dogs, this is usually not a problem. However, in larger dogs (e.g., >30 kg) or very long-bodied dogs (e.g., Greyhounds), insufflation may result in the insertion tube being too short to enter the duodenum. If this is a concern, one should start by insufflating as little air as possible into the esophagus. Once in the stomach, one should slightly deflect the tip of the endoscope up about 30 degrees and gently advance it (blindly at times) while insufflating minimally in an attempt to slide into the antrum. This technique can usually be done, although a small amount of air must sometimes be insufflated to see the direction to the antrum (i.e., rugal folds point towards the antrum). If this approach is taken, the stomach cannot be examined until after the duodenum has been examined and biopsied, which can be a problem if blood refluxed from the duodenum into the stomach obscures focal gastric lesions.

Occasionally it becomes impossible to direct the tip of the endoscope into the antrum. This can be caused by the configuration of the stomach (e.g., after gastropexy) or because of abdominal viscera (e.g., an enlarged spleen) pushing into the stomach and diverting the tip of the scope as it travels along the greater curvature of the stomach. This usually occurs when scoping larger dogs.

**CLINICAL PEARLS**

Repositioning the dog into dorsal recumbency while the endoscope is still in the stomach will usually allow the endoscopist to direct the tip of the endoscope into the antrum.

Then, with the tip of the endoscope in the antrum, the dog is repositioned into left lateral recumbency allowing for the pylorus to be entered.

#### 1.5.2.2.1 Intraoperative gastroduodenoscopy

Sometimes it is necessary to view the gastric mucosa during abdominal exploratory surgery to pinpoint lesions that cannot be identified from the serosal surface during laparotomy. For intraoperative endoscopy, the patient is typically in dorsal recumbency, which sometimes makes it more challenging to enter the antrum and duodenum. However, the surgeon can help to direct the endoscope in such cases.

### 1.5.2.3 Colonoileoscopy

Food should be withheld for at least 24 and preferably 36 hours before the procedure. The colon must be cleaned thoroughly, which can be achieved by using gastrointestinal lavage solutions (e.g., Colyte®, Schwarz Pharma, Milwaukee, WI), enemas, or both.[8]

**Enemas** are easier and less expensive, but it is crucial to perform several enemas before the procedure. Properly performed enemas consist of administering copious amounts of warm water (no soap) with the enema tube inserted as far into the colon as possible. At least one liter of warm water is administered per enema to dogs weighing >10 kg. For large breeds (i.e., >30 kg), 2 L per enema can be used. Water may start exiting the anus before the enema is finished, but the full amount should be administered. 3–4 such enemas should be given the night before the procedure and 1–2 more enemas the next morning, at least 2–3 hours before the procedure. Administering bisacodyl (5 mg/dog) the night before the procedure also can be useful. The colon in cats is particularly hard to clean with enemas. Also, one must avoid overdistension of the colon with the enema, which could result in reflexive vomiting. Cats usually receive 50–60 mL of warm water via a soft latex catheter and a syringe.

**Lavage solutions** are more effective for cleaning the colon than enemas alone.[4,9] These solutions are especially useful in large patients (i.e., >30 kg) or in patients with rectal pain that resent having their anus touched. A volume of 25–30 ml/kg of the lavage solution is administered twice, at least 2 hours apart, the night before the procedure. Another dose of the solution is administered again on the morning of the procedure. An enema will then be administered to wash out the lavage solution. Very rarely, gastric dilatation-volvulus (▶Chap. 6.3.3) occur after giving such large volumes of lavage solution.

**CLINICAL PEARLS**

Aspiration of lavage solutions can be devastating as they are hypertonic and draw copious amounts of fluid into the lungs. If this happens, immediately hold the patient vertically by the hind feet to try to remove as much solution as possible by gravity and strongly consider immediate bronchoscopy to aspirate the fluid and iatrogenic pulmonary edema.[10]

Almost any anesthetic regime may be used for colonoscopy. Severely ill patients may only need sedation or manual restraint unless an ileoscopy is also planned. Ileal biopsies typically require anesthesia, and one should avoid drugs like oxymorphone and fentanyl.

Flexible colonoscopy is simple to perform compared with gastroduodenoscopy, and rigid colonoscopy is very easy.[4] A digital rectal examination should always be performed immediately before either endoscopy to detect potential problems (e.g., perineal hernia or a rectal mass) and help straighten out the rectal canal to make entry into the colon easier. For **rigid colonoscopy**, the patient is positioned in right lateral recumbency so that any fluid present in the colon will pool in the ascending and transverse colon.[8] The tip of the colonoscope is inserted about 3 cm into the rectum with the obturator in place. Then, the obturator is removed, the glass window is closed, and air is insufflated into the colon. As the colonic lumen opens up, the operator can follow the lumen orad until the entire length of the endoscope is inserted, or the descending colon turns and becomes the transverse

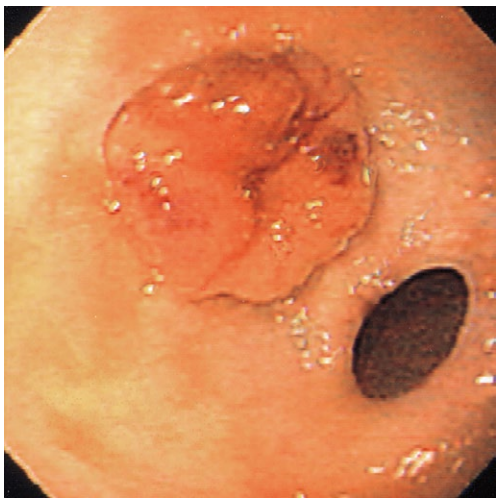


**Fig. 1-62** Ileocolic valve of a dog

The ileocolic valve is the mushroom-shaped structure near the center of the photograph. The orifice below and to the right is the opening to the cecum.

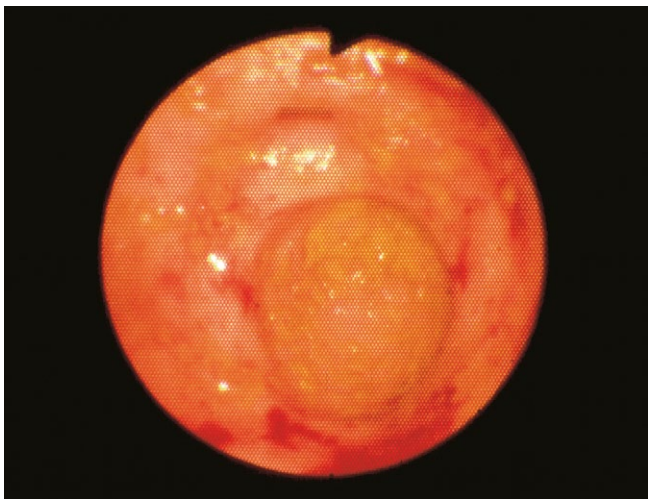


**Fig. 1-63** Cecum and ileocolic valve in a cat

The cecum is the blind pouch, and the ileocolic valve is the horizontal "slit" seen above the cecum.

colon. Rigid colonic biopsy forceps provide tissue samples that are far superior to those obtained by using flexible biopsy forceps. However, rigid colonoscopy can only examine the descending colon. Most, but not all, diffuse colonic lesions involve the descending colon.

If the entire colon is to be examined, **flexible colonoscopy** is required. The patient is positioned in left lateral recumbency, preventing other abdominal organs from pushing down on the ileocolic valve area. The endoscope is advanced along the lumen until the ileocolic valve is seen. If the colon does not distend because air is escaping from the rectum, an assistant can hold the rectum tightly against the endoscope, thus trapping the air.

The ileocolic valve region is often not as clean as the rest of the colon because of ingesta continually exiting the small bowel and entering the colon. In the dog, it is easy to bypass the ileocolic valve obscured with ingesta and inadvertently pass the endoscope tip into the cecum, thinking that the endoscope is still in the colonic lumen. If the colon appears to be making a spiral curve and the endoscope cannot be further advanced, it should be withdrawn as the operator carefully looks for the ileocolic valve that was previously missed.

The ileocolic valve is a dynamic structure in the dog. It can appear as a "mushroom" with a slit in the center (▶Fig. 1-62), it can retract and look like an opening in the colonic wall, or it can appear as something between these two extremes.[4] The feline ileocolic valve region is different. The cecum is simply a blind sac, and the ileocolic valve is usually a slit opening in the mucosa (▶Fig. 1-63). This region is seen immediately after the tip of the endoscope negotiates the flexure between the descending colon and the ascending/transverse colon. In some cases, the tip of the endoscope will pass the ileocolic valve, and the endoscope will have to be partially withdrawn to see the valve.

In dogs weighing >7 kg, one can typically enter the ileum with an endoscope with an outer diameter of <9.0 mm. The technique is similar to that used to enter the duodenum.[3] In small dogs or cats, the operator can blindly pass a biopsy forceps through the ileocolic valve and biopsy the ileum without visualizing the mucosa. The endoscopist should not use too much force when entering the ileum, as iatrogenic perforation can occur.[11]

#### 1.5.2.4 Proctoscopy

Rigid proctoscopy is the best diagnostic modality to evaluate rectal lesions.[8] Proctoscopy does not require insufflation of air. It is simple, easy, and quick. The distal rectum is cleaned out with one or two enemas about 1 hour before the procedure. The patient is sedated or anesthetized (depending on the need). A digital rectal examination is performed, and then the proctoscope is carefully inserted to its maximum depth in the rectum. The obturator is removed, and the mucosa is examined as the scope is slowly withdrawn.

### 1.5.3 Collection of biopsies

Generally, during esophagogastroduodenoscopy, the esophagus, stomach, and duodenum are carefully examined before taking biopsies. Collecting tissue samples produces bleeding,



**Fig. 1-64** Endoscopic biopsy forceps

The forceps on the far left are for a 2.0 mm biopsy channel. They obtain a sample substantially smaller than the next three forceps, which are all for a 2.8 mm channel. The second forceps from the left has an ellipsoidal jaw with fenestrated cups and serrated jaws; these are the more desirable forceps. The third forceps from the left have round jaws and obtain a relatively small tissue sample. The forceps on the far right are disposable biopsy forceps.

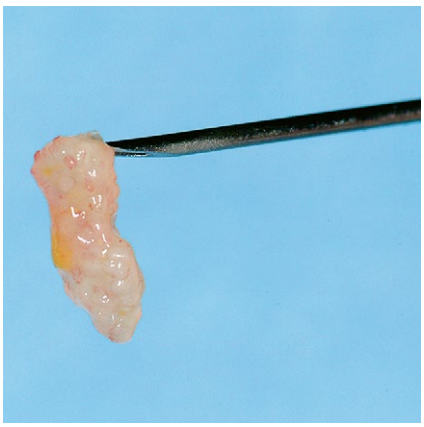


**Fig. 1-65** Duodenal biopsy

An example of a good-quality duodenal biopsy sample. This section of mucosa is intact and can be held up much like a fillet of meat.

which can obscure some lesions, and biopsying the duodenum can result in blood being refluxed into the stomach.

### 1.5.3.1 Gastric biopsies

It is relatively easy to obtain good quality gastric tissue samples by approaching the gastric mucosa at as near to a 90° angle as possible, pushing the jaws of the biopsy forceps into the mucosa with enough pressure to cause a slight indentation but without having the forceps sliding off the mucosal surface, closing the jaws firmly, and pulling the forceps back into the endoscope.[2] Better samples are obtained if the stomach is not overly distended. The antral and pyloric mucosa is tougher than that of the rest of the stomach, and one must close the forceps more tightly and sometimes vigorously pull the forceps back or "snap" the biopsy instrument back into the endoscope to obtain good quality tissue samples. It is necessary to biopsy the antrum, greater curvature, lesser curvature, and fundus because lesions are often localized. Two samples of each area are desirable. If an obvious lesion (e.g., ulcer, mass, erosion, or discolored area) is detected, it should be biopsied first so that bleeding from other biopsy sites does not obscure the lesion(s). Biopsies from such lesions should be placed into a separate formalin container.

If an **ulcer** is found, biopsies of both the center (take care not to push so hard as to perforate the stomach) and the periphery of the ulcer should be collected. Although the center of the ulcer can be necrotic, diagnostic samples often have been collected from that area. Ulcers caused by scirrhous tumors can be very dense, and one may not be able to obtain a diagnostic biopsy using flexible endoscopy forceps. For masses below the mucosa, a "well digging" technique may be employed by biopsying the same site repeatedly, each time placing the biopsy forceps into the hole made by the previous biopsy.[12]

### 1.5.3.2 Duodenal biopsies

The duodenum is the most difficult site from which to collect high-quality tissue samples. The author prefers biopsy forceps that are ellipsoid (as opposed to round) with fenestrated cups, serrated jaws, and without a needle (▶Fig. 1-64). However, there are numerous opinions as to which is the best biopsy instrument.[13–15] Poor biopsy quality is sometimes explained as being due to dull forceps. While this may be true for biopsies from the antral mucosa, it is not an acceptable excuse for inadequate or poor duodenal, colonic, ileal, or gastric body biopsies. Disposable biopsy forceps typically have the sharpest edges, but in the author's experience, this is not usually important.

An excellent sample of duodenal mucosa generally has the following characteristics:

**a)** it tends to have a white or near-white color (as opposed to the reddish-brown to very dark tan color of most poor quality samples),

**b)** it is an intact piece of tissue (as opposed to the non-distinct material that characterizes samples primarily composed of villus tips) that can be unfolded and handled (▶Fig. 1-65), and

**c)** it fills the cup of the biopsy instrument.[16]

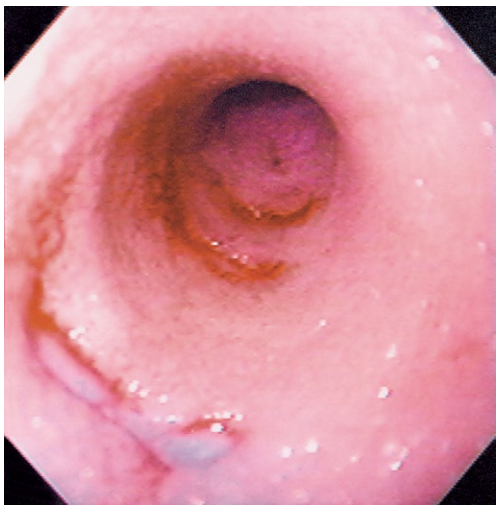


**Fig. 1-66** Biopsy site

Endoscopic view of a site where a biopsy has been taken. Note the white submucosal tissue showing that a full-thickness section of mucosa was obtained.



**Fig. 1-67** Biopsy forceps

The top one is a "double spoon" forceps, which is preferred for laparoscopic liver biopsies. The lower one has a smaller punch that fits into the lower cup, much like a pair of scissors, which is preferred for biopsy of colonic mucosa.

Pushing the biopsy forceps into the mucosa at as near to a 90° angle as possible (as opposed to a more acute angle) is desirable.[15] One technique, known as the "turn and suction" technique, involves inserting the biopsy instrument until the jaws extend several millimeters in front of the scope tip.[12] Then, the biopsy instrument jaws are opened, and the forceps are gently withdrawn until the opened jaws are resting against the tip of the endoscope. Now, the tip of the endoscope is maximally deflected up or down, whichever makes the tip of the scope as near perpendicular to the mucosa as possible. This will produce a "red out" (i.e., the scope tip rests against the mucosa causing the endoscopist to see a red blur). Next, suction is applied, and then the biopsy instrument is advanced into the mucosa for 2–4 mm. The biopsy instrument is closed when there is substantial resistance to advancing the tip. The scope is straightened to avoid damaging the biopsy channel, and the forceps are withdrawn. Sometimes one may look at the mucosa after performing an excellent biopsy and see obvious, whitish submucosa, which indicates that a full-thickness mucosal biopsy was obtained (▶Fig. 1-66). Another technique is the "push-off" technique, which is, however, not described here.[12] If the duodenum cannot be entered, one may blindly pass the biopsy forceps through the pylorus to biopsy duodenal mucosa. However, such biopsies typically yield non-diagnostic, artifact-riddled tissue samples. At least eight excellent tissue samples from the duodenum should be collected in the hope that several of them will be oriented optimally for evaluation by the pathologist.[17]

### 1.5.3.3 Ileal and colonic biopsies

For flexible endoscopic biopsy of the colon and ileum, the same technique is employed. If a rigid endoscope is used, one can obtain a tissue sample superior to anything that a flexible scope can provide. A fold of colonic mucosa is created by gently moving the endoscope back and forth a little, and then the edge of this fold is cut off using rigid forceps.[8] The best biopsy forceps for collecting colonic mucosal biopsies are those where the small upper punch fits into a larger lower cup and cuts the tissue much like a pair of scissors rather than the "double spoon" type (▶Fig. 1-67).

### 1.5.3.4 Rectal biopsies

For rectal lesions with a dense submucosal infiltrate (e.g., scirrhous carcinomas), it is imperative to biopsy the underlying submucosa and not just the overlying mucosa. To collect these tissue samples, heavy, rigid forceps with the shearing action described above are necessary (▶Fig. 1-68).

**CLINICAL PEARLS**

It can be challenging to sample a densely infiltrated submucosa, and it sometimes works best if the endoscope is removed from the anus, and a gloved finger is used to guide the forceps to the thickest part of the lesion.



**Fig. 1-68** Biopsy forceps

Heavy-duty rigid forceps that will be able to cut through very dense, infiltrative lesions.

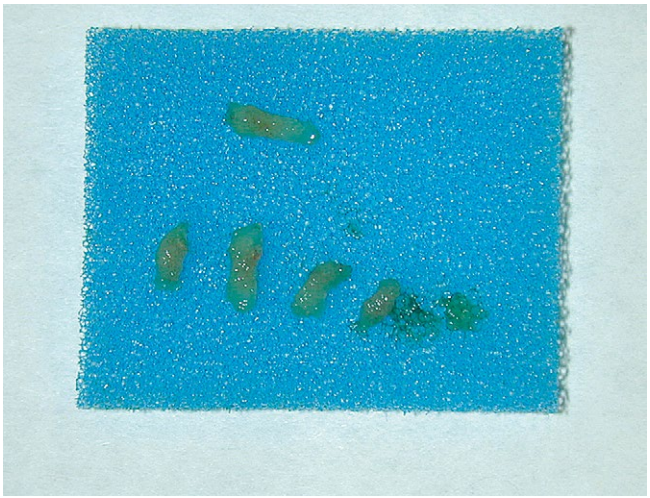


**Fig. 1-69** Biopsy handling

Example of how tissue samples should be placed on a sponge or other media prior to fixation. Note how the biopsies have been gently unfolded after they were taken from the biopsy forceps.

The opened jaws of the forceps are carefully placed over the thickest part, pushed firmly into the lesion, and forcefully closed. This often results in an audible "crack" as the dense underlying tissue is cut.[8] The tissue must be inspected after removal from the forceps. If the presence of submucosa is not apparent, the biopsy must be repeated.

### 1.5.3.5 Mounting and handling tissue samples

It is critical that the clinician consults with the pathologist to establish how the tissue samples are to be submitted and how the laboratory will process the samples. In particular, duodenal samples can be challenging to get embedded correctly. The author places tissue samples on a non-absorbent plastic sponge that fits into the histopathology cassette.[18,19] Duodenal and ileal samples are oriented such that the submucosal side of the sample is on the sponge, and the villi are pointing away from the sponge (▶Fig. 1-69). It is crucial not to allow the tissue samples to dry out. The sponges with the attached tissue samples are placed upside down in formalin and submitted to the laboratory. The laboratory embeds these samples in paraffin by turning them 90 degrees to be sectioned longitudinally. This should enable the pathologist to see a well-oriented section of mucosa from the villus tips to the junction of the mucosa and muscularis mucosa (▶Fig. 1-70). For gastric and colonic mucosal samples, it does not matter which side is against the sponge. However, care must be taken not to stretch colonic or gastric mucosa and cause artifacts when placing it on the sponge.

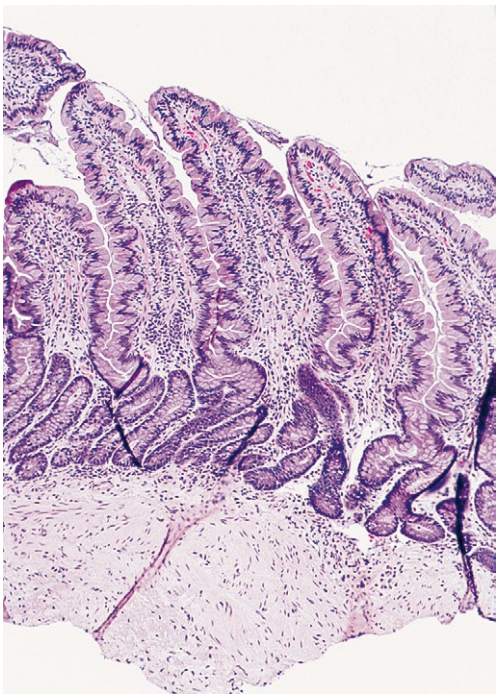


**Fig. 1-70** Duodenal mucosa

A photomicrograph of a good-quality, well-oriented section of duodenal mucosa. Note that the entire thickness of the mucosa can be seen and that some submucosa is included. Not all endoscopic biopsies are as high-quality as the one shown, but it should be the aim of the clinician and pathologist that at least some samples from every case are oriented this well.

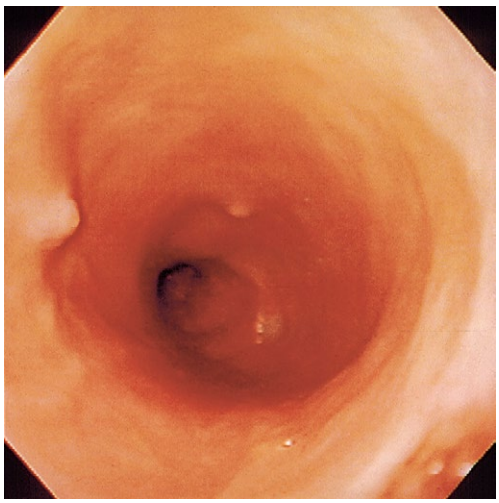


**Fig. 1-71** Duodenal papilla

Endoscopic view of a duodenum showing the duodenal papilla at the 9 o'clock position. (Used with permission from Fossum T, 2002[33])

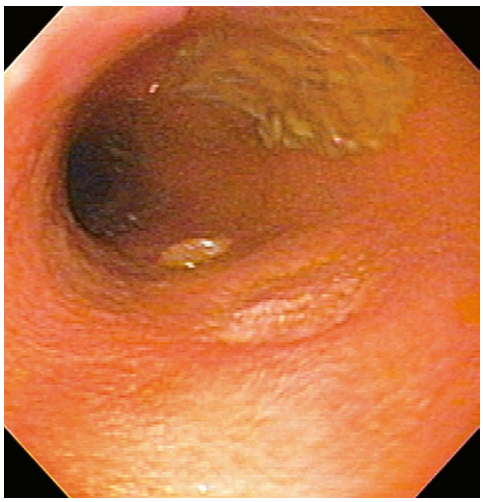


**Fig. 1-72** Lymphoid follicle

Endoscopic view of a duodenum showing a crater-like depression at the 5 o'clock position, which represents a normal lymphoid follicle.

## 1.5.4 Endoscopical findings

### 1.5.4.1 Physiologic findings

The normal esophagus has a smooth texture, except in the cat, where the distal esophagus has a ribbed texture, where the striated muscle is replaced with smooth muscle.[1,7] Black pigment is usually visible in chow chows or shar-peis. The lower esophageal spincter (LES) may have a reddened area protruding slightly into the esophageal lumen, which is normal. The stomach should have a smooth texture.[2] One may see numerous dots on the mucosa in some patients. The duodenum has a definite, fine texture due to the villi.[3] One can typically see the duodenal papilla (▶Fig. 1-71) and depressions that represent lymphoid follicles (▶Fig. 1-72). When using a video endoscope, the examiner can often appreciate individual villi.

### 1.5.4.2 Abnormal findings

#### 1.5.4.2.1 Esophagus

Although endoscopy may help to detect a grossly **distended esophagus** (i.e., megaesophagus, ▶Chap. 5.3.8), endoscopy is a poor diagnostic tool for esophageal weakness.[7] Only patients with marked esophageal dilation will be obvious during endoscopy; fluoroscopy is a much more sensitive (and less invasive) way to diagnose esophageal weakness. Also, some preanesthetics (e.g., ketamine or xylazine) can cause the esophagus, stomach, and intestines to become flaccid.[20]

Some **esophageal tumors** present as distinct masses, while others cause strictures (▶Chap. 5.3.12).[7,21] Sarcomas may be caused by *Spirocerca lupi*. *S. lupi* granulomas appear as nodules, with some having a small "crater" or "nipple" from which a red worm may occasionally protrude. Sarcomas, carcinomas, and melanomas are all easily diagnosed by biopsy. Leiomyomas are typically submucosal and are covered with normal mucosa (▶Fig. 1-73). It is often impossible to diagnose these tumors with flexible endoscopic forceps because such forceps cannot cut through the stratified esophageal mucosa. In some dogs, leiomyomas at the LES may only

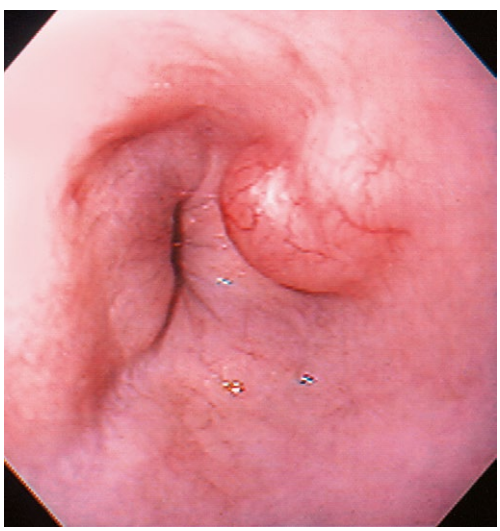


**Fig. 1-73** Submucosal leiomyoma in a dog

(Used with permission from Nelson R, 2003[32])

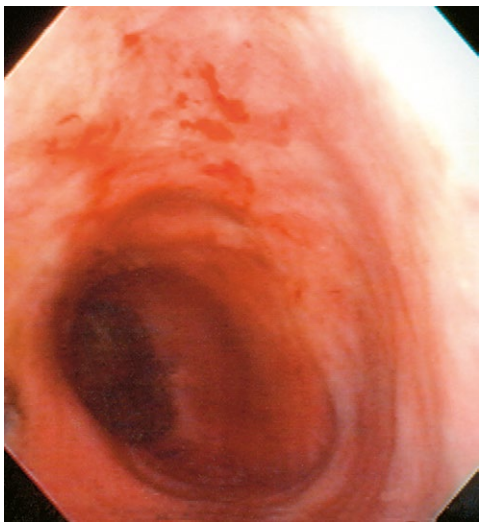


**Fig. 1-74** Esophagitis
Note distinct areas of hyperemia.

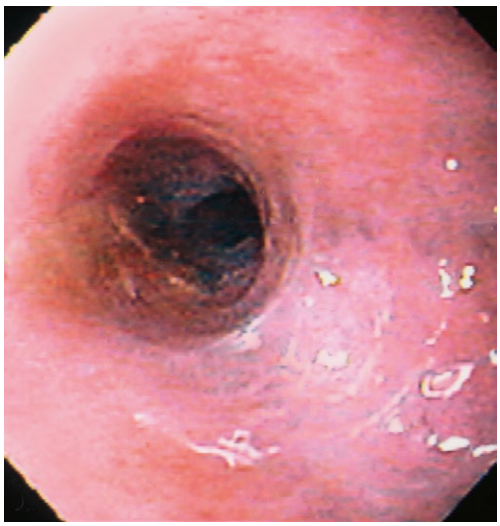


**Fig. 1-75** Esophageal stricture
Note the narrowing of the lumen and the white tissue (scar tissue) at the 4 o'clock position.

be visible through the retroflexed position from inside the stomach. Finally, esophageal polyps are rare and, if found, may represent an underlying malignancy that has produced a benign, adenomatous growth over it. A deep biopsy (i.e., surgical or performed with rigid biopsy forceps) that includes the submucosa is necessary for diagnosis.

**Esophagitis** is usually obvious (▶Chap. 5.3.2). The mucosa is roughened, hyperemic, bleeding, or a combination of those (▶Fig. 1-74).[21,22] Care should be taken to not further damage the esophagus by excessive or rough endoscopic technique. The esophageal mucosa may be biopsied to confirm the diagnosis. Rare patients may have fungal infections (especially pythiosis). The clinician should always seek to identify the cause of esophagitis and carefully examine the stomach and intestines in affected patients for concurrent lesions. Hiatal hernias are sometimes responsible and may be obvious or occult at endoscopy (▶Chap. 5.3.9). Obvious hiatal hernias can have a wide opening at the LES with gastric mucosa protruding into the opening. However, not all patients with a hiatal hernia have esophagitis.

**Strictures** secondary to esophagitis are usually apparent (▶Fig. 1-75).[23,24] They may occur anywhere but seem more common near the LES. Larger animals may have their esophageal lumen decreased by >75% and still allow the endoscope to easily pass through it. Strictures adjacent to the LES may be mistaken for the LES, especially if the endoscope readily passes through it. Benign and malignant esophageal (i.e., intramural) strictures must be distinguished from extramural strictures (e.g., vascular ring anomaly, ▶Chap. 5.3.11).

#### 1.5.4.2.2 Stomach

Many animals with moderate to severe gastritis have grossly normal-appearing gastric mucosa. Therefore, the gastric mucosa should be biopsied in any vomiting or an anorexic patient undergoing gastroduodenoscopy. Most gastric lesions are not uniformly distributed throughout the entire gastric mucosa. Therefore, one must carefully inspect the entire gastric mucosal surface and biopsy multiple spots throughout the stomach.[7] Any food or water in the stomach should be aspirated, and hairballs or other foreign material removed so that the entire mucosal surface can be examined. If blood is present, one should aspirate as much as possible so that all bleeding lesions may be identified and more closely examined. The operator can also infuse water into the stomach through the tip of the endoscope to help wash out the stomach. The inside of the pylorus is perhaps the hardest place to visualize adequately, but ulcers and *Physaloptera rara* are sometimes found there.

**Tumors** (▶Chap. 6.3.4) can cause obvious proliferations (▶Fig. 1-76). However, gastric antral mucosal hypertrophy (▶Fig. 1-77) and benign gastric polyps can closely mimic their appearance.[25] Tumors can also cause mucosal ulcerations without any noticeable proliferation (▶Fig. 1-78). Lymphosarcoma is usually easily diagnosed with flexible biopsy forceps, but scirrhous tumors, leiomyomas, or pythiosis may be impossible to diagnose with flexible biopsy instruments. A gastrostomy site can be seen as an elongated

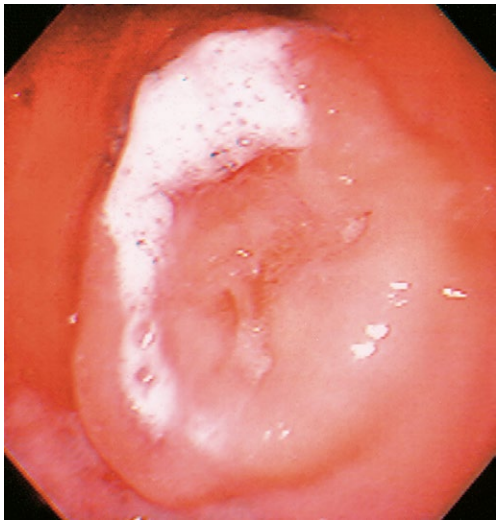


**Fig. 1-76** Gastric tumor

This image shows a leiomyoma on the greater curvature of the stomach.

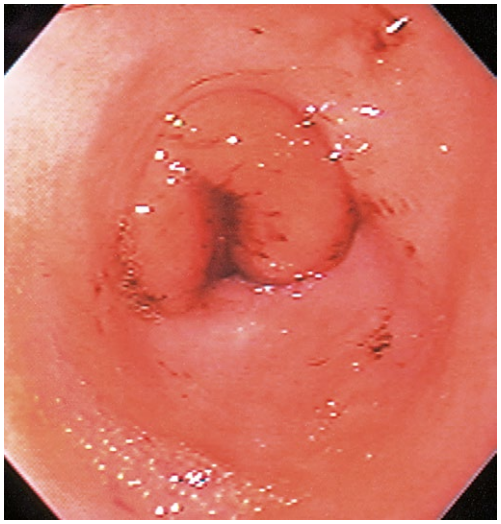


**Fig. 1-77** Antral mucosal hypertrophy

Endoscopic view of a dog's pyloric area. The pylorus is obscured by a mass. This lesion is non-neoplastic and represents antral mucosal hypertrophy.

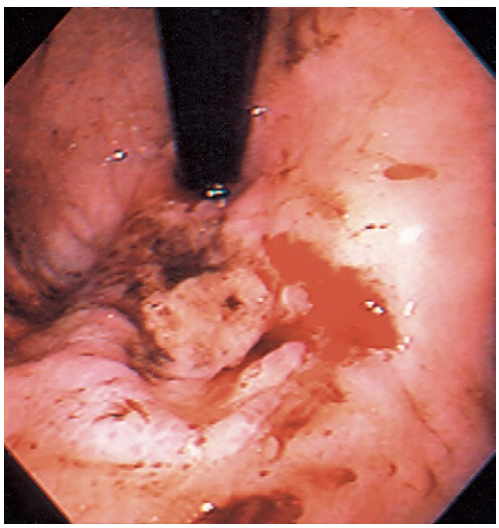


**Fig. 1-78** Neoplastic ulcer

Endoscopic view of a large neoplastic ulcer near the lower esophageal sphincter. This ulcer is caused by a scirrhous carcinoma. It was not possible to diagnose this tumor with an endoscopic biopsy because the tissue was too tough and dense to collect a biopsy from it.

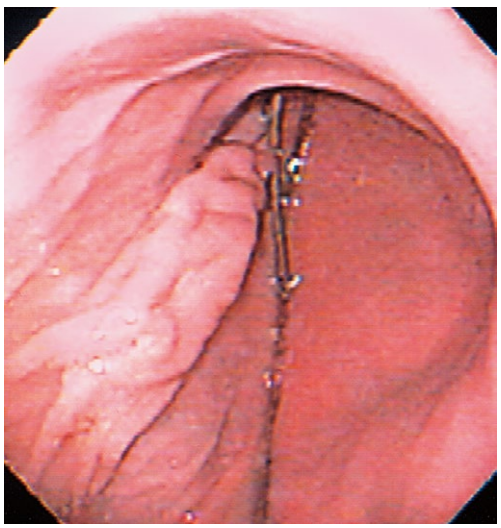


**Fig. 1-79** Greater curvature and antrum

Endoscopic view of the greater curvature and entrance to the antrum with an incision line extending into the antrum. The incision line is raised and could be mistaken for an infiltrative lesion.



**Fig. 1-80** Non-neoplastic ulcer
Note the obvious defect in the mucosa plus marked hyperemia at the site.

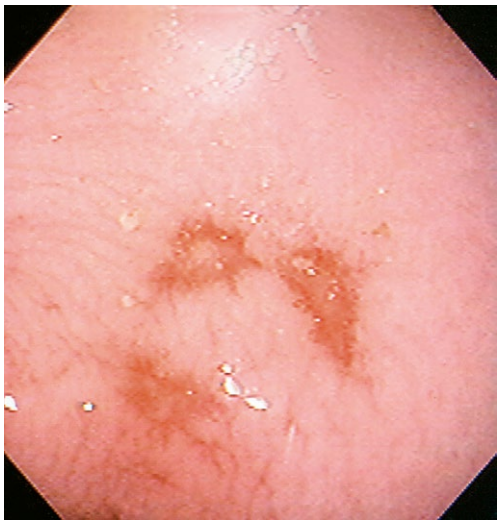


**Fig. 1-81** Gastric erosions
There is marked hyperemia, but a defect is not apparent.

mucosal mass that could be mistaken for a tumor (▶Fig. 1-79). Sometimes areas that have diffuse submucosal infiltrates are detected because they remain collapsed and cannot be distended by air insufflation, which may be more obvious in the gastric antrum.

**Ulcers and erosions** can be surprisingly easy to miss. Digested blood is dark brown-black and absorbs light, making it difficult for the operator to critically examine the mucosa. Also, debris often accumulates on top of erosions or ulcers, making the aspiration of debris necessary. Unless the stomach is adequately distended, erosions and ulcers can also be hidden in between rugal folds. Ulcers are deep mucosal defects that often are discolored (▶Fig. 1-80), while erosions are hyperemic areas, which sometimes can be seen to have a minor mucosal defect (▶Fig. 1-81).[2] Healed ulcers may cause a "stellate" appearance in which "rays" seem to radiate out from a central flat area. Submucosal hemorrhage (▶Fig. 1-82) may be caused by coagulopathies or may signify areas of ulcer formation. Linear gastric lesions can be caused by over-inflating a diseased stomach or pushing an endoscope into the stomach wall with too much pressure.

Rarely, a previously unsuspected, non-distended gastric torsion will be diagnosed when the endoscopist cannot find the entrance to the antrum.

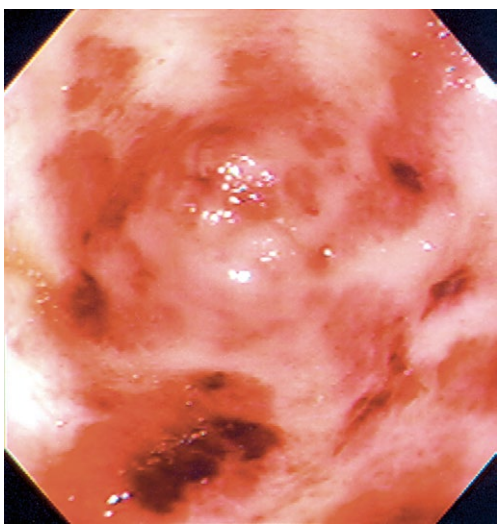


**Fig. 1-82** Submucosal hemorrhage
Endoscopic view of submucosal hemorrhage. This lesion was caused by a coagulopathy, but could also represent a site that is in the process of ulceration.

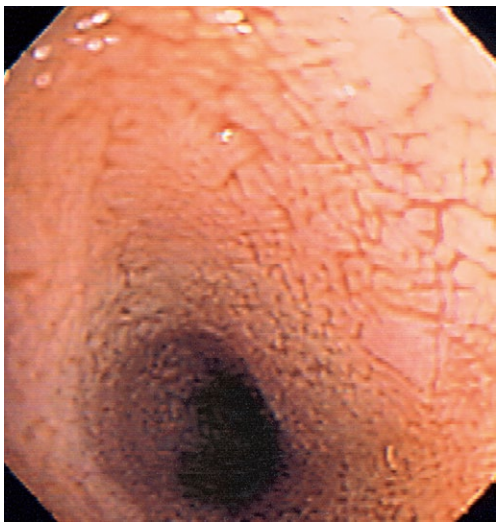


**Fig. 1-83** Duodenal infiltrative disease

Endoscopic view of duodenal mucosa with a very coarse pattern consistent with marked infiltration. Instead of a fine-textured rug appearance, it looks more like cracks in drying mud. This cat had alimentary lymphoma. However, severe inflammatory infiltrates could appear similar.



**Fig. 1-84** Lymphangiectasia

Endoscopic view of a dog with numerous, large white villi that are not associated with lymphoid follicles. This finding is very suggestive of lymphangiectasia.

#### 1.5.4.2.3 Duodenum

The duodenal mucosa typically has a fine texture. Infiltration can cause the surface to be coarser, and severe infiltrates may cause the mucosa to resemble dried mud with cracks (▶Fig. 1-83). **Duodenal ulcers** may have visible craters or may appear as focal areas of exudate or spots of hemorrhage. Large, deep ulcers that occur near the pylorus may represent damage due to excessive gastric acid secretion. Extensively eroded areas can have a smooth appearance due to a lack of villi. Areas of hyperemia may indicate infiltration, erosion, or coagulopathy. **Masses and strictures** may be obvious, although sometimes the only hint of a focal infiltrative lesion (e.g., tumor or fungal granuloma) is a roughened section of mucosa that does not smooth out when the rest of the bowel distends. However, the operator must ensure that such findings are not due to inadequate insufflation.

Finding large white dots scattered over the mucosa (▶Fig. 1-84) suggests **lymphangiectasia** (▶Chap. 1.8.1.6).[26] The white dots represent dilated lacteals and are different from the generalized, delicate, fine-textured white villi that can be seen in any healthy animal that has recently had a fatty meal. Large white lacteals are often seen in the area of lymphoid follicles but are not diagnostic of lymphangiectasia. Finding a substantial amount of white froth in the duodenum during and after biopsy also suggests lymphangiectasia because biopsying disrupts dilated lymphatics, allowing chyle to escape into the lumen.

#### 1.5.4.2.4 Colon

Occasionally areas of overt colonic inflammation (e.g., histoplasmosis, pythiosis; ▶Chap. 7.3.1.5) or ulceration are seen (e.g., histiocytic ulcerative colitis; ▶Chap. 8.3.1.2). However, most of the dramatic colonic lesions are seen near the anus, where tumors and polyps are most common (▶Fig. 1-85).[4] Tumors are occasionally seen further up the colon (▶Chap. 8.3.7). One cannot distinguish benign polyps from malignant tumors based on gross appearance alone. Sometimes, polyps can be multiple and small, resembling inflammatory disease. Occasionally, unsuspected whipworm infestation is noted. Intussusception of the ileum or cecum into the colon can occasionally be found (▶Fig. 1-86).

## 1.5.5 Interventional procedures

### 1.5.5.1 Foreign body removal

#### 1.5.5.1.1 Esophagus

Esophageal foreign bodies (FB) can often be removed with flexible equipment.[21,27] However, the use of a rigid colonoscope and rigid forceps is superior to flexible endoscopy in many cases.[28] The length of the rigid scope is the major limiting factor. Fortunately, most dogs with esophageal FB are small to medium-sized. Plain radiographs are taken immediately before endoscopy to look for pneumothorax,

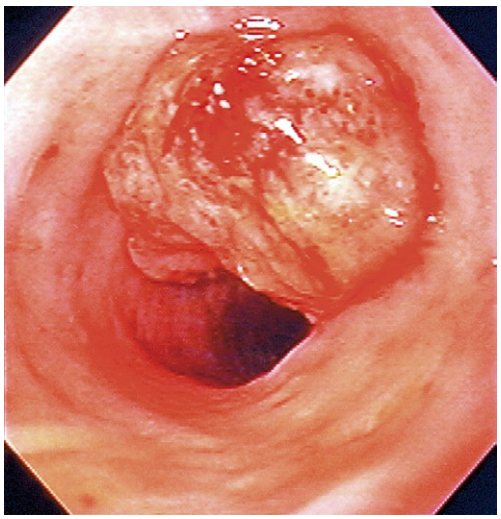


**Fig. 1-85** Polypoid mass

Endoscopic view of the distal colon of a dog with a polypoid mass. This lesion turned out to be an adenocarcinoma.

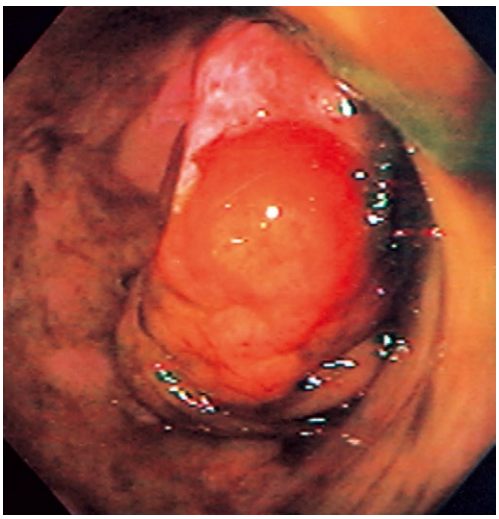


**Fig. 1-86** Ileocolic valve area of a dog

The mass that is protruding is an intussuscepted cecum.

pneumomediastinum, or pleural effusion, which may indicate esophageal perforation (radiographic contrast procedures are rarely appropriate). The rigid endoscope is carefully advanced to the FB. Although not visible, the edges of the FB will often have eroded into the mucosa. Thus, simply pulling on the FB can cause perforation. Instead, the operator must gently manipulate the FB so that the edges are no longer caught in the erosions before pulling with any force. In the case of bones (especially poultry bones), one can advance the endoscope until the tip of the scope puts slight pressure against the bone. One may then use the rigid grasping forceps to grasp the bone, pull it snugly against the end of the rigid endoscope, and then tear off pieces or break it, thus facilitating removal. Once the FB is freed from the erosions, it may be pulled partially or entirely inside the scope while being removed, thus protecting the rest of the esophagus and making it easier for the remaining fragments to be pulled through the cricopharyngeal sphincter.

Fishhooks can often be removed, depending on the size of the barb and the location of the hook.[21,29] Small barbs can easily be torn out of the mucosa with a rigid scope, but hooks with large barbs often cannot. If the hook has passed completely through the esophagus, it can still be removed endoscopically by tearing it back out of the esophagus, as long as the hook is not in the vicinity of any critical vessels. If the point of the hook is directed caudally, then the bend of the hook is tightly grasped with rigid forceps, and the hook is pulled cranially while keeping the hook as straight as possible. If the point of the hook is directed cranially, a rigid scope is passed until the edge of the endoscope is against the bend of the hook. The eye of the hook is grasped with the forceps to keep the shaft of the hook straight, and then the scope and forceps are pushed about 1 cm further into the esophagus. This action will push the hook out of the esophageal mucosa.

In some cases, when a FB cannot be removed, it may be pushed into the stomach, where it can either be removed or, in the case of bones, allowed to dissolve.[21,28] This must only be done if one can be certain that there are no sharp edges on the FB, as pushing a FB with sharp edges may lead to esophageal perforation. In the case of a textured FB (e.g., racketball), one may need to apply lubrication around the FB to be pushed through the LES. Another technique is to insert a large Foley catheter such that the balloon is between the foreign body and the LES. Then one maximally distends the balloon and seeks to push the foreign body and balloon into the stomach. The inflated balloon may make it easier and safer to push the foreign body through the LES.

The operator should be conscientious when insufflating air during the endoscopic removal of an esophageal FB. If one causes gastric distension by insufflating air into the esophagus, but cannot enter the stomach with the endoscope, one may have to trocharize the stomach to relieve the pressure. Also, insufflating too much air may cause a severely ulcerated esophagus to rupture and produce a tension pneumothorax. In any case, a lateral thoracic radiograph should always be taken after removing an esophageal FB to look for evidence of pneumothorax as a sign of perforation. If the esophagus is severely diseased, endoscopic placement of a gastrotomy tube may also be valuable.



**Fig. 1-87** Foreign body retrieval devices

The pair on the left are W-type coin forceps. In the middle are "shark's tooth" forceps, and on the right are "alligator jaws" forceps. The one on the left can fit in a 2.0 mm biopsy channel, but the other two require a 2.8 mm channel.



**Fig. 1-88** Foreign body retrieval devices

A four-wire basket is shown on the left. Note how widely it opens. In the middle is a snare that can be used to retrieve foreign bodies or remove polyps with electrocautery. On the right is a three-prong wire snare, which does not have the grabbing power of any of the devices shown in ▶Fig. 1-87.

#### 1.5.5.1.2 Stomach and intestines

It is important to have several suitable FB retrieval devices.[27] Some of the more useful devices require a 2.8 mm working channel (i.e., shark's tooth, alligator jaws; ▶Fig. 1-87), although some fit through a 2.2 mm channel (i.e., W-type coin forceps; ▶Fig. 1-87). A W-type coin forceps are useful for many objects besides coins. Objects that create a lot of resistance when being pulled across the mucosa require obtaining a substantial "grip" to remove them, and a "shark's tooth" or an "alligator jaws" forceps allows perhaps the most tenacious hold possible. A four-wire basket is very useful for removing balls and rocks. However, the wires should be very soft and pliable and must open widely (i.e., at least 2 cm) to reliably snare most FB (▶Fig. 1-88). A simple snare is also useful. Three-wire graspers are often supplied with endoscopes but are poor substitutes for the preferred instruments (▶Fig. 1-88).

When a FB is located, it should first be studied to consider the best way to remove it. Pulling a FB through the LES is usually the most difficult task, and one must carefully decide which side should be grasped and pulled into the esophagus first. Objects with sharp points should be grasped so that sharp points or edges are oriented away from the mouth. It sometimes helps to

**a)** partially deflate the stomach and

**b)** gently rotate the endoscope as one pulls the object through the LES.

An overtube can also help remove FBs.[27] The endoscope is passed through the larger diameter overtube. After snaring a sharp FB, one may pull the endoscope and the sharp FB into the overtube, thus protecting the esophagus. Additionally, because the overtube is larger than the endoscope, one may also use it to dilate the LES more than the endoscope alone. By opening the LES those few additional millimeters, one may be able to pull a FB through the LES that would not otherwise pass. Also, administering ketamine or xylazine will relax the LES, which sometimes helps to pull a FB through the LES.

#### 1.5.5.1.3 Linear foreign bodies

Linear FB, which have lodged at the pylorus and trail down the duodenum, present a particular challenge. In the author's experience, about 20% of these linear FB can be removed via endoscopy. First, the duodenum should be entered. Then the endoscope tip should be carefully advanced to as near the end of the FB as possible. This technique can be very tedious and may require the endoscope tip to repeatedly be advanced and pulled back. The goal is to grab the FB as near the distal (i.e., aborad) end as possible and then pull it out of the duodenum and into the stomach. In rare cases, one may be able to push the orad end of the linear FB (which has lodged at the pylorus) into the duodenum. Doing this often alleviates the problem because a linear FB only causes a problem if one end is lodged (usually at the base of the tongue or the pylorus), and the rest is trailing off into the intestines. Because of the

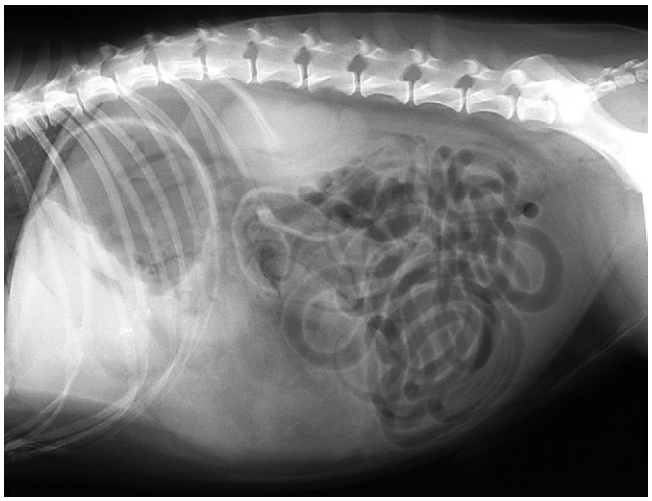


**Fig. 1-89** Duodenal perforation

Lateral radiograph of a dog in which biopsy of a deep duodenal ulcer resulted in perforation. Free air is noted by the ability to see both the serosal and mucosal surfaces of the stomach.




**Fig. 1-90** Balloon catheter

This balloon catheter is used to dilate esophageal strictures. Note the length of the balloon. It is useful to keep the balloon in the center of the stricture when inflating it.

risk for perforation, one should perform a lateral abdominal radiograph after endoscopically removing a linear FB to look for free air as evidence for perforation (▶Fig. 1-89).

### 1.5.5.2 Percutaneous gastrostomy tube

There are many techniques for placing percutaneous endoscopic gastrostomy tubes (PEG tubes), including devices that do not require endoscopy. Endoscopy is advantageous as PEG tubes can easily be placed incorrectly (i.e., too near the LES or too far caudally), or the mesentery or other organs can be damaged or impaled when using "blind" devices.

### 1.5.5.3 Dilation of esophageal strictures

Benign esophageal strictures (▶Chap. 5.3.5) can be dilated using either bougienage or balloon dilation.[21,22] It has been suggested that balloon dilation is associated with less shearing effects and therefore causes less unnecessary trauma, but studies in humans have shown that both bougienage and balloon dilation methods are effective if the operator is well trained. To date, balloon dilation is performed more commonly in small animals and will thus be discussed here. One needs to have balloon catheters specially designed for this purpose. Round balloons, as found on Foley catheters and endotracheal tubes, do not work well for this purpose. Balloons of catheters designed for this purpose are long (▶Fig. 1-90), making it easier to position the middle of the balloon at the stricture so that the balloon will not migrate as it is being inflated. There are balloon catheters that are passed through the endoscope biopsy channel (usually a single-use device) and those that are passed over a transfer wire (typically a multiple-use device). If using the latter, first, a transfer wire is placed through the endoscope and the stricture. The endoscope is then removed while the wire is held in place by continually feeding it into the scope as the scope is removed. Next, the endoscope is replaced into the esophagus so that the stricture can be visualized with the transfer wire running alongside the endoscope. An over-the-wire balloon catheter is passed down over the wire and through the stricture, so that the stricture is at the middle of the balloon. First, a small diameter balloon is chosen, and then the size is progressively increased for repeated ballooning. The balloon is maximally inflated for a few seconds. If the stricture is being torn, the patient typically shows increased heart or respiratory rates and some bleeding. Visualization will confirm that the stricture has been torn. How much to dilate the stricture is debatable and a matter of personal choice. The goal is not to restore the esophagus to its former size but rather to make the patient able to consume regular or softened food. For most cats and small dogs, 15–20 mm balloons provide more than adequate dilation.

It is crucial to avoid causing excessive trauma to prevent restricturing. When aspirating blood and fluid from the esophageal lumen, one should be careful not to also aspirate strips of esophageal mucosa. The more esophageal mucosa

that is damaged, the more likely is a reformation of a stricture. Some patients are permanently cured after one ballooning procedure. However, some patients, especially those with concurrent esophagitis (▶Chap. 5.3.5) or with very dense, mature strictures, have recurrent strictures, and repeat ballooning procedures are necessary. Anywhere from 1–20 ballooning procedures may be needed, but most patients require three to four.[23,24] In some patients with recurrent strictures, repeating the ballooning 2–3 times a week for 1–4 weeks will resolve the problem. Systemic steroids help prevent inflammation, but their efficacy in preventing restricturing is debatable. Endoscopic injection of steroids at the stricture site has been beneficial in humans, but there are no objective data to support or refute their routine application in dogs and cats.[23,30] If dilation can be done frequently enough, the majority of patients return to functionality (but may require softened food). Esophageal stents may be used, but they have potential problems and are not recommended for the novice. The balloon dilatation esophagostomy tube (BE tube) has become a more common approach in severe or recurrent benign strictures and appears reasonably effective.[31]

In some cases of very thick or very mature strictures, dilation is associated with severe, deep tearing that primarily occurs in one part of the stricture. Such deep tearing promotes reformation of the stricture. One technique that has been used is to make 3–4 equidistant cuts into the stricture with either an electrocautery snare (▶Chap. 1.5.5.4) or a papillotomy knife so that dilation causes a more uniform breaking of the stricture at that three or four locations, as opposed to just one place.[19] Rarely, there will be substantial bleeding after the dilation procedure. As during FB removal, one should take care not to overly insufflate air into the esophagus as this may lead to gastric dilation. Finally, if there is substantial damage to the esophagus, placement of a PEG tube might also be useful.

#### 1.5.5.4 Electrocautery techniques

Numerous endoscopic instruments can be attached to an electrocautery unit (i.e., biopsy forceps, cutting snares, coagulation probes, or papillotomy knives). These instruments should only be operated by individuals trained in their use. It is easy to cause substantial damage to the patient or destroy the endoscopic video processor if these tools are used incorrectly. The main indications for their use are

**a)** removal of gastric or colonic polyps,
**b)** performing three- or four-quadrant cuts of benign esophageal strictures prior to dilation, and
**c)** stopping severe, potentially life-threatening hemorrhage while waiting to surgically remove a lesion.

### 1.5.6 Capsule endoscopy

Recently, endoscopic capsules have become available for use in dogs of sufficient size (i.e., >5 kg). The capsule is administered orally, passes through the GI tract taking pictures, and is eliminated into the feces, from which it is recovered and sent to the laboratory for analysis. While initially recommended for patients with gastrointestinal bleeding, the author is especially impressed by its usefulness in patients with suspected lymphangiectasia. It helps to feed the patient a high-fat meal a day before administering the capsule. Rarely, the capsule is not passed out of the stomach or is delayed in passing out of the stomach, but this is not a common problem.

**KEY FACTS**

- Not every dog and cat with signs of gastrointestinal disease need gastrointestinal endoscopy. Cases for gastrointestinal endoscopy must be carefully selected.
- In general, the largest diameter endoscope with the largest diameter biopsy channel that can safely be used for a procedure is the best choice.
- Normal and abnormal tissue can often not be distinguished by gross appearance alone, and a biopsy must be collected.
- Taking adequate endoscopic samples of gastrointestinal mucosa requires training.
- To be able to remove most foreign bodies requires a selection of 3–5 assorted baskets, snares, and forceps.

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
svg.to/9842-01-05

# 1.6 Diagnostic laparoscopy

David C. Twedt

## 1.6.1 Introduction

Diagnostic laparoscopy is a technique for viewing and biopsy of organs in the abdominal cavity. The procedure involves distension of the abdominal cavity with carbon dioxide ($CO_2$) followed by placement of a rigid telescope through a portal in the abdominal wall to view the contents of the peritoneal cavity. Biopsy forceps or other instruments are then passed into the abdomen through adjacent portals to perform various diagnostic procedures. Even with the advancement of laboratory tests and imaging techniques, laparoscopy has remained a valuable diagnostic tool for many hepatic, pancreatic, and gastrointestinal cases when appropriately applied. The limited degree of invasiveness, diagnostic accuracy, and rapid patient recovery make laparoscopy an ideal technique for tissue biopsy or performing selected ancillary procedures. There is also an ever-increasing number of laparoscopic surgical procedures described, but this chapter only concentrates on laparoscopic diagnostic techniques associated with the liver, pancreas, and GI tract.

## 1.6.2 Indications

The most common indications for diagnostic laparoscopy in gastroenterology include the examination and biopsy of abdominal organs or masses (▶Tab. 1-20). Laparoscopy is frequently used to obtain liver, pancreas, kidney, splenic, and intestinal biopsies.[1,2] Laparoscopy can also be used to diagnose and stage the extent of neoplastic conditions within the abdominal cavity.[3] Laparoscopy may reveal small (0.5 cm or less) metastatic lesions, peritoneal metastases, or other organ involvement not easily observed by other techniques. Unexplained abdominal effusion is also a potential indication for laparoscopy when other diagnostic modalities used to determine the cause are unsuccessful. Full-thickness intestinal biopsies can also be performed using laparoscopic assistance. Other ancillary diagnostic techniques using laparoscopic guidance include aspiration of the gallbladder (cholecystocentesis), organs, masses, or cysts.[1]

**Tab. 1-20** Laparoscopic procedures in gastroenterology

| Diagnostic procedures | Surgical procedures |
|---|---|
| • Liver biopsy<br>• Cholecystocentesis<br>• Pancreatic biopsy<br>• Intestinal biopsy | • Feeding tube placement<br>• Gastropexy<br>• Gastric or intestinal foreign body removal |

The advantages of laparoscopy over a conventional surgical laparotomy include improved patient recovery because of small surgical sites and lower postoperative morbidity coupled with decreased infection rate, postoperative pain, and hospitalization time. Other less obvious benefits of laparoscopy are related to fewer stress-mediated factors released than during traditional surgery.[4]

Due to the limited degree of invasiveness of this procedure, there are few contraindications for laparoscopy. Often, the high-risk surgical patient may be a good candidate for a less invasive laparoscopic procedure. Abdominal effusion, abnormal clotting times, and poor patient condition are only relative contraindications. Abdominal fluid can be removed prior to or during a laparoscopic procedure and has little influence over the success rate of the procedure. Abnormal clotting times may also not definitively preclude the use of laparoscopy, as abnormal coagulation does not always correlate with excessive bleeding at the biopsy site.[2] Laparoscopy further makes it possible to visually select areas that appear to be less vascular and monitor the extent of bleeding following the collection of a biopsy. If bleeding is considered to be excessive, various laparoscopic techniques can be used to control hemorrhage.

Contraindications for laparoscopy include septic peritonitis or conditions for which surgical intervention is indicated, such as a resectable liver mass. Relative contraindications include the patient's condition, small body size, and obesity. The procedure is more difficult to perform in extremely small (<4 kg body weight) patients. However, small pediatric laparoscopic instruments facilitate the evaluation of cats and small dogs.

## 1.6.3 Laparoscopic equipment

The basic equipment required for diagnostic laparoscopy includes the telescope, corresponding cannulas, light source, $CO_2$ insufflator, Veress needle (for insufflation), and various forceps and ancillary instruments.

**Telescopes** most frequently used in small animal laparoscopy generally range in diameter from 3–10 mm. The author recommends and uses a 5 mm diameter 0-degree field of view telescope for routine diagnostic laparoscopy.[1] The 0-degree designation means that the telescope views straight forward. Angled viewing telescopes enable the operator to look in a downward direction, which is useful for seeing over the top of organs and into small spaces. However, the angulation also makes the orientation more difficult for the inexperienced operator. The telescope is connected to a light source using a light guide cable. Newer

cold LED light sources are now preferred for laparoscopy.[1] A video camera is attached to the telescope and allows the image to be viewed on a video monitor.

**A Veress needle** is the traditional means of insufflation of the abdominal cavity.[5] The needle consists of an outer cannula with a sharp cutting tip. Within the needle is a spring-loaded obturator that retracts into the needle shaft as it traverses the abdominal wall. Once through the abdominal wall, the blunt-tipped obturator springs forward, preventing needle injury to internal abdominal organs. The Veress needle is then connected to the automatic $CO_2$ insufflator. Most automatic insufflators are similar and function to dispense gas at a prescribed rate while maintaining a predetermined intra-abdominal pressure. Carbon dioxide is used to prevent air emboli and spark ignition during cauterization.[1]

**The traditional cannula units** are required to enter the abdominal cavity and are of a corresponding size to receive either the telescope or the biopsy instruments. Several different types of cannula units are available, but the most common ones consist of a sharp trocar housed in an outer cannula. Together they are used to penetrate the abdominal wall. Once in the abdomen, the trocar is removed. Simultaneously, the cannula remains in place, traversing the abdominal wall, and it becomes a portal for the introduction of the telescope or instruments into the abdominal cavity. Cannulas include a one-way valve for maintaining the pneumoperitoneum when instruments are removed.

**Common accessory instruments** include a palpation probe used to move and palpate abdominal organs and biopsy forceps. The author prefers a 5 mm diameter biopsy forceps with oval biopsy cups to obtain liver, spleen, abdominal mass, and lymph node biopsies. A variety of other biopsy forceps, tissue graspers, and aspiration needles are also available for diagnostic laparoscopy. A "true-cut" type or similar biopsy needle is used both for kidney and deep tissue biopsies. Biopsy needles are passed directly through the abdominal wall and guided to the area to be sampled, much like ultrasound-guided techniques, except the biopsy is visually directed to the area of interest.

#### 1.6.3.1 Procedural considerations

The patient should be fasted for at least 12 hours before the procedure, and the urinary bladder should be evacuated. Laparoscopy is commonly performed using general gas anesthesia, and most patients tolerate the anesthesia and laparoscopy well.[6,7] In some situations, ventilators are used to overcome the potential respiratory effects of abdominal gas distention.

To select the appropriate cannula portal placement sites, one must first determine the objectives of the laparoscopic procedure. The two most common approaches are the right lateral and ventral midline approaches. The author used the right lateral approach for diagnostic evaluation of the liver, gallbladder, right limb of the pancreas, duodenum, right kidney, and right adrenal gland. A ventral approach is useful for many operative procedures and offers good visualization of the liver, gallbladder, pancreas, stomach, intestines, reproductive system, urinary bladder, and spleen. In the ventral approach, visualization is sometimes hindered by the location of the falciform ligament. A complete step-by-step description of the laparoscopy procedure is beyond the scope of this chapter and has been previously described.[1]

### 1.6.4 Biopsy techniques

#### 1.6.4.1 Intestinal biopsy

Full-thickness small intestinal biopsies can be obtained using a laparoscopy-assisted technique. This involves selecting a portion of the intestine to biopsy, grasping the intestine using atraumatic Babcock forceps, and then exteriorizing the bowel loop through the cannula port site in the abdominal wall. The intestine is then biopsied as it would be done when performing a standard open surgical procedure.[1] The intestine is then returned into the abdomen.

It is often necessary to "run" the bowel first with two grasping forceps to select a section of the bowel for biopsy. The antimesenteric border is then firmly grasped with the Babcock forceps, and the intestine is pulled to the cannula (▶Fig. 1-91). Using a scalpel blade, the grasping forceps cannula incision is extended large enough to exteriorize the loop of bowel. One should visualize the scalpel blade enter the abdominal cavity parallel and adjacent to the cannula shaft. The blade then cuts away from the cannula, increasing the length of the abdominal incision. The cannula, forceps, and intestine all in one are then withdrawn through the incision. Small Gelpi retractors are helpful to keep the incision open. When a 3–4 cm loop of intestine is exteriorized, stay sutures are placed in the intestine to prevent falling back into the abdominal cavity. A small full-thickness biopsy is then obtained in the same manner as one would do when performing an open laparotomy. Following the biopsy and closure of the intestine, the intestinal loop is then returned to the abdominal cavity.

An intestinal biopsy should always be the last laparoscopic procedure to be performed as the pneumoperitoneum is

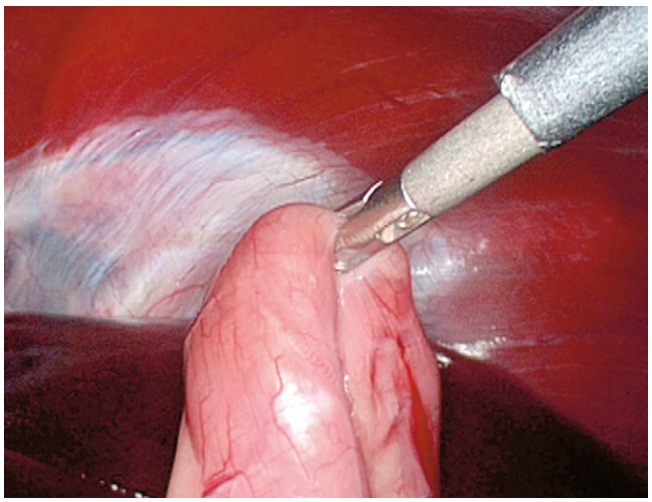


**Fig. 1-91** Small intestinal biopsy

View of grasping forceps holding a portion of the small intestine to be exteriorized for a full-thickness biopsy.

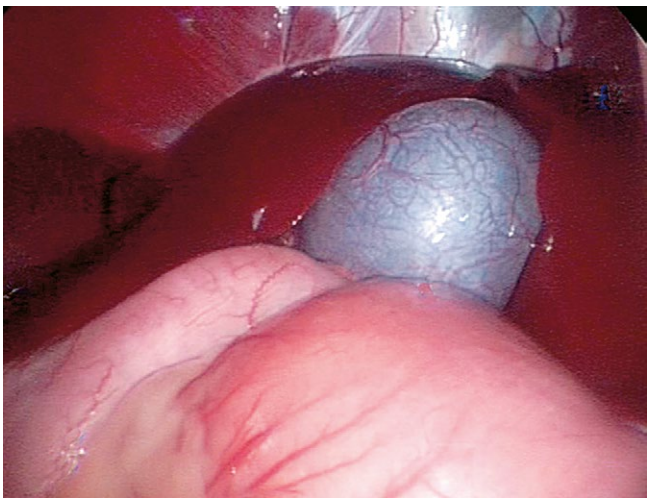


**Fig. 1-92** Liver, gallbladder, and intestine

Laparoscopic view through a right lateral abdominal approach showing the liver, gallbladder, and intestines of a normal dog.

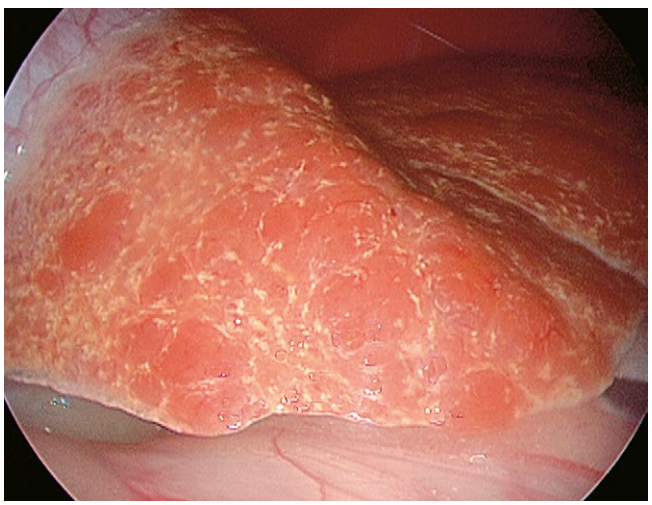


**Fig. 1-93** Nodular liver

View of a nodular liver in a dog with hepatocutaneous syndrome.

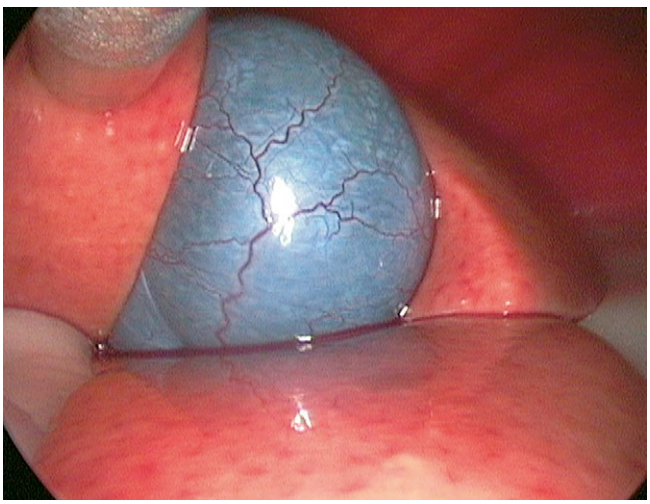


**Fig. 1-94** Hepatic lipidosis

View of the liver and gallbladder of a cat with idiopathic hepatic lipidosis.

lost during the procedure. If additional intestinal biopsies or other laparoscopic procedures are to be performed, the trocar cannula must be reintroduced through the abdominal incision, and the incision must be sealed around the cannula to reestablish a pneumoperitoneum. Some use a towel clamp or forceps to close the abdominal wall around the cannula.[8]

### 1.6.4.2 Liver biopsy

Laparoscopic liver biopsy is considered by many clinicians to be the preferred method of liver biopsy.[9,10] Often, other diagnostic modalities do not provide sufficient tissue or information on the gross appearance of the liver and adjacent organs (▶Fig. 1-92, ▶Fig. 1-93 and ▶Fig. 1-94). Either a right lateral or ventral approach can be used to evaluate most of the liver and extrahepatic biliary system. One can often examine approximately 80% of the hepatic surface but not the entire liver. An ultrasound examination prior to laparoscopy may help plan entry sites and areas to examine. Laparoscopic liver biopsies also provide enough tissue for culture, metal analysis, or other diagnostic uses (▶Chap. 1.8.2 and ▶Chap. 9.3).[1,11]

Prior to liver biopsy, coagulation parameters, including a buccal mucosal bleeding time, are frequently evaluated, but results do not always correlate with the risk of post-biopsy

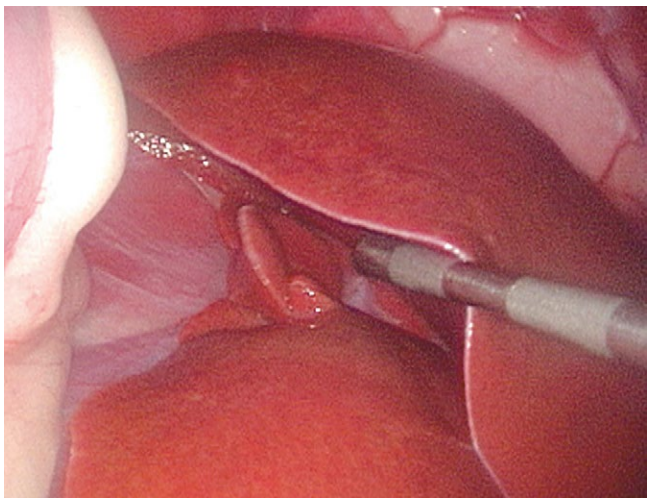


**Fig. 1-95** Palpation probe

View of a palpation probe with centimeter markings used to elevate a liver lobe in a normal dog.

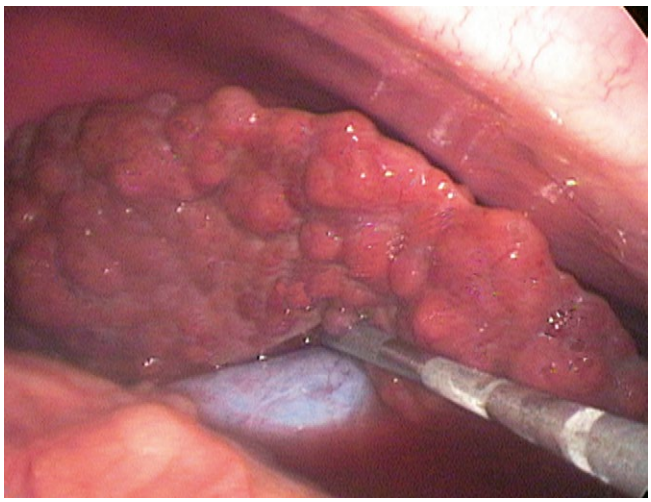


**Fig. 1-96** Hepatic cirrhosis

View of a palpation probe elevating a liver lobe in a dog with liver cirrhosis and ascites.

bleeding. Mild coagulopathies are generally considered as only a relative contraindication for hepatic biopsy. The high-risk patients are ones with anemia (hematocrit <30%), hypoalbuminemia, thrombocytopenia (<50,000/µL), or prolonged prothrombin time or activated thromboplastin time (>2× normal).[10] Once the liver and extrahepatic biliary system have been examined, palpated, and the decision to obtain a liver biopsy has been made, the palpation probe is removed (▶Fig. 1-95 and ▶Fig. 1-96). For liver biopsies, the author recommends using a 5 mm oval cup biopsy forceps. A recent study emphasized the benefit of laparoscopic cup "5×10 mm wedge" biopsies compared with 18 gauge needle biopsies finding that histopathology findings from evaluating the smaller needle biopsies correlated only in approximately 50% of the cases when compared with the larger laparoscopic cup biopsies.[11] The author will biopsy either at the edge of the liver or obtain samples over the surface of the liver. It is important to biopsy areas that appear normal as well as those that appear abnormal. Some authors suggest that biopsies taken at the edge of the liver may not reflect deeper lesions as the histopathology at the subcapsular edge of the liver is usually more reactive. However, the author believes that the samples collected by laparoscopic cup biopsy taken from the edges of the liver are so large that this is of little concern. In rare instances when a deep hepatic lesion is suspected but not readily evident over the surface of the liver, a biopsy needle can be directed into the lesion. Needles of 14–16 gauge are required to obtain samples of adequate size.

Once the location of the biopsy site is selected, the biopsy cups are opened, then closed around the sample area (▶Fig. 1-97). The author generally holds the cups tightly closed for approximately 30 seconds before pulling the sample away from the liver. Generally, 3–4 representative biopsy samples from different liver lobes should be taken. The author also takes a sample for hepatic copper analysis and culture (▶Chap. 9.5.4.2). Following a biopsy, the sites are visually monitored for excessive bleeding (▶Fig. 1-98). Usually, little, if any, blood (<0.5 mL) is lost at the biopsy site. If bleeding is considered to be excessive, several steps can be taken. First, the palpation probe can be directed to the biopsy site to apply pressure over the bleeding site. Alternatively, a small piece of saline-soaked Gel-Foam® or other coagulation material can be placed into the biopsy site using either laparoscopic grasping or biopsy forceps. In most cases, this is sufficient for controlling bleeding. If continued excessive bleeding occurs, electrocoagulation or other vessel sealing system may be required. The patient should be carefully monitored for the first 4 hours following the procedure, as that is the time period when postoperative bleeding may likely occur.

### 1.6.4.3 Pancreatic biopsy

Laparoscopic biopsy forceps are also used to biopsy the pancreas (▶Fig. 1-99 and ▶Fig. 1-100).[7,12,13] The author finds pancreatic biopsies to be generally free of complications, and a study evaluating laparoscopic pancreatic biopsies in normal dogs found no postoperative complications or evidence of secondary pancreatitis.[10] Indications for pancreatic biopsies include cases suspected of having either acute or chronic pancreatitis, pancreatic abscess (▶Fig. 1-101), cyst, or pancreatic neoplasia (▶Chap. 10.3). The author has used laparoscopy not only to confirm the presence of acute pan-

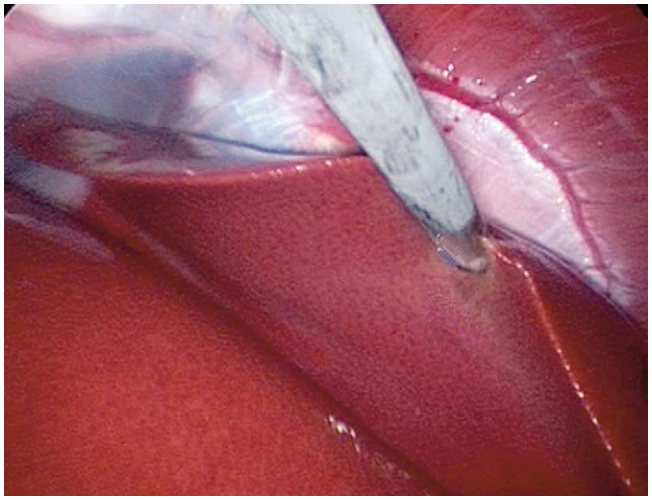


**Fig. 1-97** Liver biopsy

View of a liver biopsy taken at the edge of a liver lobe using an oval biopsy cup forceps.

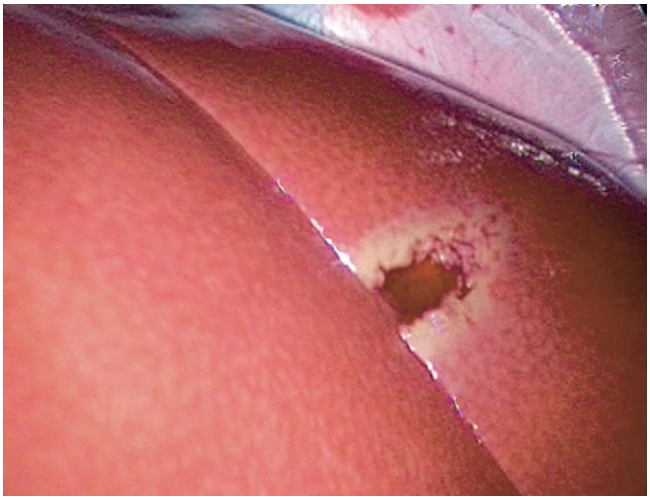


**Fig. 1-98** Liver after biopsy

View of the liver following a biopsy taken with an oval biopsy cup in a normal dog.

creatitis in a patient but also to place a jejunostomy feeding tube (▶Chap. 3.2). It is also possible to lavage the pancreatic area using laparoscopic guidance of a lavage and suction apparatus. Chronic pancreatitis is a common finding in the cat and is often associated with concurrent cholangitis or inflammatory bowel disease (IBD; ▶Fig. 1-102). Laparoscopy is well suited for the diagnosis of these conditions and the biopsy of all three organs.

Generally, "punch type" biopsy forceps work well for the collection of a pancreatic biopsy. Care should be taken if using larger 5-mm oval cup biopsy forceps because of the large sample size retrieved. When using the oval cup forceps, the author only fills half the cup with pancreatic tissue. For evaluation of the pancreas, a right lateral approach is ideal. This approach gives an excellent view of the duodenum, the right limb of the pancreas, as well as the extrahepatic biliary system and the liver. The left limb of the pancreas is very difficult to examine and requires a ventral approach and retraction of the omentum. The suggested best biopsy location is on the edge of the right limb of the pancreas, away from the pancreatic ducts that traverse the center of the gland and avoiding the location where they enter the proximal duodenum. The author generally only takes one or two representative biopsy samples of the pancreas unless

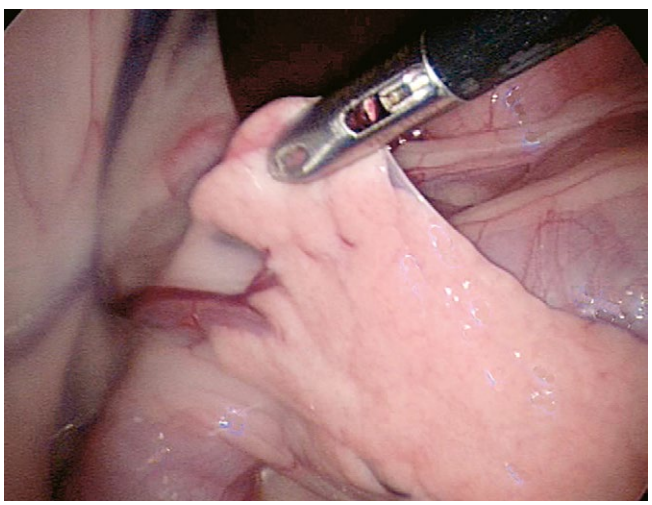


**Fig. 1-99** Pancreatic biopsy

View of an oval cup biopsy forceps taking a pancreatic biopsy in a normal dog.

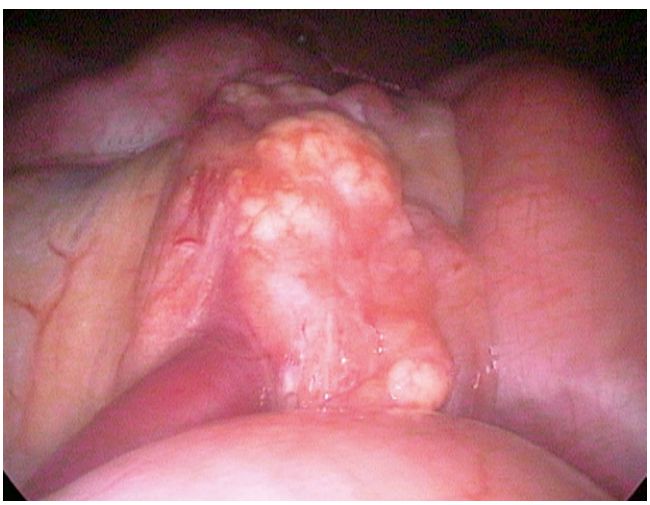


**Fig. 1-100** Pancreatic atrophy

A laparoscopic view of pancreatic atrophy in a dog with clinical and laboratory evidence of exocrine pancreatic insufficiency.

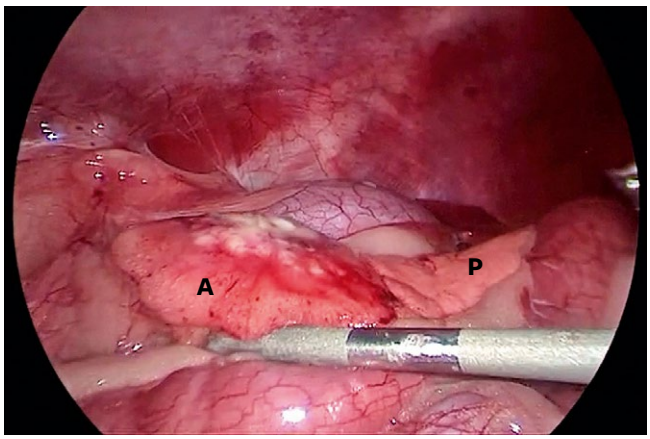



**Fig. 1-101** Pancreatic abscess
View of the right limb of the pancreas showing a local abscess (**A**) with the palpation probe below and more proximal normal pancreas (**P**).

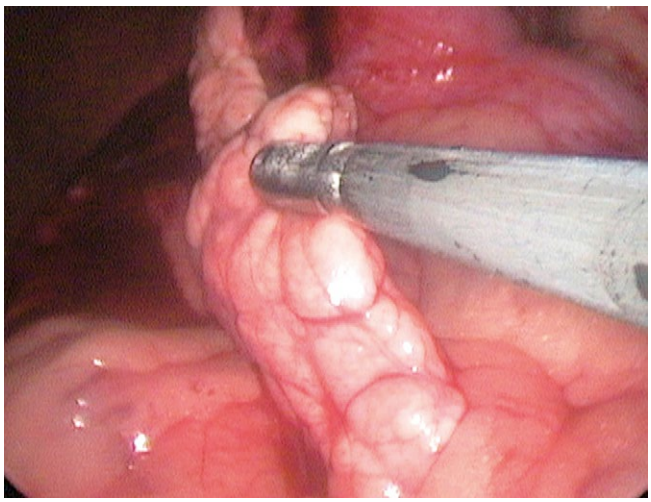


**Fig. 1-102** Chronic fibrosing pancreatitis
View of an oval cup biopsy forceps taking a pancreatic biopsy from a cat having chronic fibrosing pancreatitis.

multiple lesions are present. Because the pancreas is freely movable within the omentum when pulling the biopsy forceps away, and if the biopsy sample remains partially attached to the pancreas, the entire limb of the pancreas may follow the forceps to the cannula, at which point the pancreas will fall back into the abdomen.

#### 1.6.4.4 Other biopsy techniques

A number of other biopsy techniques can also be performed using laparoscopic direction, including biopsy of the kidneys, mass lesions, lymph nodes, spleen, and other organs. Splenic biopsies are generally safe to perform using cup-type biopsy forceps. Technique, precautions, and coagulation control are similar to those of a liver biopsy. Laparoscopy may also be used to determine the cause of an unexplained abdominal effusion. The fluid is aspirated under laparoscopic guidance to enable examination of the abdominal contents.

### 1.6.5 Ancillary procedures

Additional diagnostic procedures that can also be performed using laparoscopic guidance include cholecystocentesis, cholecystography, and portography.

#### 1.6.5.1 Cholecystocentesis and cholecystography

The gallbladder and common bile duct are best evaluated in a right lateral or ventral approach. The normal gallbladder should be soft and fluctuant, and the ductal system should not be distended. Obstructive biliary tract disease (▶Chap. 9.6.1) is often associated with a hard, firm gallbladder and a distended duct system (▶Fig. 1-103). In these cases, the liver and biliary ducts are also often bile stained, and the biliary lymphatics are generally distended.

When inflammatory or infectious biliary tract disease is suspected (▶Chap. 9.6.3), a laparoscopic-guided cholecystocentesis is performed using a 20–22 gauge, 10 cm or longer needle to collect a sample for culture and cytology.[1] Bile cytology and culture often aid in the diagnosis of liver disorders (▶Chap. 9.5).[14] The needle is directed through the abdominal wall near the gallbladder; the gallbladder is punctured under visual direction, and the contents are aspirated (▶Fig. 1-104).

**NOTE**
It is important to remove as much bile as possible to empty the gallbladder and prevent leakage when the needle is removed.

The bile should be submitted for both culture and cytology. It is also important to make sure the aspiration needle is placed through the abdominal wall caudal to the diaphragm. Piercing the diaphragm may produce a pneumothorax from abdominal gas passing into the thoracic cavity through the needle track in the diaphragm.

An alternative technique for gallbladder aspiration involves passing the needle through the right middle lobe of the liver and then into the gallbladder, where it is attached to the liver

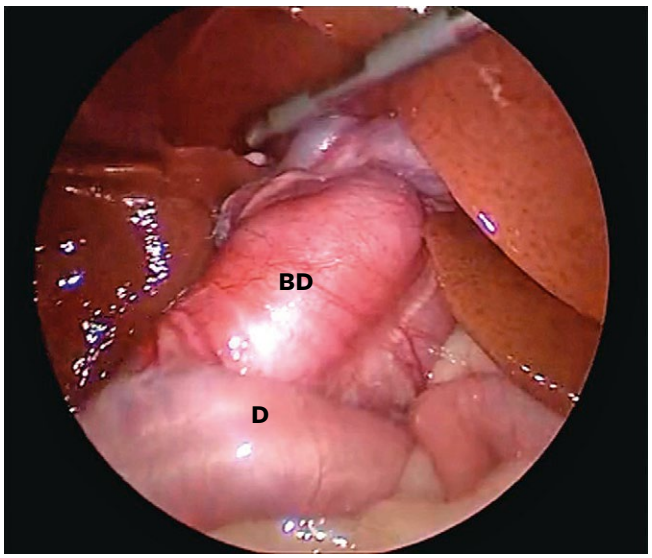



**Fig. 1-103** Bile duct obstruction

View of a dilated common bile duct (**BD**) due to choleliths in the distal BD of a cat before entering the duodenum (**D**).

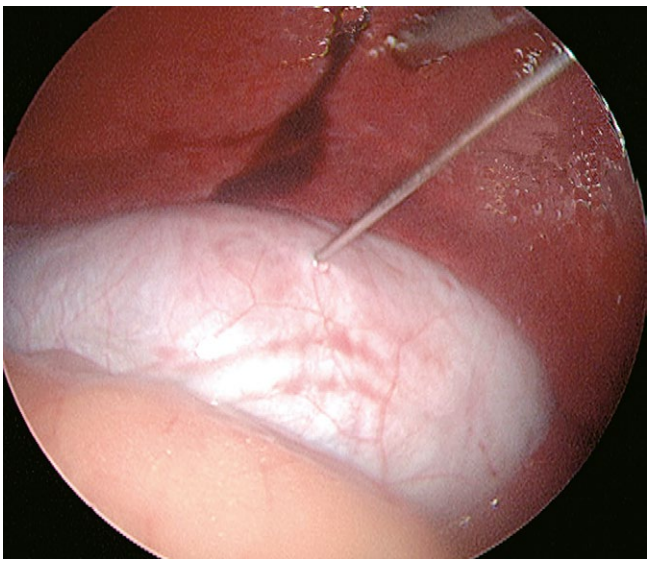


**Fig. 1-104** Cholecystocentesis

View of a laparoscopy-guided cholecystocentesis using a 20G needle.

surface. With this technique, bile leakage is minimal because bile drains back into the liver and not into the peritoneal cavity. Performing this technique can only be accomplished in a ventral abdominal approach to avoid passing the aspiration needle through the diaphragm.

If obstruction of the extrahepatic biliary system is suspected, a contrast study can also be performed following cholecystocentesis. A needle is placed into the gallbladder, bile is removed, and a radiopaque iodine contrast agent designed for IV use is injected into the gallbladder lumen to perform cholecystography.[1] A volume of 5–15 mL is usually adequate to delineate abnormalities. Care should be taken not to overly distend the gallbladder to avoid leakage. Static radiographs or fluoroscopy are then used to evaluate the bile duct system for any blockages. The contrast agent should normally flow freely into the duodenum.

### 1.6.5.2 Portography

It is possible to also evaluate the portal system using laparoscopic guidance.[8] Both congenital and acquired portal-systemic shunts can be identified using this technique. This procedure should always be performed in conjunction with a liver biopsy. Splenoportography involves placing an iodine radiographic contrast medium into the portal vascular system to outline portal blood flow downstream to where the splenic or mesenteric vein enters the portal vein. Laparoscopic portography should be performed in the radiology suite so that radiographs can be taken immediately following injection.

Splenoportography requires a left lateral approach. The spleen is located, and an 18–20 gauge, 10 cm spinal needle with stylet is inserted through the ventrolateral abdominal wall near the area of the spleen. The needle is inserted into the body of the spleen parallel to the long axis of the spleen. The needle should be inserted 1–3 cm into the splenic parenchyma. Once the needle is firmly seated in the spleen, the telescope is withdrawn, and the pneumoperitoneum is evacuated. The needle hub is then attached to extension tubing and gently flushed with several milliliters of heparinized saline. It is now also possible to measure splenic pulp pressure in centimeters of water by attaching the extension tubing to a standard water manometer zeroed to right atrial pressures. The pressure in the splenic parenchyma becomes a reflection of portal blood pressure. Normal splenic pulp pressures range from 10–15 cm of water.[8] Animals with portal hypertension will have much higher pressures.

Following pressure measurements, an iodine contrast agent intended for IV use is hand-injected at a dose of 0.25–0.5 ml/kg body weight over approximately 10–20 seconds. Radiographs are obtained halfway through the injection and immediately after completing the injection. In almost all cases, one can delineate the portal blood flow to document congenital or acquired shunting. We find this procedure to be safe and associated with minimal complications.

An alternative method for portography and pressure measurements involves exteriorizing a jejunal vein for direct catheter placement into that vein.

#### 1.6.5.3 Other procedures

Several other laparoscopic procedures include gastrostomy or jejunostomy feeding tube placement and preventive laparoscopic-assisted gastropexy.[15] For these three techniques, the bowel is exteriorized through a trocar-cannula site. Feeding tubes are then placed, or, in the case of the preventive gastropexy, the antral muscle is sutured to the abdominal wall. Laparoscopic-assisted GI foreign body removal has also been described.[16]

### 1.6.6 Complications of laparoscopy

The complication rate of laparoscopy is low.[17,18] In a review by the author of a series of cases involving diagnostic laparoscopy, the complication rate was <2%.[1] Potential complications are listed in ▶ Tab. 1-21. Serious complications include anesthetic- or cardiovascular-related death, bleeding, or air embolism. A pneumothorax can occur during insufflation when a patient has an undiagnosed diaphragmatic hernia. Minor complications are generally operative and are associated with inexperience or failure to understand the limitations and potential complications.

**Tab. 1-21** Potential laparoscopic complications

| Anesthesia-related |
|---|
| **Veress needle/trocar insertion** |
| • Injury to abdominal wall vasculature<br>• Penetration of organs<br>• Perforation of hollow viscus |
| **Insufflation** |
| • Subcutaneous emphysema<br>• Peritoneal tenting<br>• Inappropriate insufflation<br>• Pneumothorax<br>• Gas embolism |
| **Operative complications** |
| • Bleeding<br>• Tissue injury |
| **Technical problems** |
| • Lack of operator experience<br>• Equipment-related problems |

**KEY FACTS**

- Laparoscopy is a valuable diagnostic tool used in small animal gastroenterology.
- Laparoscopy is less invasive than exploratory laparotomy for obtaining biopsy samples from organs of the abdominal cavity and is associated with a low complication rate.
- Laparoscopy is considered the best means for obtaining liver biopsies for histology, culture, and metal analysis.
- Laparoscopic pancreatic biopsies can confirm pancreatitis and/or pancreatic neoplasia and are rarely associated with complications.
- Full-thickness intestinal biopsies can be obtained using laparoscopy-assisted techniques.

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
svg.to/9842-01-06

## 1.7 Cytology

Jelena Palić, Johannes Hirschberger

### 1.7.1 Introduction and technique

Fine-needle aspiration (FNA) is a minimally invasive technique. FNA of internal organs, such as the liver, pancreas, stomach, and intestines, is usually well tolerated in small animal patients and can be performed immediately after identifying an ultrasonographic abnormality, even without sedation or local anesthesia in some cases. Despite some limitations, this technique has good diagnostic utility, especially when interpreted together with the patient's clinical signs and physical examination, hematology, clinical chemistry, and diagnostic imaging findings. FNA should be performed under ultrasonographic guidance. To avoid excessive blood contamination of FNA specimens from organs with a rich blood supply (e.g., liver, spleen), the duration and attempts of aspiration should be kept as minimal as possible. The operator should only aspirate during brisk advancement of the needle into the organ and approximately one second. Commercially available aspiration guns can also be used for obtaining FNA samples. Alternatively, a needle can be merely advanced into the organ without subsequent aspiration.

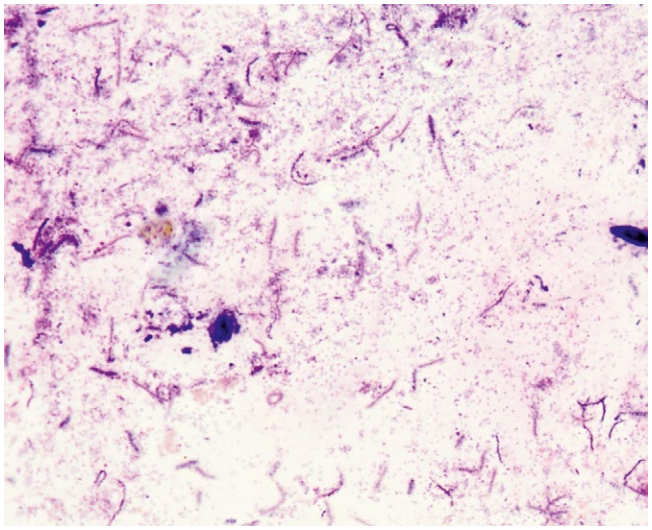


**Fig. 1-105** *Helicobacter*-like bacteria in a gastric brush preparation from a 6-year-old male domestic shorthair cat with chronic weight loss, anorexia, and chronic mild lymphocytic gastritis on histopathology

Numerous large spiral-shaped bacteria are embedded in eosinophilic mucus. These organisms can be found in asymptomatic dogs and cats and diseased patients (modified Wright's stain, original magnification 1000x).[2,3]

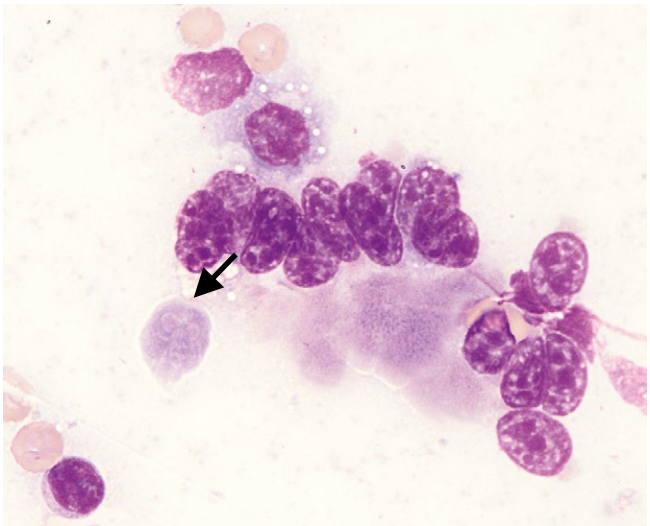


**Fig. 1-106** *Giardia duodenalis* infection in a dog with ascites and chronic moderate to marked lymphoplasmacytic enteritis on histopathologic examination

Note the pear-shaped *Giardia* trophozoite (**arrow**), one granular lymphocyte, partially preserved plasma cells, and intestinal epithelial cells (modified Wright's stain, original magnification 1000x).

### 1.7.2 Stomach and intestines

FNA and brush cytology preparations of lesions in the GI tract detected during ultrasonographic or endoscopic evaluation of the patient, and also impression smears of endoscopically obtained biopsy specimens, can be used to identify infectious organisms (▶Fig. 1-105 and ▶Fig. 1-106) and diagnose inflammation (▶Fig. 1-107) or neoplasia (▶Fig. 1-108).[1]

#### 1.7.2.1 Gastrointestinal inflammation

Gastric and intestinal inflammation can be associated with numerous etiologies and, depending on the predominant cell population present, described as neutrophilic, lymphoplasmacytic, eosinophilic, or granulomatous.[3] Rectal scrapings containing fecal material can be used to diagnose infectious organisms, such as *Histoplasma capsulatum* (▶Fig. 1-109), *Prototheca* spp. (▶Chap. 7.3.1.5), and different amoeba species.[2,3]

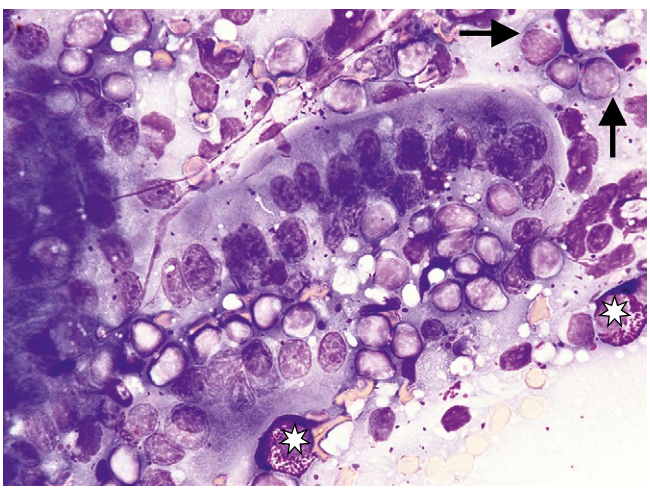


**Fig. 1-107** Lymphocytic enteritis in a 10-year-old female Yorkshire terrier with ascites and panhypoproteinemia

The majority of lymphocytes are lined along the columnar intestinal epithelial cells. The lymphocyte population is mixed, with some granular lymphocytes present (**arrows**). Two mast cells (**asterisks**) are also seen (modified Wright's stain, original magnification 1000x).

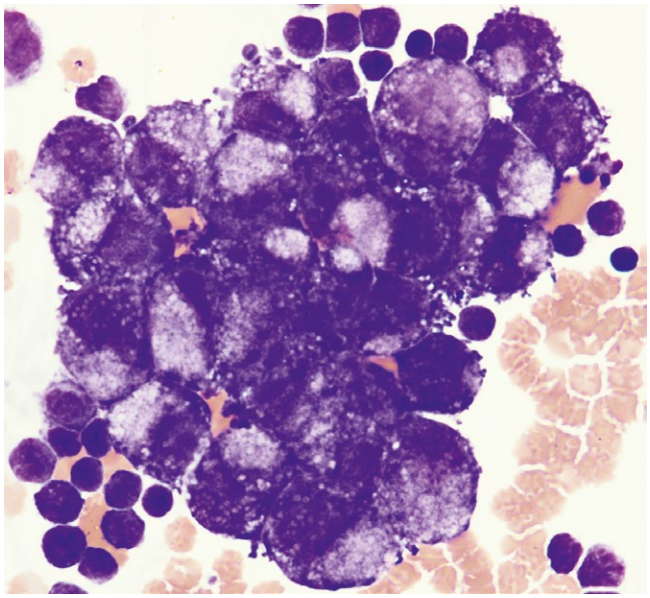


**Fig. 1-108** Gastric carcinoma in an 8-year-old male Hovawart with a thickened gastric wall on ultrasonographic examination

Neoplastic epithelial cells show marked anisocytosis, prominent nucleoli, increased nuclear: cytoplasmic (N:C) ratio, and dark basophilic vacuolated cytoplasm. Lymphocytic inflammation is also present (modified Wright's stain, original magnification 1000x).

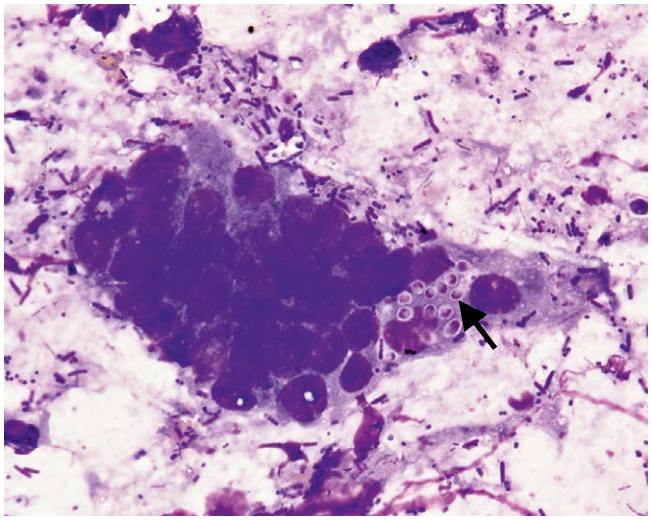


**Fig. 1-109** *Histoplasma capsulatum* organisms found in the rectal scraping of a 3-year-old male Yorkshire terrier with chronic watery diarrhea and hematochezia

Note the macrophage containing small oval yeast forms (**arrow**) measuring 2–4 µm (modified Wright's stain, original magnification 1000x).

### 1.7.2.2 Gastrointestinal neoplasia

Benign and malignant primary neoplasms (epithelial, round cell, and spindle cell) can occur in the stomach (▶Chap. 6.3.4) and intestines (▶Chap. 7.3.9 and ▶Chap. 8.3.7) in addition to non-neoplastic lesions (e.g., hyperplastic polyps).[4,5] Epithelial neoplasms of the stomach and intestines are adenomas, adenocarcinomas, and neuroendocrine carcinomas.[4] Common primary round cell tumors in the stomach and intestines are gastrointestinal lymphoma, plasma cell tumors, and mast cell tumors. The most common neoplasia in both the stomach and intestines is adenocarcinoma (▶Fig. 1-110) in dogs and lymphoma (▶Fig. 1-111) in cats.[4,5] Gastrointestinal lymphoma (▶Chap. 11.3) can be part of a multicentric disease or present a primary alimentary lymphoma.

In cats, alimentary lymphomas are categorized into three separate entities:

- Large granular lymphocyte (LGL) lymphoma (in most cases of T-cell origin; ▶Fig. 1-112)
- Intermediate/high-grade alimentary lymphoma (variably of B- or T-cell origin; ▶Fig. 1-113)
- Low-grade alimentary lymphoma (epitheliotropic small T-cell lymphoma)[6]

Small T-cell lymphoma in cats (also named enteropathy-associated T-cell lymphoma [EATL] type 2) can be difficult to differentiate from lymphoplasmacytic enteritis. A stepwise diagnostic algorithm that uses histologic assessment, followed by immunophenotyping and clonality testing, is recommended for more accurate differentiation.[7]

Similarly challenging is the diagnostic differentiation of canine intestinal lymphoma (that is not large-cell) from lymphoplasmacytic enteritis.[8] Spindle cell neoplasia commonly described in the GI tract includes leiomyoma, leiomyosarcoma, and gastrointestinal stromal tumors (GIST). Cytologic differentiation of these tumors is challenging, and immunohistochemistry (IHC) is often necessary (▶Fig. 1-114).[4]

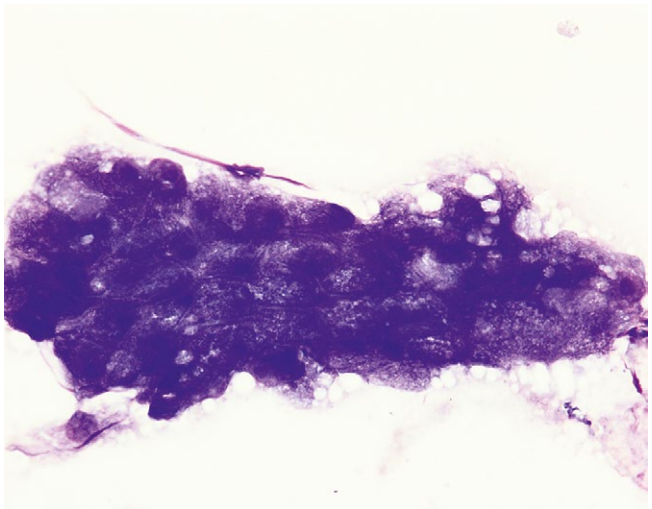


**Fig. 1-110** Intestinal adenocarcinoma in a 9-year-old male domestic shorthair cat

Abdominal ultrasonography revealed a mass at the ileocolic junction and enlarged mesenteric lymph nodes. A mucinous adenocarcinoma with intraabdominal metastasis was diagnosed on histopathology. Epithelial cells with large nuclei and prominent nucleoli are seen on cytology (modified Wright's stain, original magnification 1000x).

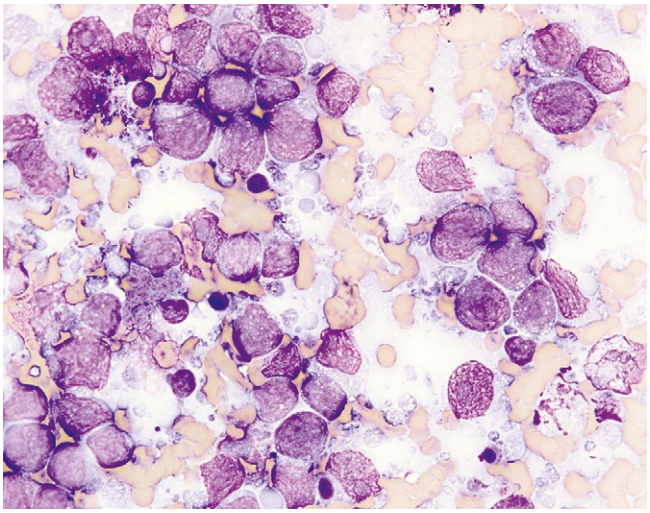


**Fig. 1-111** Gastric lymphoma in a 17-year-old female domestic shorthair cat with recurrent vomiting and increased liver enzyme activities

The gastric wall was thickened on ultrasonographic examination, with loss of wall layering, and the gastric lymph nodes were enlarged and hypoechogenic. Lymphocytes are large, with one prominent nucleolus and a rim of cytoplasm containing fine punctate vacuoles. Gastric lymphomas in cats are usually of B-cell origin (modified Wright's stain, original magnification 1000x).[3,6]

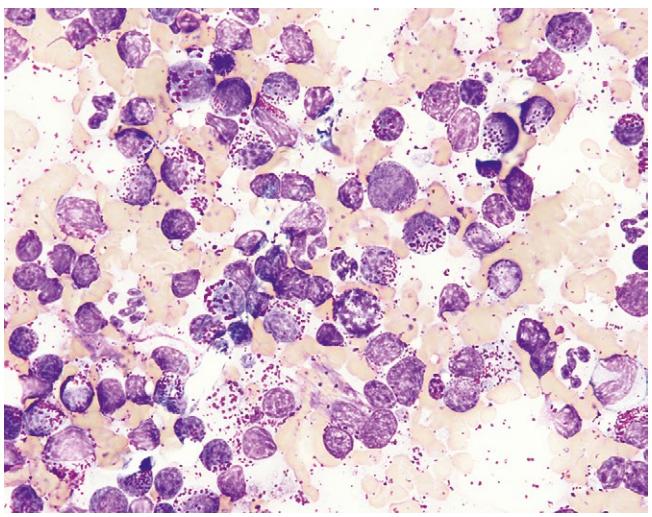


**Fig. 1-112** Large granular lymphocyte lymphoma in a 6-year-old female British shorthair cat with an intraabdominal mass (5.5×5.3 cm) in the ileocecal region

Note the large lymphocytes with coarsely stippled chromatin and variably sized magenta cytoplasmic granules. Numerous free granules from lysed cells are seen in the background (modified Wright's stain, original magnification 1000x).

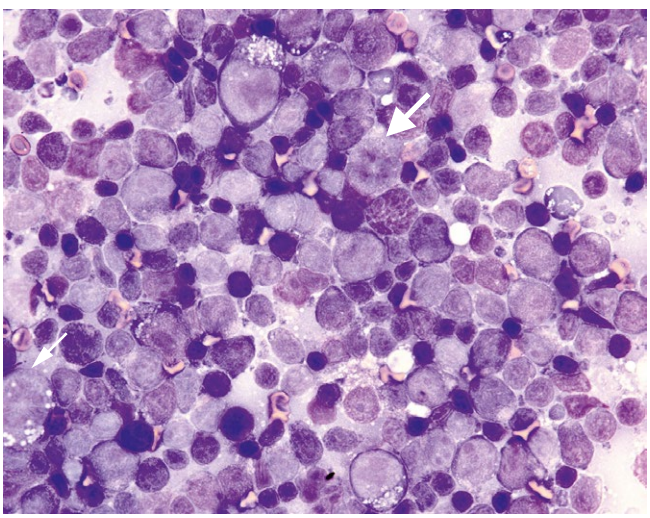


**Fig. 1-113** Intestinal T-cell lymphoma in a 14-year-old male domestic shorthair cat with weight loss and a large jejunal mass

Fine-needle aspiration (FNA) cytology shows a mixed population of lymphocytes with large immature lymphocytes predominating. Large lymphocytes have round to indented nuclei with finely stippled chromatin, one or more prominent nucleoli, and scant cytoplasm. Note also the two bizarre mitotic figures marked with **arrows** (modified Wright's stain, original magnification 1000x).

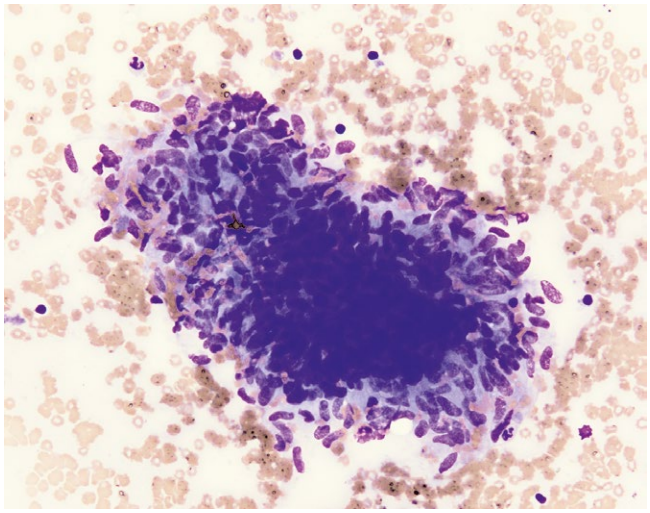


**Fig. 1-114** Gastrointestinal stromal tumor in an 11-year-old male mixed-breed dog with a duodenal mass

A tight group of slender spindle cells with oval nuclei and pale cytoplasm is seen. Neoplastic cells stained positive for KIT (CD117) and negative for smooth muscle actin on immunohistochemistry (modified Wright's stain, original magnification 500x).

**KEY FACTS**

- Fine-needle aspiration (FNA) is usually without complications.
- Tumors of the gastrointestinal tract can often be diagnosed based on cytology.
- Infectious organisms are routinely identified on cytology.
- Vacuolar hepatopathy displays characteristic cytological features.
- Histopathologic examination is necessary for the diagnosis of feline lymphocytic cholangitis and canine chronic hepatitis.
- Full-thickness intestinal biopsy is recommended for differentiation of enteropathy-associated T-cell lymphoma type 2 and lymphoplasmacytic enteritis in cats.

## 1.7.3 Liver

Liver cytology can be used to assess non-neoplastic diseases and establish a diagnosis of neoplasia (▶Chap. 9.5.7). A comparison of liver cytology and biopsy diagnoses suggests that cytologic evaluations are useful for determining disease processes in cases with diffuse lesions (e.g., discrete vacuolar changes, diffuse neoplasia) because these are more likely to be represented in the FNA.[9] On the contrary, lesions with zonal distribution and architectural changes are more difficult to assess and can be missed.[9] Evaluating inflammation in canine liver aspirates by cytology and histopathology has a good correlation when suppurative and chronic active inflammation is present.[10] Lymphocytic hepatitis, however, is commonly misdiagnosed by cytology.[10] It is important to acknowledge the benefits and limitations of cytology when choosing diagnostic modalities and interpreting the findings.[10]

### 1.7.3.1 Normal liver cells

Hepatocytes observed on cytology preparations can be present as individual cells or in sheets and clusters. Normal hepatocytes are large oval to polygonal cells with a centrally located round nucleus containing coarsely stippled chromatin and one prominent round nucleolus. The nuclear: cytoplasmic (N:C) ratio ranges from 1:4 to 1:5. Hepatocyte cytoplasm is lightly basophilic, with a slightly granular appearance. Binucleated hepatocytes can occasionally be seen, noting that their number is usually higher in older dogs. Sheets of uniform-appearing biliary epithelial cells and mesothelial cells can also be seen on cytology preparations if aspirated during sampling. Leukocytes detected on cytology may originate from peripheral blood contamination and do not necessarily indicate an inflammatory process in the liver. Therefore, this finding should be interpreted relative to erythrocytes and the complete blood cell count (CBC).

### 1.7.3.2 Non-neoplastic disorders

Non-neoplastic changes that can be observed on cytologic examination of the liver include nodular hyperplasia, cytoplasmic and/or nuclear changes, pigments, inflammation, amyloidosis, and extramedullary hematopoiesis.[12]

#### 1.7.3.2.1 Nodular hyperplasia

Nodular hyperplasia of the liver parenchyma is often found in older dogs. It cannot be distinguished cytologically from normal hepatocytes or hepatocytes obtained from regenerative nodules, hepatocellular adenoma, or well-differentiated hepatocellular carcinoma.

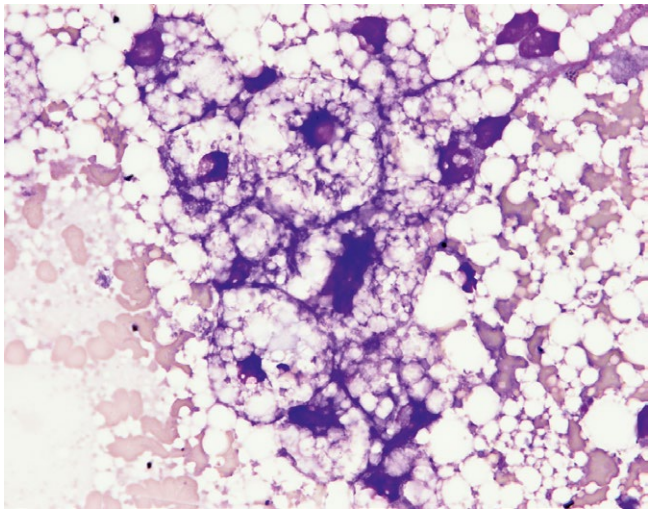


**Fig. 1-115** Hepatic lipidosis in a 9-year-old male domestic shorthair cat with anorexia, increased liver enzyme activities, and hyperbilirubinemia

Hepatocytes are distended by variable-sized, discrete, and well-demarcated clear vacuoles (modified Wright's stain, original magnification 1000x).

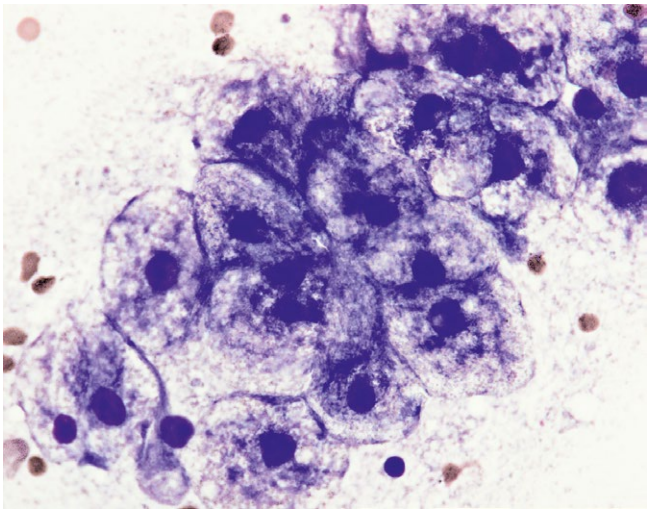


**Fig. 1-116** Hepatic glycogen accumulation in a 10-year-old mixed breed female dog receiving long-term glucocorticoid treatment due to immune-mediated thrombocytopenia

Hepatocytes are swollen and have a moth-eaten appearance, which is more severe at the edges of the cells and extends towards the centrally located nuclei (modified Wright's stain, original magnification 1000x).

#### 1.7.3.2.2 Cytoplasmic and nuclear changes

Cytoplasmic changes in hepatocytes can be seen with metabolic diseases and secondary to hepatocellular injury.[12,13] The accumulation of lipids in hepatocytes (microvesicular or macrovesicular changes) is termed hepatic lipidosis (▶Chap. 9.5.4.1.1). Feline hepatic lipidosis is characterized by the accumulation of excessive triglycerides in more than 80% of the hepatocytes, resulting in a greater than 50% increase in liver weight, secondary impairment of liver function, and intrahepatic cholestasis.[6] The primary cause for this condition is a negative energy balance, usually caused by a prolonged period of anorexia. Commonly observed diseases associated with the development of feline hepatic lipidosis are diabetes mellitus, pancreatitis, inflammatory hepatobiliary disease, gastrointestinal disease, renal failure, and neoplasia.[6] On cytology, lipid vacuoles are clear and sharply delineated (▶Fig. 1-115). In contrast to the well-delineated vacuoles seen with lipid accumulation, glycogen accumulation in hepatocytes (due to exogenous glucocorticoid administration or spontaneous hyperadrenocorticism; ▶Chap. 9.5.4.1.5) presents a diffuse vacuolar change, also termed vacuolar rarefaction (▶Fig. 1-116).[12,13] Similar cytoplasmic changes can also be observed in hepatocellular injury caused by hypoxia or hepatic toxins (▶Chap. 9.5.1). In those cases, the water content of hepatocytes is increased (also termed hydropic or ballooning degeneration).[12]

In dogs with infectious canine hepatitis (caused by canine adenovirus-1; ▶Chap. 9.5.2.2.1), large magenta-colored nuclear inclusions can be detected in affected hepatocytes.[4]

Hepatocellular necrosis is cytologically characterized by the presence of pyknotic nuclei and swollen, eosinophilic cytoplasm in individual cells or a large amount of amorphous basophilic necrotic material.[13] Chronic inflammation, chemical and toxic damage leading to hepatocellular necrosis, and apoptosis initiates a repair process of the hepatic parenchyma known as hepatic fibrosis (▶Chap. 9.5.5.2.4). Because this is a structural change, histopathologic examination and special stains are the gold standard for a definitive diagnosis and grading of fibrosis (▶Chap. 1.8.2).[12,13] A tentative cytologic diagnosis of hepatic fibrosis can be made when increased numbers of spindle cells and mast cells are observed among hepatocytes (▶Fig. 1-117).[15]

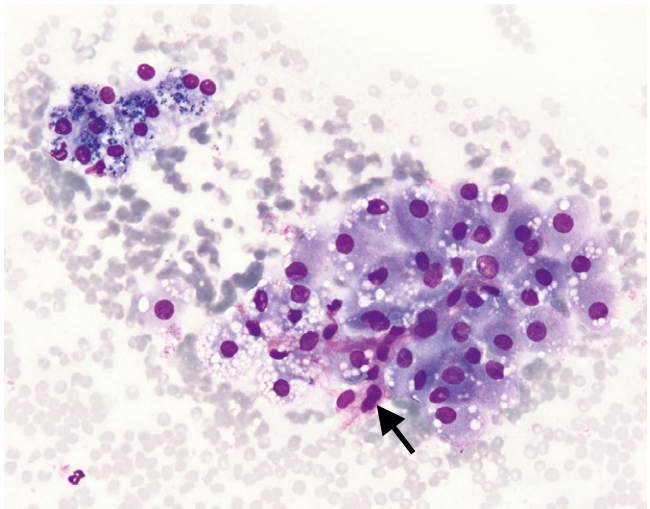


**Fig. 1-117** Mild lipid vacuolization and liver fibrosis in an 11.5-year-old female Yorkshire terrier with increased liver enzyme activities and a heterogeneous liver parenchyma with possible fibrotic liver nodules on ultrasonographic examination

Several spindle cells with ovoid nuclei and elongated eosinophilic cytoplasm are seen between hepatocytes (**arrow**). A cluster of hepatocytes with cytoplasmic blue-green lipofuscin pigment is present in the upper left corner (May-Grünwald-Giemsa stain, original magnification 500x).

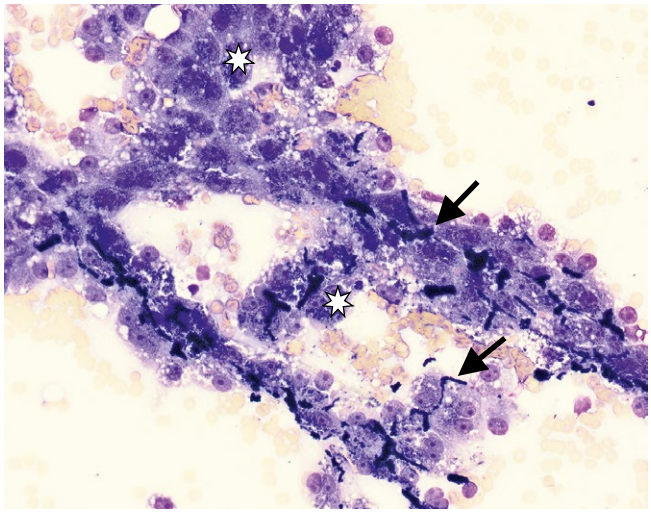


**Fig. 1-118** Cholestasis in an 8-year-old neutered male Labrador retriever with an acute onset of anorexia and lethargy, increased liver enzyme activities, hyperbilirubinemia, hypoproteinemia and hypoalbuminemia, and hepatic enlargement on ultrasonographic evaluation

The dog was diagnosed with pancreatic adenocarcinoma and hepatic metastasis. Note the blue-green intracellular bile pigment (**asterisks**) and blue-black bile canalicular plugs (accumulations of bile within the biliary canaliculi, marked with **arrows**) (modified Wright's stain, original magnification 500x).

#### 1.7.3.2.3 Pigments

Pigments that are commonly seen on liver cytology include bile, lipofuscin, hemosiderin, and copper.[12,13] **Bile** is a dark green-blue to blue-black pigment that can accumulate in hepatocytes or bile canaliculi in several pathologic conditions (▶Fig. 1-118). Accumulation and retention of bile is termed cholestasis. **Lipofuscin** granules, a normal finding in hepatocytes of older animals, cannot be reliably differentiated on cytology from intra-cytoplasmic bile pigment (▶Fig. 1-117). **Hemosiderin** is seen as a dark blue-black pigment and is associated with hemolytic disease or congenital portosystemic shunts. **Copper accumulation**, noted as light blue-green refractile crystalline granules within hepatocytes, causes copper-associated hepatitis and cirrhosis in particularly predisposed dog breeds (Bedlington terriers, Labrador retrievers, West Highland white terriers, skye terriers, Dalmatians, and Doberman pinschers; ▶Chap. 9.5.4.2).[12,13,16] Differentiation of various hepatic pigments, lipids, and glycogen can be achieved using special stains (▶Tab. 1-22), which may easily be performed on cytologic preparations.[12,13,17]

**Tab. 1-22** Special stains used for differentiating hepatic pigments, lipids, and glycogen.[12,13,17]

| Pigment | Special stain |
|---|---|
| Bile | Hall's |
| Lipofuscin | Long Ziehl-Neelsen, Luxol fast blue |
| Hemosiderin | Prussian blue |
| Copper | Rubeanic acid, rhodanine |
| Lipid | Oil red O (ORO), Sudan III |
| Glycogen | Periodic acid-Schiff (PAS) |

#### 1.7.3.2.4 Inflammation and infectious organisms

Inflammatory liver disorders are classified based on the predominant leukocyte population (▶Chap. 9.5.5).[12,13] Neutrophilic inflammation has been reported in sterile inflammatory processes, feline neutrophilic cholangitis, FIP, or septic inflammation (with the finding of bacteria and markedly degenerate neutrophils).[12,13] On cytology, the neutrophils are detected within hepatocyte clusters (▶Fig. 1-119).[10] Lymphocytic inflammation is common in cats and rarely reported in dogs.[13] Feline lymphocytic cholangitis (▶Chap. 9.6.3.2) is characterized by slowly progressing illness, hepatomegaly, and/or ascites. It is suspected to be immune-mediated and possibly associated with bacterial infections. Liver histopathology is required to detect the moderate to marked aggre-

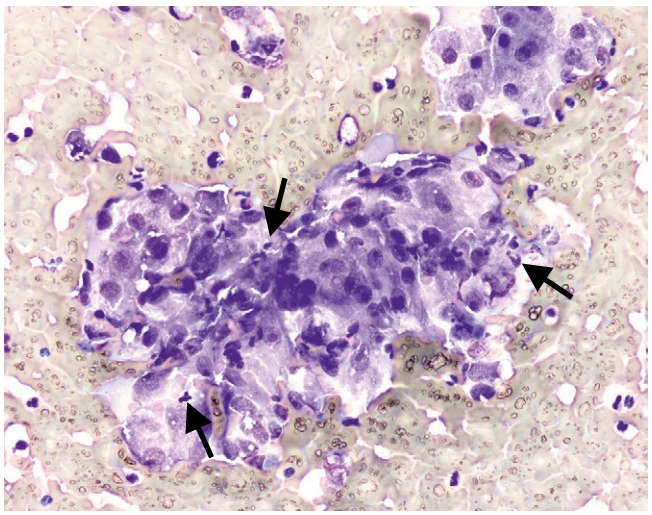


**Fig. 1-119** Neutrophilic inflammation in a 14-year-old diabetic male dog with weight loss and increased liver enzyme activities

Note the degenerate neutrophils (**arrows**) associating with hepatocyte clusters (modified Wright's stain, original magnification 500x).

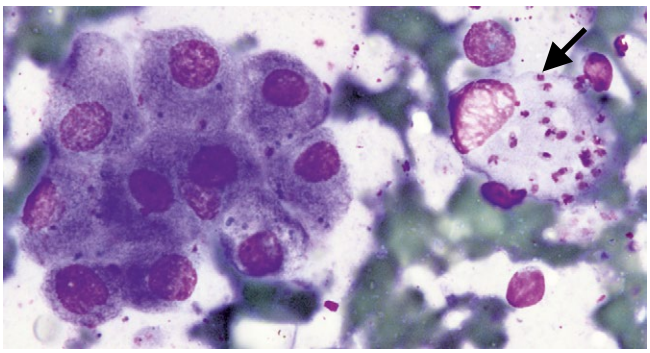


**Fig. 1-120** *Leishmania* spp. infection in a 3-year-old male golden retriever with a 6-month history of intermittent epistaxis, generalized lymphadenopathy, and weight loss

Splenomegaly and hepatomegaly were seen on ultrasonography. The macrophage on the right side of the image contains multiple *Leishmania* spp. Amastigotes (**arrow**). A well-differentiated hepatocyte cluster is seen on the left side (May-Grünwald-Giemsa stain, original magnification 1000x).

gates of small lymphocytes infiltrating the portal areas, often associated with variable degrees of portal fibrosis and bile ductular proliferation.[10] In some cases, IHC and clonality testing can assist in differentiating lymphocytic cholangitis from lymphoma.[18] Mixed inflammation with variable numbers of neutrophils, macrophages, and small lymphocytes is a non-specific finding associated with mycotic, protozoal, and mycobacterial infections.[12,13] Canine idiopathic chronic hepatitis (▶Chap. 9.5.5.4) is characterized by the presence of lymphocytic, plasmacytic, or granulomatous inflammation, hepatocyte cell death, fibrosis, and regeneration, progressing to end-stage cirrhosis.[19] Inflammation can often be missed on cytology if areas of fibrosis are sampled, or the distribution is not uniform. Histopathologic evaluation and copper quantification should be performed in all cases.[19] Eosinophilic inflammation can be a part of a mixed inflammatory response or can be a primary response in patients with eosinophilic enteritis, systemic mast cell tumors, hypereosinophilic syndrome, or the presence of liver flukes (*Platynosomum* spp.) in some parts of the United States (Florida, Caribbean Islands, and Hawaii).[12,13] Infectious organisms can also be detected during cytologic examination (▶Fig. 1-120 and ▶Fig. 1-121).

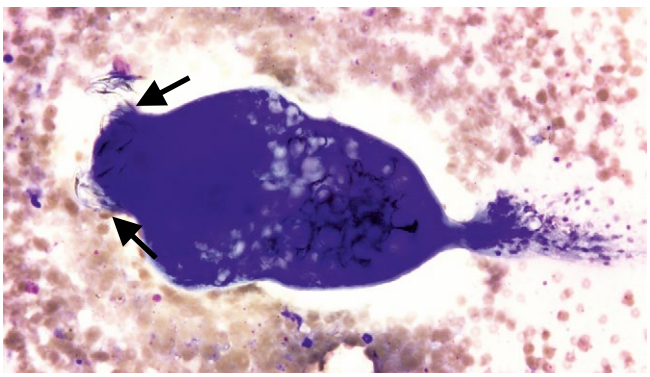


**Fig. 1-121** *Echinococcus multilocularis* larval stage infection in a 3-year-old female Labrador retriever

Several liver lobes had multiple avascular fluid-filled cysts (up to 20 cm diameter) with an irregular wall and hypoechoic content on ultrasonography (alveolar echinococcosis). Note the protoscolex (**arrow**) with hooks (modified Wright's stain, original magnification 500x).

#### 1.7.3.2.5 Amyloidosis

Amyloid deposition in the liver is a familial disease in some breeds (Chinese shar-pei dogs, Abyssinian, Oriental shorthair, and Siamese cats) and can result from chronic inflammation.[12,13] Amyloid is seen on cytology as eosinophilic amorphous extracellular material and can be confirmed with Congo red staining.[12,13]

#### 1.7.3.2.6 Extramedullary hematopoiesis

Extramedullary hematopoiesis is characterized by the presence of hematopoietic precursor cells (megakaryocytes, erythroid or myeloid precursors) in various maturation stages and can be detected in some anemic and/or thrombocytopenic patients.[13]

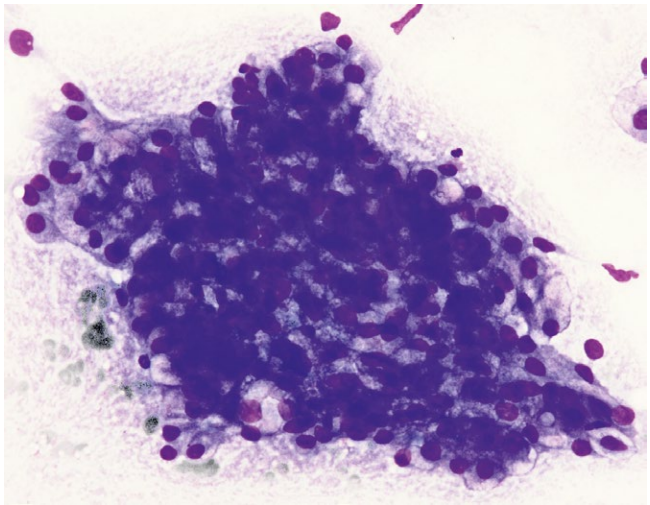


**Fig. 1-122** Well-differentiated hepatocellular carcinoma (confirmed by histopathology) in a 13-year-old mixed-breed dog with a surgically removed massive (10 cm diameter) liver mass 1 year prior to fine-needle aspiration (FNA)

Note the large uniform-appearing hepatocyte cluster. Mild diffuse vacuolar changes are present in the cytoplasm (May-Grünwald-Giemsa stain, original magnification 500x).

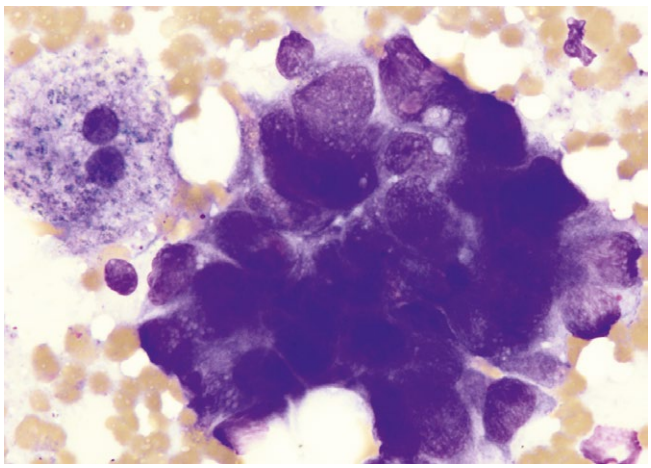


**Fig. 1-123** Hepatocellular carcinoma in a 13-year-old female mixed breed dog with multiple hypoechogenic liver masses noted during ultrasonographic examination

Note the moderate anisocytosis, anisokaryosis, prominent nucleoli, variable nuclear: cytoplasmic (N:C) ratio, and nuclear molding. One well-differentiated binucleated hepatocyte is present in the upper left corner of the image (modified Wright's stain, original magnification 1000x).

### 1.7.3.3 Neoplasia

Hepatic neoplasia (▶Chap. 9.5.7) is classified either as primary (commonly reported neoplastic conditions are hepatocellular adenoma, hepatocellular carcinoma, cholangiocellular [biliary] adenoma, cholangiocellular [biliary] carcinoma, hepatic carcinoid, and hemangiosarcoma) or secondary neoplasia (arising in another organ and metastasizing to the liver).[20] Morphologically, primary hepatic tumors can be subclassified as massive (a single large tumor involving only one liver lobe), nodular (multiple tumors located in different liver lobes), and diffuse (seen as either multifocal nodular changes in several liver lobes or diffuse changes throughout the liver parenchyma).[20,21] The most common primary hepatic tumor in dogs is hepatocellular carcinoma (▶Fig. 1-122 and ▶Fig. 1-123) and, in cats, cholangiocellular carcinoma (▶Fig. 1-124).[20,21] Metastatic tumors in the liver are observed more often than primary liver tumors (▶Fig. 1-125), and metastasis occurs in more than 30% of malignant neoplasms in dogs.[20] The most common metastatic hepatic tumors in dogs are lymphoma (▶Fig. 1-126), pancreatic adenocarcinoma (▶Fig. 1-127), and hemangiosarcoma (▶Fig. 1-128).[20]

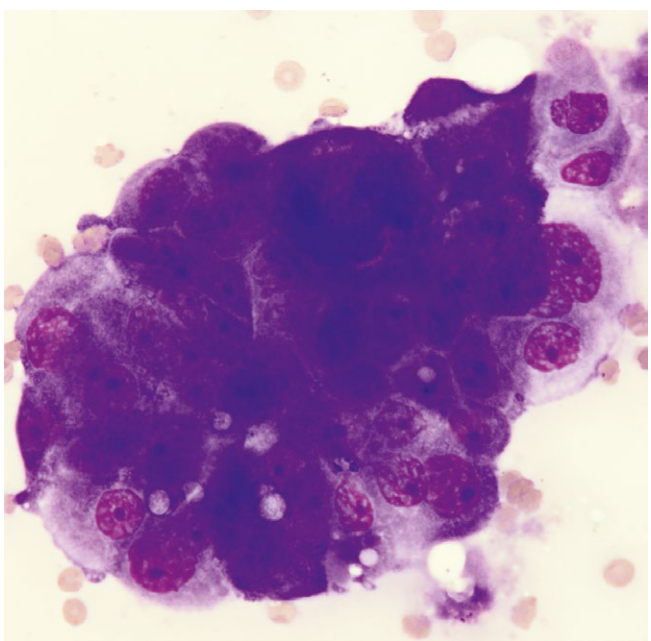


**Fig. 1-124** Cholangiocellular carcinoma in a 16-year-old male Persian cat with ascites and marked ultrasonographic changes of the liver parenchyma

Note the moderate anisocytosis, anisokaryosis, and prominent round nucleoli (modified Wright's stain, original magnification 1000x).

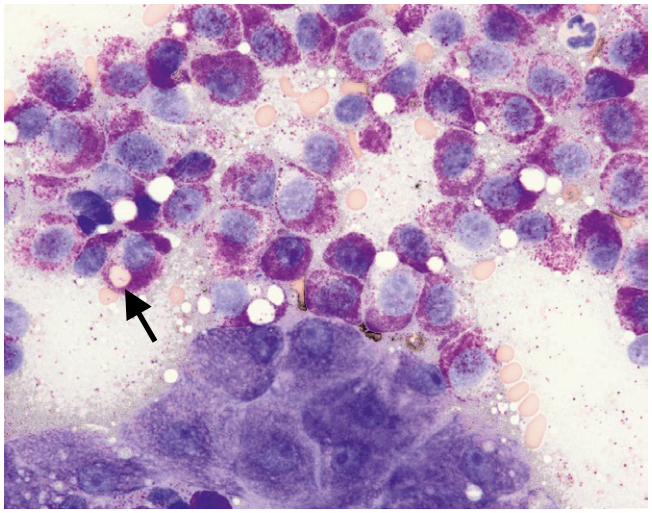


**Fig. 1-125** Mast cell tumor in the liver of a 9-year-old male cat with multiple cutaneous mast cell tumors, splenomegaly, and hepatomegaly

Note that some mast cells are erythrophagocytic (**arrow**). A hepatocyte cluster is present at the bottom of the image (modified Wright's stain, original magnification 1000x).

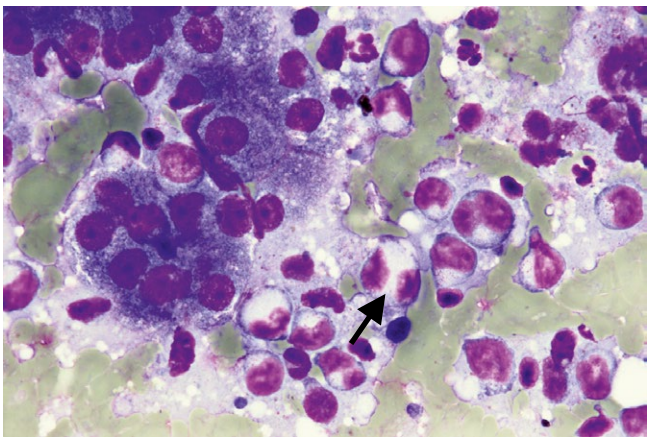


**Fig. 1-126** Lymphoma in an 8-year-old male mixed breed dog with hepatomegaly and increased liver enzyme activities

Large immature lymphocytes (likely of T-cell origin) are seen between hepatocytes. Some lymphocytes contain small magenta cytoplasmic granules. Lymphoglandular bodies (cytoplasmic fragments from the neoplastic lymphocytes) are noted in the background. A bizarre mitotic figure [**arrow**] is seen in the center (modified Wright's stain, original magnification 1000x).

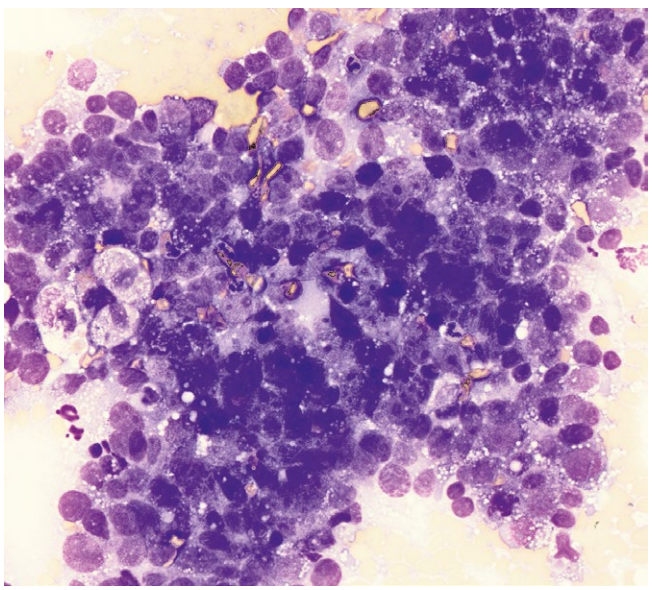


**Fig. 1-127** Metastatic pancreatic adenocarcinoma in the liver of an 8-year-old male Labrador retriever with increased liver enzyme activities, hyperbilirubinemia, hypoproteinemia, and hypoalbuminemia

Pancreatic adenocarcinoma with hepatic, intestinal, lymph node, and mesenteric metastases was diagnosed on histopathology. Fine-needle aspiration (FNA) cytology is highly cellular, containing clusters of epithelial cells that fulfill cytologic criteria of malignancy (modified Wright's stain, original magnification 500x).

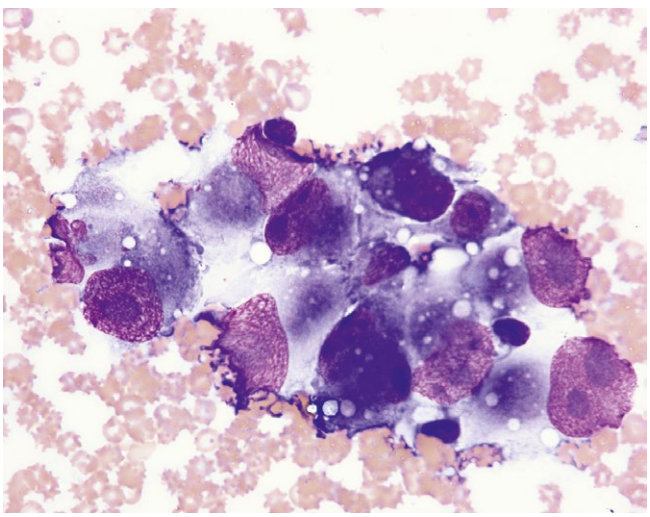


**Fig. 1-128** Hemangiosarcoma in the liver of a 10-year-old male German shepherd dog with a splenic mass, enlarged and ultrasonographically heterogeneous liver, and increased liver enzyme activities

Note the large spindle cells with stippled chromatin, multiple prominent nucleoli, macronucleoli, and a plump cytoplasm (modified Wright's stain, original magnification 1000x).

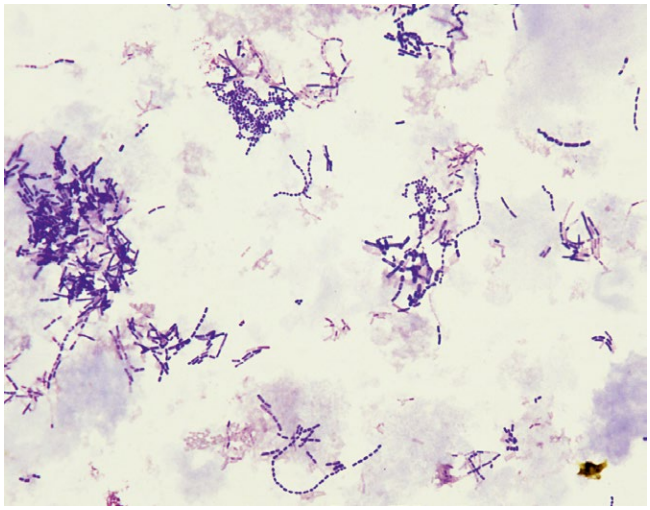


**Fig. 1-129** Bactibilia in a 10-year-old female mixed-breed dog with a large gallbladder filled with sludge (microlithiasis) and a thickened gallbladder wall on ultrasonography

Note the large number of bacterial rods and cocci in the absence of inflammatory cells (modified Wright's stain, original magnification 1000x).

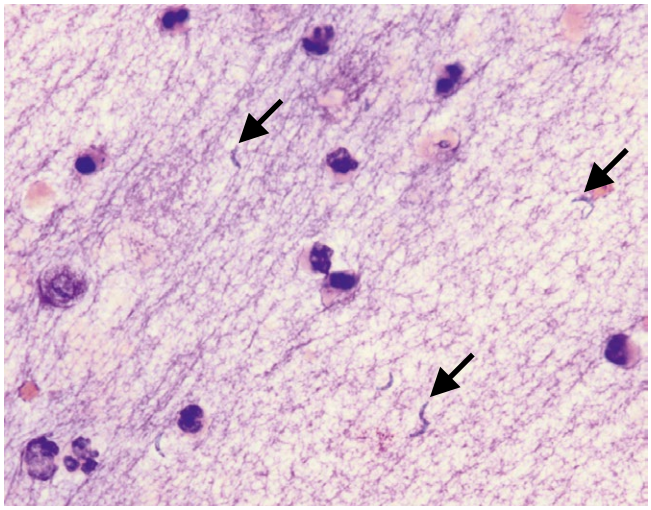


**Fig. 1-130** *Toxoplasma gondii* crescent-shaped zoites (**arrows**) and neutrophilic inflammation in the bile fluid from a 10-year-old female domestic shorthair cat presented for intermittent vomiting

The cat had a thickened gallbladder wall on abdominal ultrasonography (modified Wright's stain, original magnification 1000x).

### 1.7.4 Bile

Cytologic examination of bile fluid is warranted in hepatobiliary disease cases with abnormalities detected on ultrasonographic examination.[22] Bile can be obtained by percutaneous ultrasound-guided cholecystocentesis for cytologic evaluation and aerobic and anaerobic bacterial cultures. In patients with bacterial cholangitis (▶Chap. 9.6.3.2), bacteria can be present with or without inflammatory cells (▶Fig. 1-129). In some symptomatic patients, bactibilia can be detected on cytology even if bacterial cultures are negative. Cytologic examination of the bile fluid is also useful for monitoring antimicrobial treatment and diagnosing protozoal diseases (▶Fig. 1-130).

### 1.7.5 Pancreas

#### 1.7.5.1 Pancreatitis

Pancreatic FNA is a safe and useful diagnostic tool that frequently generates diagnostic-quality samples and correlates well with histopathologic findings.[23] Non-neoplastic pancreatic lesions, including acinar cell hyperplasia (incidental finding in older dogs and cats), ductular hyperplasia (in cats), and pancreatic cysts, are not diagnosed by cytology. In cases of acute pancreatitis in dogs (▶Chap. 10.3.1), FNA of the pancreas may be performed to support the diagnosis made by diagnostic imaging and measurement of canine pancreas-specific lipase (cPL) and rule out the presence of concurrent pancreatic neoplasia (▶Chap. 10.3.3).[2] Inflammation is characterized by numerous non-degenerate to moderately degenerate neutrophils, small numbers of macrophages, and necrotic material.[2,24] Pancreatic inflammation also causes mild dysplasia of pancreatic cells (▶Fig. 1-131).

**NOTE**

Pancreatitis is frequently localized, and a negative result of a single fine-needle aspiration (FNA) does not rule out the presence of pancreatitis.

FNAs are rarely performed in chronic pancreatitis cases and may yield mixed (mainly lymphocytic) inflammation and calcified cellular debris.[2]

#### 1.7.5.2 Tumors of the exocrine pancreas

Tumors of the exocrine pancreas in dogs and cats are pancreatic adenomas (rare and difficult to differentiate from pancreatic nodular hyperplasia on cytology) and pancreatic adenocarcinomas (▶Chap. 10.3.3).[4] Cytologically, pancreatic adenocarcinomas are characterized by the presence of marked anisocytosis, prominent round to angular nucleoli, nuclear molding, increased N:C ratio, vacuolated cytoplasm, and occasional acinar formation (▶Fig. 1-132). Malignant neoplasia can cause extensive secondary inflammation, making the diag-

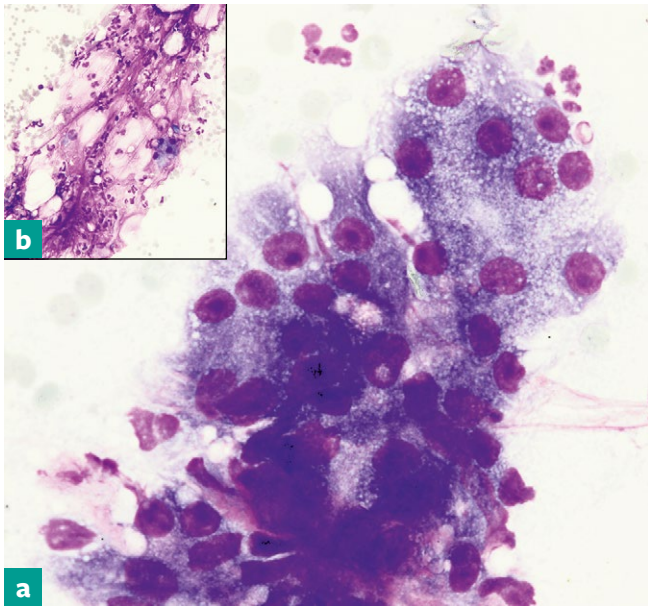



**Fig. 1-131** Pancreatitis in a 9-year-old male English springer spaniel

**a** Neutrophils are associated with a cluster of pancreatic acinar cells that exhibit mild dysplastic changes. Another area on the slide (**b** left upper corner) shows many moderately degenerate neutrophils, free lipids, and lysed cellular material (May-Grünwald-Giemsa stain, original magnification 1000x, inset 500x).

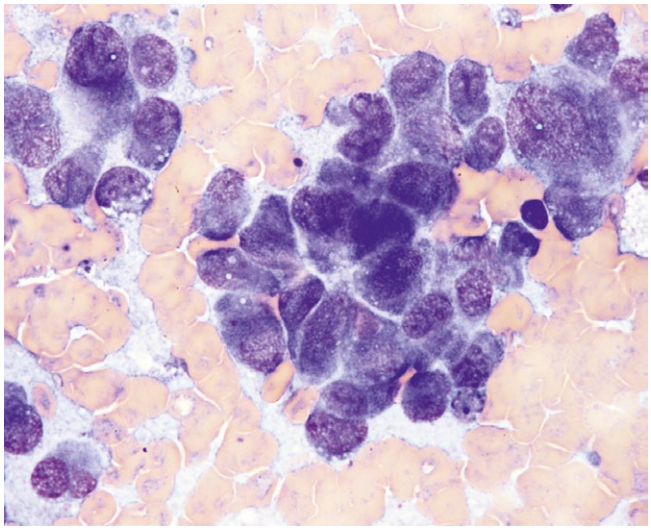


**Fig. 1-132** Pancreatic adenocarcinoma in a 15-year-old female mixed-breed dog

Note the marked anisocytosis and anisokaryosis, prominent nucleoli in some cells varying from round to linear, rare binucleated cells, and a central cell cluster with acinar formation (modified Wright's stain, original magnification 1000x).

nostic differentiation of pancreatitis and pancreatic adenocarcinoma by cytology difficult. Pancreatic adenocarcinomas are more common than adenomas in both dogs and cats.[4,25,26] In addition to primary pancreatic tumors, metastatic neoplasia can also be diagnosed in the pancreas based on FNA.

### 1.7.5.3 Tumors of the endocrine pancreas

The most frequently occurring tumor of the endocrine pancreas originates from insulin-secreting beta cells and results in clinical hypoglycemia ranging from mild to marked (▶Chap. 11.4.2). In dogs and cats, carcinomas of the pancreatic islets (malignant insulinomas) are more common than adenomas (insulinomas).[27–29] On cytology, insulinomas yield highly cellular samples with poorly defined cell borders, individual cells, and numerous free nuclei (▶Fig. 1-133). Non-beta cell tumors of the pancreatic islets are rare, and the diagnosis is made by a combination of clinical syndromes, IHC, and serum hormone analyses (▶Chap. 11.4.2.6).[27]

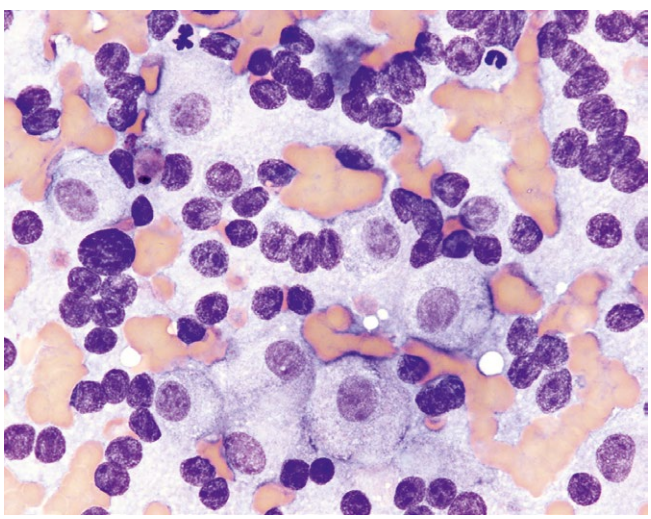


**Fig. 1-133** Pancreatic insulinoma in a 13-year-old female mixed-breed dog with hypoglycemia and a pancreatic mass approximately 1.4 cm in size

Note the high numbers of bare nuclei and loosely cohesive cellular groups. Individual cells appear uniform, have round nuclei with finely stippled chromatin, no prominent nucleoli, moderate nuclear: cytoplasmic (N:C) ratio, and pale basophilic cytoplasm (modified Wright's stain, original magnification 1000x).

## References

The complete list of references for this chapter can be downloaded from vetline.de:
svg.to/9842-01-07

# 1.8 Histopathology

## 1.8.1 Gastrointestinal tract

Mark R. Ackermann, Paula Giaretta

### 1.8.1.1 Introduction

Gross lesions in the GI tract include ulcers and erosions, some types of foreign bodies, neoplastic masses, constrictions, parasites, hemorrhage, infarction, lipogranulomas, serosal fibrosis/fibrin, adhesions, and volvulus/torsions. Gastrointestinal inflammation can produce gross lesions, but some inflammatory conditions do not. Even if gross lesions are present, these lesions are often not pathognomonic for a specific inflammatory disease condition. Thus, histopathologic assessment of gastrointestinal tissues can identify microscopic lesions that help diagnose the disease. Also, morphometric analysis can contribute important information about numerous other changes, including villous alterations, crypt hyperplasia, inflammatory cell infiltration, goblet cell and other epithelial changes, and vascular/lacteal lesions. At the same time, histopathology and morphometry have limitations. Many enteric conditions cause alterations resulting in clinical signs but lack microscopic lesions.

Examples of such conditions:

1. Increased permeability at the tight junctions of villous enterocytes or the endothelial cells of blood vessels and lacteals can result in luminal fluid shift, apoptosis of enterocytes, and altered transcytosis.[1]
2. Alterations in nerve function can affect gastrointestinal motility.
3. Certain antigens can incite acute/peracute inflammatory cell (e.g., mast cell/eosinophil) reactions by releasing pre-formed peptides, cytokines/chemokines, and/or $Th_2$-biased responses.[2]
4. Some toxins can invoke secretion or alter intestinal absorption.[1]
5. Alterations in the intestinal microbiota (dysbiosis) can result in diarrhea.[3,4]
6. Hormone changes (e.g., cholecystokinin, gastrin, pancreatic polypeptide, cortisol) can have various effects.
7. Systemic conditions (e.g., cardiovascular conditions, stress, hyper- or hypothermia, neurotic/psychotic conditions) can affect digestion, absorption, and motility.
8. Changes in gene transcription, translation, and the expression of numerous genes (e.g., *MUC* genes in goblet cells or cyclin genes in crypt cells) can affect cellular functions.

Other factors may also affect histopathology. Sampling can miss regions with histologic lesions, or lesions can be transient and not be present at the time of sampling. Histopathology cannot predict whether a patient will respond to diet changes, antibiotics, or immunosuppressors. Reaching a final diagnosis requires cooperation between the clinician and the pathologist, as the quality and number of endoscopic biopsies and histopathology processing impact the results.[5] Histopathology is a very old diagnostic workhorse that has value and merit, but with limitations.

Special stains, immunohistochemistry (IHC), in situ hybridization (ISH)/fluorescence ISH (FISH), genome sequencing, transcriptome, proteome, and microbiome studies can provide information that is supplemental and synergistic to histopathology. Special stains (e.g., Alcian blue for mucin and periodic acid Schiff [PAS] stain for basement membranes) can help assess the expression of endogenous molecules or detect certain microbial agents (e.g., acid-fast for mycobacteria, Gram stain for Gram-negative and Gram-positive organisms). The sensitivity of microbial stains is generally low, and a negative result does not completely rule out the presence of a pathogen. IHC stains have an increased sensitivity compared with special stains, although IHC also has limitations in sensitivity and interpretation. ISH, FISH, and RNAScope are highly sensitive and used to detect microbial agents or endogenous gene expression. However, these techniques require precise sample preparation and additional time, as do genome sequencing, transcriptome, proteome, and microbiome studies.

### 1.8.1.2 Inflammation of the stomach

#### 1.8.1.2.1 Acute gastritis

Acute gastritis is characterized by the sudden onset of vomiting related to mucosal injury or inflammation.[6] Biopsies are infrequently taken in acute gastritis cases. The lesions are usually associated with chemical or mechanical injury, use of drugs such as NSAIDs, dietary indiscretion, shock, and ischemia.[6] Microscopic findings are superficial and characterized by degeneration, erosion of the epithelium (▶ Fig. 1-134), mucosal congestion, hemorrhage, edema, and infiltration of neutrophils within the lamina propria.[6] Neutrophils are not seen within the normal gastrointestinal mucosa. Therefore, their presence usually suggests acute inflammation.[7]

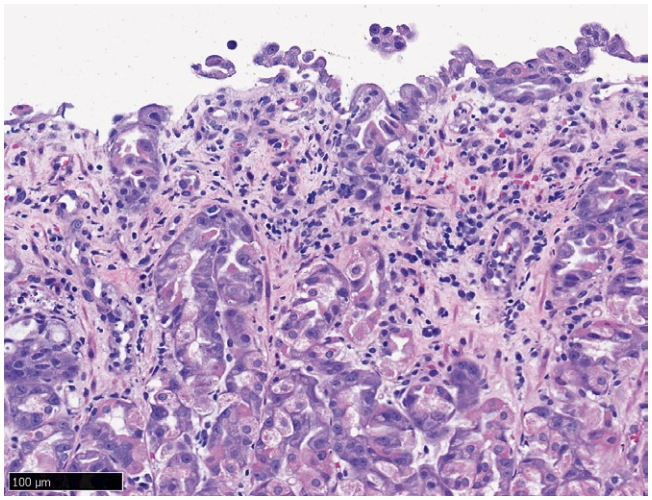



**Fig. 1-134** Acute gastritis in a dog

The epithelium is eroded and ulcerated with infiltration of neutrophils in the superficial lamina propria (H&E stain).

### 1.8.1.2.2 Chronic gastritis

Chronic gastritis is classified based on the predominant type of cellular infiltrate (i.e., lymphoplasmacytic, eosinophilic, granulomatous), the presence of architectural changes (e.g., fibrosis, glandular atrophy, epithelial injury, hyperplasia), and the severity of the lesions.[6] Pronounced epithelial erosion and ulceration are uncommon in cases of gastritis in dogs and cats, contrasting from peptic ulcers, where inflammation is a minor feature.[8] Gastric inflammation may occur isolated or concomitantly with enteritis and colitis as part of idiopathic IBD.[6] Lymphoplasmacytic gastritis with or without lymphoid follicular hyperplasia (▶Fig. 1-135a) is the most common form of chronic gastritis.[9] Mott cells may infiltrate the lamina propria among lymphocytes and plasma cells, and intraepithelial lymphocytes can be increased (▶Fig. 1-135b).[6] Eosinophilic gastritis is less prevalent, and it is characterized by an increase and predominance of eosinophils infiltrating the lamina propria in a diffuse manner.[9] Eosinophilic inflammation may be associated with parasitism or dietary indiscretion, or hypersensitivity, but it is not a specific finding.[10] Granulomatous gastritis results from parasitic infections, reaction to foreign material, fungal disease (e.g., histoplasmosis), or oomycosis (i.e., pythiosis; ▶Chap. 1.8.1.4 and ▶Chap. 7.3.1.5).

**Gastritis,** in general, is uncommonly associated with infectious organisms in companion animals. Infection with *Helicobacter* spp. and its association with gastritis in dogs and cats has been investigated and debated.[11] *Helicobacter pylori* (*H. pylori*) causes clinical gastritis in humans and predisposes them to gastric neoplasia.[12] However, this species is rarely associated with natural infection in dogs and cats.[11] The stomach of most healthy dogs is colonized mainly by *H. bizzozeronii* and *H. felis*,[13] while cats harbor *H. heilmannii*.[14] However, the prevalence of *Helicobacter* spp. in the GI tract of healthy dogs and cats is similar to that seen in patients with gastrointestinal signs.[15] Therefore, a direct causal relationship among gastritis, colonization by *Helicobacter* spp., and clinical signs, has not been established in companion animals.[16] Gastric strains of *Helicobacter* spp.

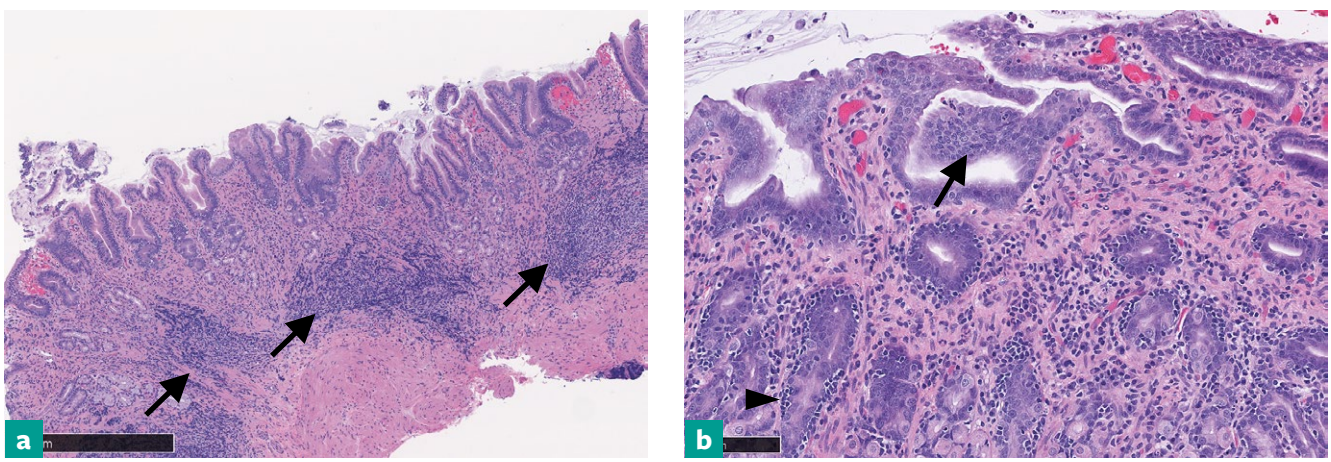



**Fig. 1-135** Chronic gastritis in a dog

**a** Lymphoid follicles (**arrows**) are prominent due to hyperplasia.

**b** The lamina propria is expanded by the infiltration of lymphocytes and plasma cells and mild deposition of fibrous connective tissue. The foveolar epithelium is thickened due to hyperplasia with increased basophilia (**arrow**). Intraepithelial lymphocytes (**arrowhead**) are also increased (H&E stain).

are Gram-negative, helicoidal to spiral-shaped. They are detected on the mucosal surface with the mucus, lumen of the glands and foveolae, and occasionally in the cytoplasm of epithelial cells.[17] Silver stains (e.g., Steiner, Warthin-Starry) and Giemsa reveal the spiral shape of the organisms.[17] Lymphoplasmacytic inflammation, epithelial degeneration, an increase in intraepithelial lymphocytes, and lymphoid follicular hyperplasia may accompany *Helicobacter* spp. in some, but not all patients.[17]

**The gastric mucosa** of small animals is susceptible to erosions and ulcers. Erosions are partial-thickness epithelial loss, and ulcers are mucosal defects with loss of the entire epithelial thickness down to the basement membrane. These lesions typically result from an imbalance between acid secretion (pH) and mucus protection. They may be associated with the use of NSAIDs, glucocorticoids, trauma, hepatic diseases, gastric foreign bodies, histamine (e.g., mast cell tumor), or gastrin-secreting neoplasia (e.g., gastrinoma), among others.[6] Acute erosions and shallow ulcers may be difficult to differentiate from artifactual loss of the epithelium or autolysis because of absent or minimal inflammation or tissue reaction.[18] Healing mucosal erosions may have basophilic, partially attached epithelial cells with mitotic figures on the surface and upper half of the glands. The microscopic aspects of deeper, progressive ulcers are variable and depend on their severity and development stage. Acute ulcers appear as loss of the epithelium covered by necrotic debris or mucosal depression with the accumulation of necrotic debris at the base. As the acute ulcer progresses to subacute and chronic, the base and sides are composed of granulation tissue with a mixed inflammatory infiltrate (▶ Fig. 1-136). The glands at the ulcer margins typically display hyperplasia and mucous metaplasia with epithelial sliding to cover the defect.[8] Progression to perforation may occur if the insult persists.[18]

**Atrophic gastritis** is a histopathological diagnosis for chronic gastritis combining glandular atrophy, regenerative glandular nesting, mononuclear inflammation, and fibrosis within the lamina propria.[17,18] The mucosa is thinner due to the reduction of parietal cells with an increased proportion of mucous cells. The condition is infrequent, and functional loss (achlorhydria) is rarely recognized clinically.[18] Atrophic gastritis is described in Norwegian lundehund dogs, where atrophy of the parietal cells and hyperplasia of neuroendocrine cells occurs isolated or in the mucosa adjacent to a gastric carcinoma.[19,20]

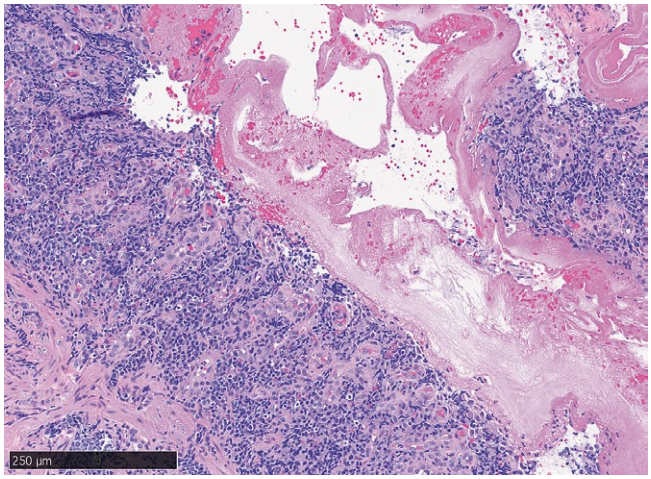



**Fig. 1-136** Gastric ulcer in a dog

The epithelium is ulcerated and partially covered by fibrin and seroproteinaceous fluid on the surface. The lamina propria has increased capillaries with reactive endothelial cells and infiltration of plasma cells, lymphocytes, and fewer neutrophils (H&E stain).

**Feline gastrointestinal eosinophilic sclerosing fibroplasia (FGESF)** is an idiopathic condition associated with the development of multiple or a single eosinophilic lesion (mass) in the gastrointestinal tract, mesenteric lymph nodes, and/or pancreas. The lesions are most frequently present near the pylorus or at the ileocecocolic junction.[21,22] The key histologic features include eosinophilic inflammation and a characteristic fibroplasia, with broad, interconnecting, and sometimes intersecting trabeculae of mature, organized collagen bundles.[22] Areas of necrosis are common and may contain bacteria, although their significance is not clear, and antibiotic therapy is not effective.[21] Special stains (PAS and Gomori methenamine silver [GMS] stain) and careful search to rule out infection by fungi, oomycetes, and nematodes are recommended.[23,24] Histologically, the lesions may also resemble a sclerosing mast cell tumor, fibrosarcoma, and osteosarcoma.[21,22]

**Chronic hypertrophic gastritis** (diffuse gastric mucosal hypertrophy, giant hypertrophic gastritis, Ménétrier-like disease) is a rare condition of dogs that resembles Ménétrier's disease in humans.[6,25] The gross lesions affect the gastric body and fundus and consist of marked thickening of the rugae in a convoluted, cerebriform pattern.[25] Microscopically, the mucosa is markedly expanded by hypertrophy/hyperplasia of the glandular and foveolar epithelium with cystic dilation of the mucous glands. The parietal cells are decreased and replaced by mucous cells.[6] Secondary folds of the muscularis mucosa and submucosa may be seen within the thickened mucosa.[25] The lamina propria be-

tween the glands may be infiltrated by variable numbers of plasma cells, lymphocytes, and macrophages.[6] In basenji dogs, gastric lesions may be seen along with lymphoplasmacytic enteritis, hypoalbuminemia, and hyperglobulinemia.[26] In the Drentse Patrijshond breed, chronic hypertrophic gastritis has been described as part of a condition called familial stomatocytosis-hypertrophic gastritis.[27] A recent report described lesions similar to Ménétrier's disease in the stomach of a cat.[28]

**Chronic hypertrophic pyloric gastropathy** is an idiopathic condition associated with the development of pyloric stenosis, particularly in small-breed dogs. Gross lesions consist of thickened mucosal folds narrowing or obstructing the pyloric canal.[29] Microscopic lesions can include mucosal hyperplasia, hypertrophy of the circular smooth muscle layer, or a combination of the two. Mucosal hyperplasia alone of the glandular and foveolar elements with branching and cystic dilation of the glands is the most common manifestation. Variable lymphoplasmacytic inflammation may be observed in the lamina propria and submucosa.[30] With endoscopically obtained mucosal biopsy specimens, the histologic lesion may be difficult to differentiate from normal antral mucosa.[29] Evaluation of hypertrophy of the muscularis externa requires a full-thickness biopsy sample. Hypertrophy of the smooth muscle layer with pyloric stenosis has also been reported in cats, especially in Siamese kittens.[31]

#### 1.8.1.2.3 Gastric parasites, fungi, and bacteria

Gastric parasites usually result in subclinical infections in dogs and cats. *Ollulanus tricuspis* is a nematode found in the gastric lumen of cats, wild felids,[32] and occasionally in dogs.[33] Adult nematodes are 1 mm long, have characteristic longitudinal cuticular projections (cuticular ridges), and can also be found in the lumen of the gastric glands.[34] Clinical signs and gastric inflammation, including lymphoplasmacytic gastritis, lymphoid follicular hyperplasia, and mucosal fibrosis, are variably present in cats infested with *Ollulanus tricuspis*.[32] Nematodes of the genus *Physaloptera* inhabit the lumen of the stomach and proximal duodenum of dogs, cats, and other carnivores. *Physaloptera* spp. may adhere to the gastric mucosa and is associated with variable lymphoplasmacytic inflammation.[35]

The spirurid nematodes *Cylicospirura* spp., *Cyathospirura* spp., *Gnathostoma* spp., and *Spirocerca* spp. can be present in nodules within the gastric wall. In cats, the nodules associated with *Cylicospirura* spp. contain a central pore and are characterized by expansion of the submucosa by broad trabeculae

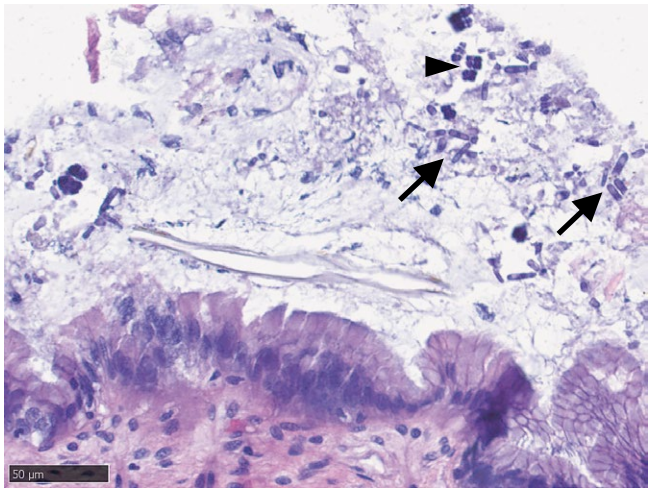



**Fig. 1-137** *Cyniclomyces* spp. and *Sarcina*-like bacteria in the stomach of a dog

The mucus on the mucosal surface contains oval to elongate, basophilic fungal yeasts (presumed *Cyniclomyces* spp.) with 2.5–3.5 µm diameter (**arrows**). Admixed with the yeasts are a few bacterial cocci (**arrowhead**) arranged in tetrad packets (presumed *Sarcina* spp.). (H&E stain)

of dense fibrous connective tissue, fibroblasts, admixed with lymphocytes and plasma cells, with occasional eosinophils and mast cells. The nematodes of *Cylicospirura* spp. are 250–450 µm in diameter with a cuticle containing serrated ridges, coelomyarian musculature, lateral chords, a pseudocoelom with female containing gravid uteri with larvated eggs.[36] *Cyathospirura* spp. can produce similar nodules in dogs and cats.[37] The gastric nodules associated with *Gnathostoma* spp. are reported in dogs and cats and consist of a submucosal granuloma with fibrosis and a central pore containing embedded nematodes. *Gnathostoma* spp. nematodes are 1 cm long and 100–150 µm in diameter, have a cuticle with spines, and coelomyarian musculature with lateral cords.[38,39] Aberrant larval migration of the esophageal nematode *Spirocerca lupi* may result in nodules within the gastric wall.[40]

Yeasts of *Cyniclomyces guttulatus* are uncommonly seen in gastric endoscopic biopsies and feces of dogs. They are found in the gastric lumen admixed with the mucus and are 4–8 × 8–20 µm, elongated cylindrical yeasts with two basophilic nuclei that have an "eyeglass case" appearance (▶Fig. 1-137). Their clinical significance is unknown, but they appear to be more prevalent in dogs with chronic enteropathies.[41]

*Sarcina*-like bacteria have been described in the gastric lumen of dogs and a cat with gastric dilatation and the stomach of an asymptomatic dog.[42,43] *Sarcina*-like bacteria are spherical, 1.8–3 microns in diameter, and form characteristic tetrads or packets of eight or more cells (▶Fig. 1-137) located in the superficial mucus with no changes in the mucosa.[42]

In young ruminants, this agent is associated with abomasal bloat,[8] but the clinical significance in dogs and cats is currently unclear.

*Cryptosporidium* spp. are rarely found in the gastric glands of dogs and cats with minimal gastritis, but their clinical importance is unknown.[44]

### 1.8.1.3 Inflammation of the small intestine

#### 1.8.1.3.1 Inflammatory bowel disease

Standards for histopathologic interpretation of gastrointestinal inflammation in endoscopic biopsy specimens from dogs and cats were set for chronic inflammatory enteropathy (CIE) and inflammatory bowel disease (IBD) by the World Small Animal Veterinary Association (WSAVA) in 2008,[7] which included descriptions of normal and abnormal findings.[45–50] IBD lesions scored by the WSAVA include alterations in surface epithelium, gastric pit epithelium, villous stunting, crypt dilation/distortion, lacteal dilation, colonic goblet cells, mucosal fibrosis, intraepithelial lymphocytes, lymphoid follicular hyperplasia, and lamina propria infiltrations of lymphocytes, plasma cells, eosinophils, neutrophils, and macrophages (▶Fig. 1-138) In practical terms, dogs and cats have variable degrees of many of these lesions. A diagnosis of IBD is often established by the clinician using information from histopathology in combination with clinical and clinicopathologic features. Of the IBD lesions, lacteal dilation and dilated crypts (crypt abscesses; ▶Fig. 1-139) can be associated with a specific clinical condition, protein-losing enteropathy (PLE).[51–53] Dilated lacteals and crypt lesions are more commonly seen in dogs than cats with IBD. They can also be seen with neoplastic infiltrates and conditions other than IBD. Epithelial cells can become eroded and lost or vacuolated with IBD. Subjacent to epithelial cells, clefts can form, and this change most often occurs concurrently with lacteal dilation. The villi can become shortened and/or widened. Often with widening, there is concurrent infiltration with lymphocytes, plasma cells, and occasional macrophages. Eosinophilic infiltrates are often minimal with IBD (▶Fig. 1-140 and ▶Fig. 1-141). They are instead seen with some parasitic infections, certain allergic ($Th_2$) responses, and some specific disease entities (e.g., eosinophilic sclerosing enteritis in cats). Crypt hyperplasia often occurs secondary to alterations in villous length, and with crypt hyperplasia, goblet cells can be interspersed between hyperplastic crypt epithelial cells. Dilated crypts containing cell debris and eosinophilic acellular material can often occur with IBD and other conditions such as neoplasia. In some IBD cases, inflammatory infiltrates can extend into the submucosa, but infiltrates do not extend into the tunica muscularis or subserosal area. Inflammation in idiopathic IBD cannot be distinguished from that seen in food-responsive enteropathy and antibiotic-responsive enteropathy (▶Chap. 11.2). Inflammatory and morphologic changes are also described in the intestine of Irish setter and soft-coated wheaton terriers dogs with gluten-sensitive enteropathy (▶Chap. 11.1.4.2).

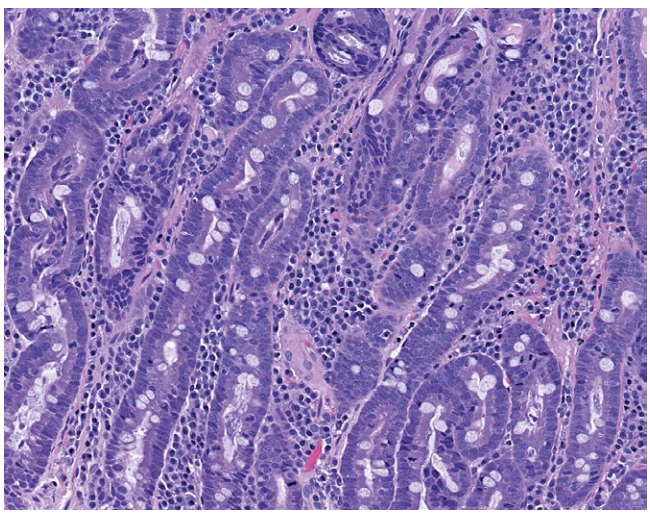


**Fig. 1-138** Lymphoplasmacytic enteritis of the duodenum in a dog
The lamina propria between the crypts is expanded by plasma cells and lymphocytes (H&E stain).

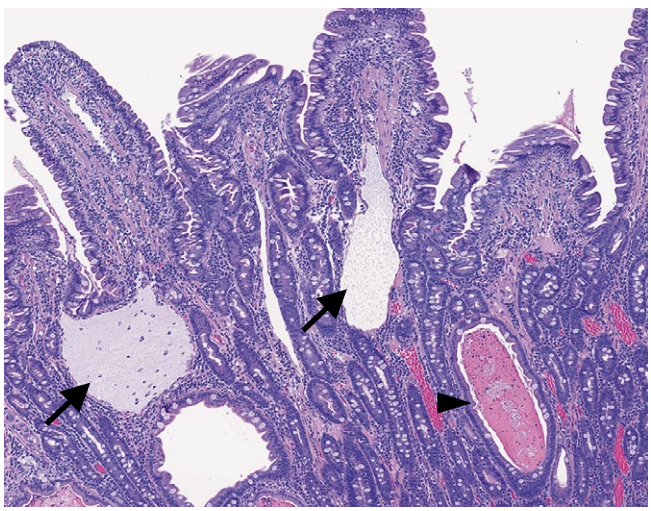


**Fig. 1-139** Protein-losing enteropathy in the duodenum of a dog
Lacteals in the lamina propria (**arrows**) are dilated (lymphangiectasia). A crypt is also dilated (**arrowhead**) and contains amorphous proteinaceous material and cellular debris in the lumen (H&E stain).

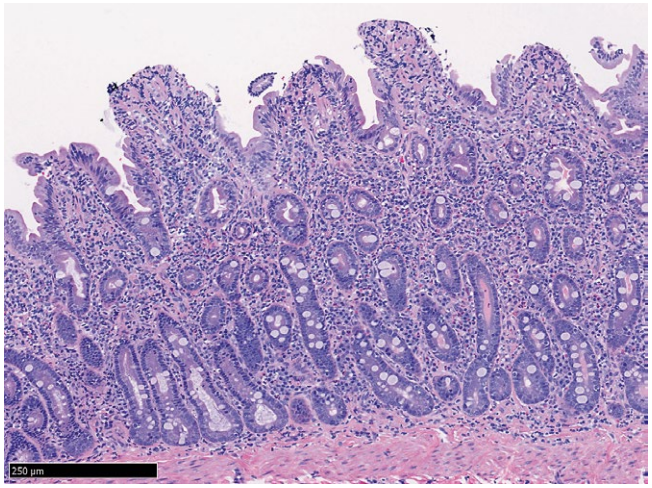



**Fig. 1-140** Chronic inflammatory enteropathy in the duodenum of a cat

Villi are diffusely blunted with multifocal erosion of the superficial epithelium and inflammatory cells infiltrating the lamina propria (H&E stain).

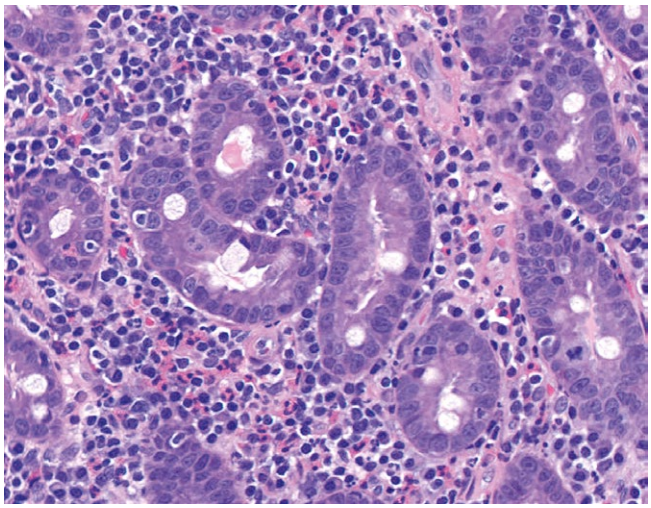


**Fig. 1-141** Chronic inflammatory enteropathy in the duodenum of a cat

The lamina propria between the crypts is expanded by eosinophils, plasma cells, and lymphocytes (H&E stain).

A major diagnostic challenge in cats is the **differentiation of severe IBD from intestinal lymphoma** (▶Fig. 1-142). In some cats, both can be present: intestinal IBD lesions with dense lymphocytic infiltration and regions with homogenous aggregates of lymphocytes that could have recently transitioned into a neoplastic cell type but do not form a distinct mass altering the mucosal architecture, and the cells lack mitotic figures and nuclear atypia. IHC stains sometimes help determine if such aggregates of homogenous appearing cells are of a single phenotype (e.g., CD3 or CD20). Increased infiltrates of intraepithelial lymphocytes with the formation of plaques are associated with lymphoma, which is also a useful diagnostic feature.

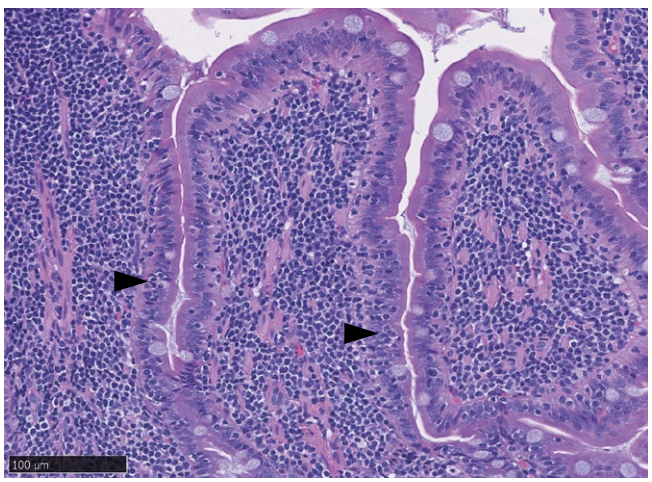



**Fig. 1-142** Chronic enteropathy in the duodenum of a cat

The lamina propria is diffusely infiltrated by small lymphocytes that occasionally form intraepithelial nests (**arrowheads**). These findings can be seen in lymphocytic enteritis and early small-cell lymphoma. Ancillary tests are necessary for differentiating between enteritis and lymphoma (H&E stain).

#### 1.8.1.3.2 Enteropathogens

**Parvovirus infections** are frequent causes of necrohemorrhagic enteritis, especially in puppies (canine parvovirus-2) and kittens (feline panleukopenia virus; ▶Chap. 7.3.1.1). Parvovirus targets the rapidly dividing epithelial cells in the crypts and lymphocytes within the Peyer's patches in the small intestine. The infection results in necrosis and loss of crypts that may be filled with cellular debris (crypt abscesses/cryptitis), leading to mucosal collapse, blunting, and fusion of the villi (▶Fig. 1-143), epithelial ulceration, and mucosal hemorrhage. Lymphoid necrosis and/or depletion is seen in the Peyer's patches. Depending on the chronicity, epithelial regeneration attempts may be noted in the crypts, with increased mitotic activity and replacement by cuboidal epithelial cells or karyomegalic, bizarre epithelial cells.[54] In a minority of the cases, the stomach and colon may have similar but less severe lesions, and intranuclear inclusion bodies are variably present in epithelial cells of the crypts. In dogs, pseudocytoplasmic inclusions have been reported in the tongue. Therefore, this tissue can be collected in necropsy cases where autolysis is a concern.[55]

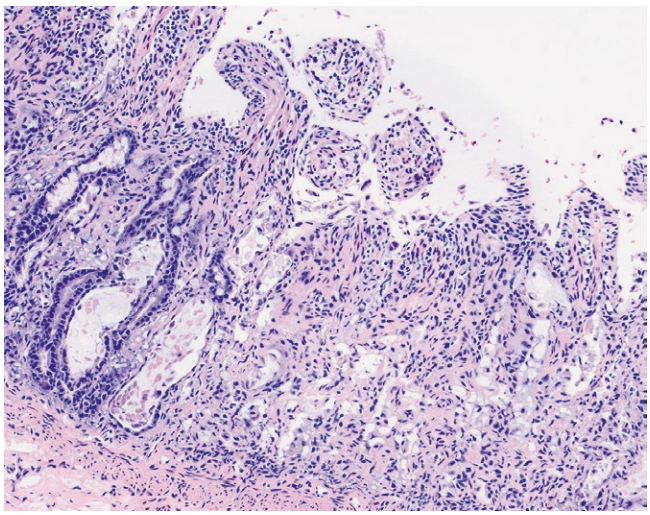


**Fig. 1-143** Parvoviral infection in the jejunum of a dog

Diffusely, villi are largely denuded of lining epithelial cells, partially collapsed, and multifocally fused. There is necrosis of epithelial cells and loss of crypts. Multifocal remaining crypts are lined by elongated epithelial cells and contain cellular debris in the lumen (H&E stain).

**Infection by canine and feline enteric coronavirus** targets the epithelial cells of the villous tips, leading to degeneration and mild villous atrophy. Clinical disease is uncommon and self-limiting and occurs, especially in young dogs and cats.[56] In clinically healthy cats, enteric coronavirus may persist for long periods in the colonic epithelium.[57] A pantropic variant of canine coronavirus has been related to fatal disease in puppies, characterized by enteritis, pneumonia, lymphopenia, and vascular lesions.[58]

**In feline infectious peritonitis (FIP)** caused by the mutated FIP coronavirus, nodular lesions target the serosa, muscularis externa, and submucosa of the intestine. They are often accompanied by fibrinous peritoneal effusion. The inflammation of the non-effusive form is typically distributed around veins and composed of macrophages, plasma cells, lymphocytes, and occasional neutrophils with variable areas of necrosis and phlebitis.[56] IHC can confirm the diagnosis with antigen detection in the cytoplasm of macrophages.[56]

**Dogs with acute hemorrhagic diarrhea syndrome (AHDS)** associated with *Clostridium perfringens* infection (▶ Chap. 7.3.3) have necrotizing lesions of variable degrees in the small and large intestine, while the stomach is spared.[59] In the small intestine, necrosis can be limited to the villous tips or extend to the entire villi and crypt epithelium with consequent villous blunting and fusion. Large rod-shaped Gram-positive bacteria adhere to the necrotic mucosa and cellular debris in the lumen. The lamina propria is infiltrated by variable numbers of neutrophils and other inflammatory cells.[59] *C. perfringens* can be cultured from the feces of healthy dogs and dogs with gastrointestinal disease.[60] Because the pathogenesis of the infection is not well characterized, there is no gold standard for definitive diagnosis, and a causal relationship is controversial.[61] Type A *C. perfringens* encoding the *netF toxin* gene is significantly more prevalent in the feces of dogs with AHDS than healthy dogs or dogs with other enteropathies.[62] However, proof of the role of the toxin is lacking (▶ Chap. 7.3.1.2.2).

***Clostridioides difficile*** (former *Clostridium difficile*) is prevalent in the feces of healthy dogs and cats, including the isolation of toxigenic strains. Hence, its role in disease is unclear.[63,64] Clinical disease seems uncommon and is poorly characterized in these species, with no descriptions of the lesions.[65] Similarly, *Campylobacter* spp.[61] and *Escherichia coli* [66] can be isolated from both asymptomatic and diarrheic dogs and cats. These infections are poorly understood (▶ Chap. 7.3.1.2).

***Salmonella* spp.** is frequently cultured from the feces of healthy dogs and cats.[67] Clinical salmonellosis is rare in domestic carnivores and is sometimes associated with young age, hospitalization, antibiotic therapy, and secondary to immunosuppressive diseases.[67] Described lesions include hemorrhagic enteritis and septicemia with consequent bronchopneumonia and necrotizing hepatitis (▶ Chap. 7.3.1.2.4).[68]

### 1.8.1.3.3 Intestinal parasites

Hookworms **nematodes** in the family Ancylostomatidae (*Ancylostoma* spp. and *Uncinaria* spp.) are the most pathogenic gastrointestinal nematodes in dogs and cats, resulting in persistent blood loss, anemia, and hypoproteinemia (▶ Chap. 7.3.1.3). Nematodes penetrate and attach to the small intestinal mucosa, resulting in hemorrhage, erosion, and variable eosinophilic and neutrophilic inflammation. Adult nematodes are approximately 300–500 µm in diameter, have a platymyarian musculature, an intestine with a brush border, and a muscular esophagus.[69]

Ascarids (*Toxascaris leonine, Toxocara canis*, and *Toxocara cati*) are larger nematodes found in the small intestinal lumen, with adults reaching up to 10–15 cm in length. Larval migration in extra-intestinal tissues may result in granulomatous inflammation, but intestinal lesions are mild and consist of eosinophilic inflammation and perhaps increased mucus production. Dogs may serve as alternative hosts for *Baylisascaris procyonis,* the raccoon nematode.

The nematode *Strongyloides* spp. can cause diarrhea in immunosuppressed and young dogs and cats.[70,71] Occasional mortality has been reported in puppies. Microscopically, there is villous atrophy, occasional "crypt abscesses," and variable inflammation in the small intestine, associated with adult and larval nematodes embedded in the mucosa. Larvae may also be found within granulomas in the intestinal lamina propria and submucosa or other organs. Adult nematodes contain platymyarian musculature, a muscular esophagus, paired genital tract, and an intestine composed of uninucleate cells.[70]

*Dipylidium caninum* is the most common intestinal **cestode** of dogs and cats. Dogs may also serve as definitive hosts of several metacestodes (*Echinococcus granulosus, E. multilocularis*, *Taenia hydatigena, T. pisiformis, T. ovis, T. multiceps, T. serialis*) harboring the adult tapeworm in the intestine. Cats occasionally are definitive hosts of taeniids (*T. taeniaeformis*, *Echinococcus* spp.). The adult cestodes inhabit the small intestinal lumen and may attach to the mucosa with minimal effects on the definitive host. Microscopically, these helminths are characterized by segmented proglottids with tegument and a parenchyma containing calcareous corpuscles. The first segment (scolex) contains suckers and may be attached to the mucosa between the villi and crypts.[69]

Dogs and other mammals may serve as definitive hosts for *Mesocestoides* spp., a cyclophyllidian tapeworm causing largely asymptomatic intestinal infections. Rarely, the ingested tetrathyridia can migrate into the abdominal cavity of dogs and occasionally cats, resulting in pyogranulomatous peritonitis, adhesions, and peritoneal effusion. In the peritoneal lesions, 1–2 µm wide tetrathyridia cestode larvae are usually degenerated, with fragments of eosinophilic tegument admixed with exudate.[72] Lesions must be differentiated from cysticerci that rarely occur in the peritoneum of dogs and cats.

The **trematode** *Nanophyteus salmincola* is the vector of salmon poisoning disease and may affect dogs and cats, especially in North America. Adult flukes may be found embedded in the villi of the small intestine with minimal tissue reaction. The fluke transmits *Neorickettsia helminthoeca,* which causes salmon poisoning disease characterized clinically by fever, anorexia, lymphadenopathy, vomiting, diarrhea, and occasionally neurological signs. On histopathology, the lymphoid tissues exhibit lymphoid depletion, necrosis, and increased numbers of histiocytes in the cortex and medulla of affected animals. Infected histiocytes have intracytoplasmic clusters of coccobacilli demonstrated by Giemsa, Macchiavello stains, or IHC. Inflammatory nodules with infected macrophages may be identified throughout the GI tract mucosa.[73]

**Giardiasis** may be asymptomatic in dogs and cats and cause minimal or no gross and histologic lesions. The protozoa do not invade the mucosa and multiply by asexual division in the intestinal lumen. The piriform to crescent-shaped trophozoites are seen on the mucosal surface or attached to the apical membrane, especially in the proximal small intestine, using hematoxylin and eosin (H&E) or Giemsa stain. The pathogenesis involves shortening of the brush border microvilli and disruption of brush border enzymes. *Giardia* spp. trophozoites and cysts are released in the feces.[74]

Similarly, infection by **cryptosporidia** (*Cryptosporidium felis* and *C. canis*) is generally asymptomatic in dogs and cats. Concurrent infections with other protozoa in kittens and puppies may exacerbate the clinical signs (▶Chap. 7.3.1.3). *Cryptosporidium* spp. develops enclosed by the apical cell membrane of enterocytes, resulting in epithelial damage and variable villous atrophy. Their endogenous stages (merozoites, gamonts, schizonts) range from 2–6 µm diameter and can be detected attached or adjacent to the small intestinal epithelium by H&E and Giemsa stain. Oocysts are shed in the feces.[75]

Intestinal **coccidia** in dogs and cats include mostly the genus *Cystoisospora* and occasionally the genera *Hammondia, Toxoplasma, Sarcocystis, Besnoitia,* and *Neospora* (▶Chap. 7.3.1.3). Endogenous multiplication of *Cystoisospora* occurs mainly in the small intestine with development in the subepithelial lamina propria and the cytoplasm of the epithelial cells. The resulting oocysts are released in the feces.[76,77]

**Granulomatous enteritis** is occasionally seen in dogs and cats and can be related to infection by *Histoplasma capsulatum, Pythium insidiosum*, and mycobacteria (▶Chap. 8.3.1.2). Mycotic enteritis and colitis (e.g., *Aspergillus* spp., *Candida* spp.) are rare in dogs and cats and can be associated with parvoviral infection or prolonged antibiotic treatment.

### 1.8.1.4 Inflammation of the large intestine

#### 1.8.1.4.1 Idiopathic colitis

Idiopathic colitis is the most common manifestation of large intestinal inflammation in dogs and cats, where a specific cause cannot be determined. The inflammation may be restricted to the colon or can be more widespread and also affect the small intestine and/or stomach as a component of idiopathic IBD (▶Chap. 11.2).[16]

#### 1.8.1.4.2 Acute colitis

In acute colitis, the lesions consist of edema within the lamina propria, hyperemic capillaries, and neutrophilic infiltration (▶Fig. 1-144). Eosinophils are variably present

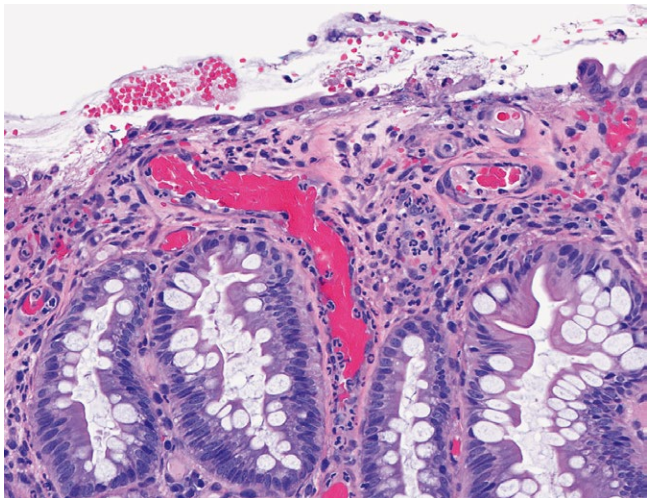


**Fig. 1-144** Acute colitis in a dog

The superficial epithelium is eroded/ulcerated, and the lamina propria is infiltrated by neutrophils (H&E stain).

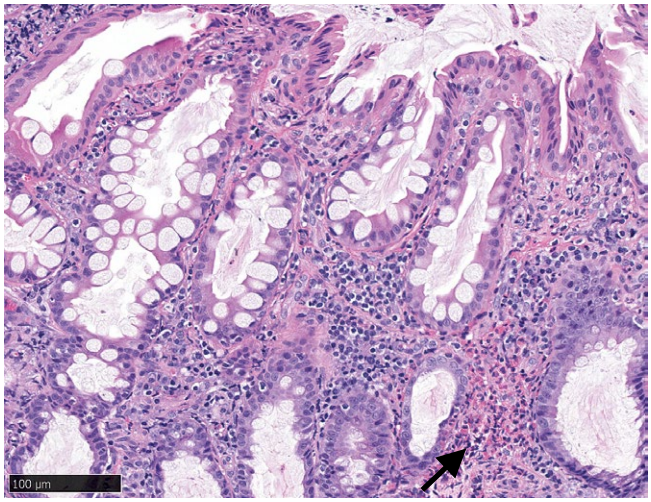



**Fig. 1-145** Eosinophilic colitis in a cat

An eosinophilic infiltrate (**arrow**) with fewer lymphocytes expands the lamina propria; crypts are mildly dilated (H&E stain).

(▶Fig. 1-145). Goblet cells may appear decreased in number due to mucous release or decreased cell differentiation.[8,78] Degenerative changes in the superficial epithelium include cytoplasmic vacuolation, attenuation, and erosion with flattening and basophilia, as well as epithelial erosion.[78] With progression to chronic colitis, lymphocytes and plasma cells are the predominant inflammatory cells. Epithelial erosion can lead to fibrosis within the superficial lamina propria and separation of the crypts with increasing chronicity. Crypts may become hyperplastic, dilated, tortuous, or irregularly oriented.[7]

### 1.8.1.4.3 Infectious colitis

**Canine histiocytic ulcerative colitis (HUC)** is a granulomatous and often ulcerative condition in the cecum and colon (▶Chap. 8.3.1.2) first described in boxer dogs and also reported in other breeds, including French bulldogs, Dobermans, mastiffs, an Alaskan malamute, and beagles.[79,80] Few cases were recently reported in cats.[81,82] The histologic lesions are distinct and characterized by the infiltration of epithelioid macrophages with abundant eosinophilic cytoplasm and the erosion of the superficial epithelium (▶Fig. 1-146a). Lesions have fewer neutrophils than macrophages, plasma cells and lymphocytes.[79] The inflammation expands the lamina propria and occasionally extends to the submucosa, lymphatics, muscularis externa, and serosa of the colon and less frequently in the ileum, caecum, and regional lymph nodes. The cytoplasm of the macrophages often stains PAS-positive (▶Fig. 1-146b). Studies using histochemistry[83] and electron microscopy[84] suggest that the intracellular PAS-positive material consists of phospholipids, mucopolysaccharides, and aged phagosomes that could originate from degenerated organisms. HUC is associated with invasive strains of *E. coli* demonstrated with FISH.[85] Patients typically respond well to treatment with fluoroquinolone antibiotics,[85,86] although there are reports of antibiotic resistance.[87]

Granulomatous colitis with infiltration of epithelioid macrophages and occasionally multinucleated giant cells is uncommon in dogs and cats except for HUC. If infectious organisms are not evident on routine H&E stain, special stains for fungi (e.g., PAS, GMS, or Grocott's stain), oomycetes (e.g., GMS or Grocott's stain), and acid-fast bacteria (e.g., Ziehl-Neelsen, Fite's stain) are recommended.

**Pyogranulomatous and eosinophilic colitis** can be a manifestation of pythiosis caused by the oomycete *Pythium insidiosum* (▶Chap. 7.3.1.5.1). The gastrointestinal form of the disease is most common in dogs, with fewer reports in cats.[88] Other than the colon, segmental thickening of the wall can be present in the stomach, small intestine, and, less commonly, the esophagus. Serosal adhesions and extension to the mesenteric lymph nodes may occur.[89] Typically, the inflammation is centered on the submucosa and muscularis externa. Therefore, the diagnosis may be missed on endoscopic biopsies.[88] Histopathology findings may include ulceration, multifocal necrosis with degranulated eosinophils and neutrophils surrounded by epithelioid macrophages, multinucleated giant cells, and deposition of fibrous con-

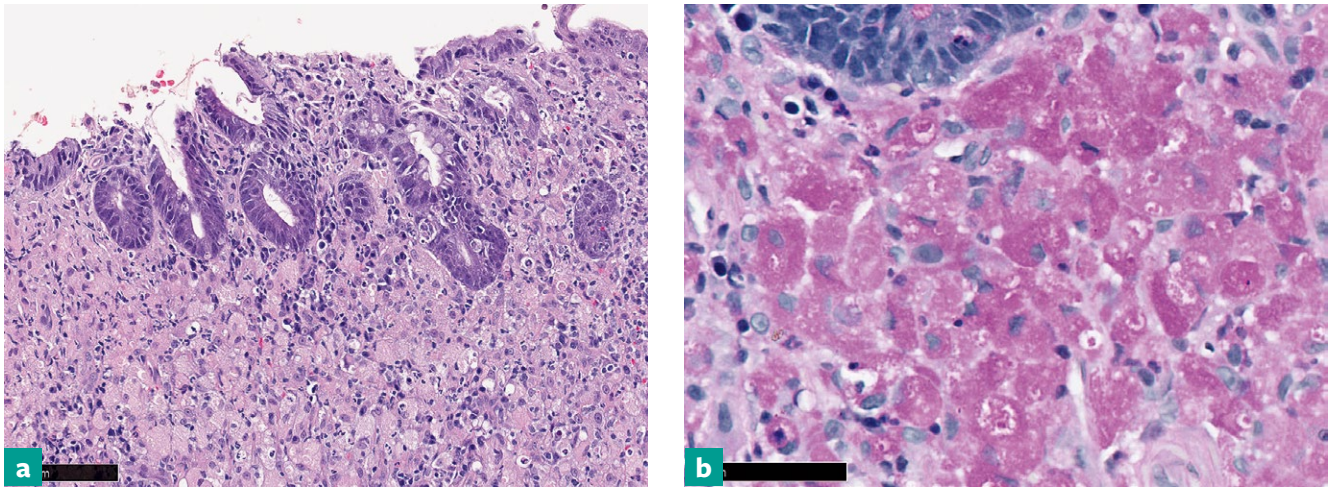



**Fig. 1-146** Histiocytic colitis in the colon of a French bulldog

**a** The lamina propria is diffusely expanded by an infiltrate of histiocytes with abundant eosinophilic cytoplasm and fewer neutrophils. The superficial epithelium is eroded (H&E stain).

**b** The cytoplasm of histiocytes is stained (magenta) by Periodic acid-Schiff (PAS) stain.

nective tissue (▶Fig. 1-147a). Vasculitis may be present.[89] The hyphae do not stain with routine H&E stain but may be surrounded by an eosinophilic sleeve.[90] Hyphae are positive with silver stains, including GMS (▶Fig. 1-147b) and Grocott's stain.[90] Because the cell wall of *Pythium* spp. contains a minimal amount of chitin, the hyphae fail to stain or stain faintly with PAS.[90] Hyphae are usually 4 µm (range: 2–8 µm) wide, have non-parallel walls, lack septation, and have irregular branching, fragmentation, and occasional bulbous swelling.[89]

Gastrointestinal infection with histoplasmosis (*Histoplasma capsulatum*) can be seen in dogs and cats (▶Chap. 7.3.1.5.2), presenting as localized colitis or a component of systemic disease.[91] Mucosal ulceration with transmural histiocytic inflammation and abundant intrahistiocytic yeasts are characteristic (▶Fig. 1-148). Round to oval yeasts typically range from 2–4 µm in diameter but may reach up to 8 µm.[92] They are surrounded by a clear halo, exhibit narrow-based budding, and stain with periodic-acid-Shiff [PAS] and GMS.[91] Rarely, hyphal (mycelial) forms may be associated with the lesions.[92]

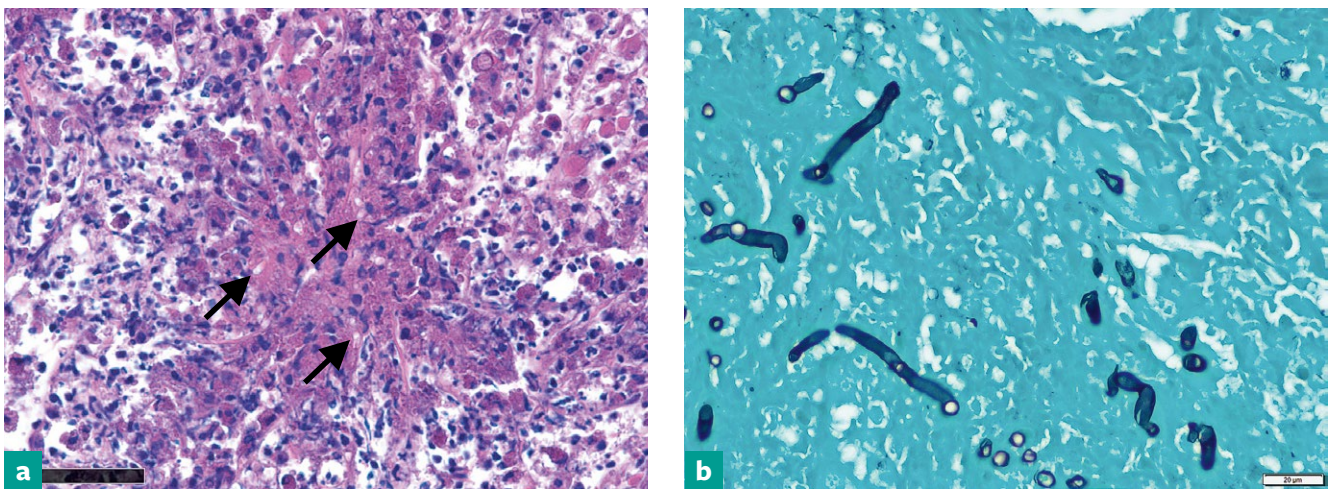



**Fig. 1-147** *Pythium* spp. infection in the jejunum of a dog

**a** The submucosa contains degranulated eosinophils surrounding cellular debris with negative figures of hyphae (**arrows**) (H&E stain).

**b** A Gomori methenamine silver (GMS) stain reveals multiple, 5–7 µm diameter hyphae with non-parallel walls and irregular branching.

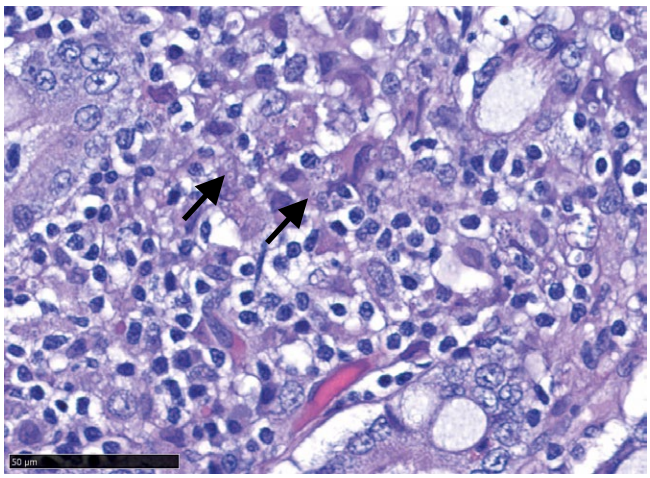


**Fig. 1-148** *Histoplasma* spp. infection in the colon of a dog
Macrophages and lymphocytes infiltrate the lamina propria. The cytoplasm of macrophages occasionally contains round, 2 µm-diameter yeasts surrounded by a clear halo (**arrows**) (H&E stain).

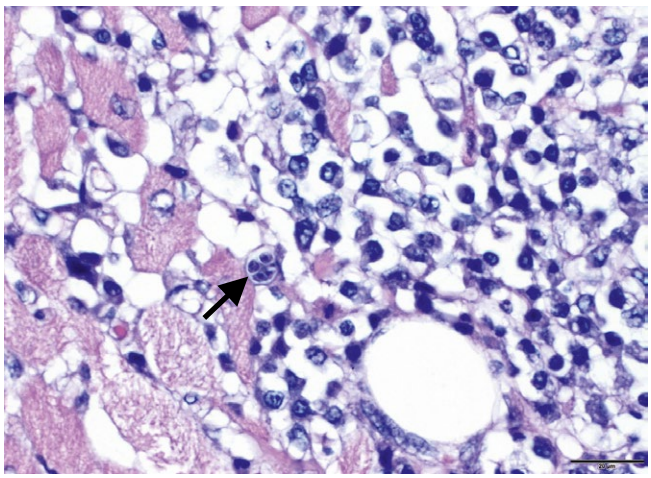


**Fig. 1-149** *Prototheca* spp. infection in the colon of a dog
Macrophages, plasma cells, and lymphocytes infiltrate the external muscularis layer. A 7 µm-diameter, oval alga with endospores (**arrow**) is seen within the inflammation (H&E stain).

In endemic areas, canine leishmaniasis (*Leishmania infantum*) may uncommonly manifest as large bowel diarrhea associated with histiocytic colitis.[93] The transmural inflammatory infiltrate is predominantly histiocytic with variable numbers of plasma cells, lymphocytes, and neutrophils.[93] Protozoal amastigotes are round to ovoid, 2.5–5 µm × 1.5–2 µm in size, and found in the cytoplasm of macrophages, often contained within round, clear, parasitophorous vacuoles.[94] *Leishmania* spp. amastigotes need to be differentiated from yeasts of *Histoplasma* spp., with the protozoa having a small, rod-shaped structure (kinetoplast) adjacent to the nucleus that may be difficult to visualize on histologic tissue sections. The protozoa typically stain with Giemsa, but not GMS, and may not stain or stain faintly with PAS.[94] The diagnosis can be confirmed with PCR or IHC.[93,94]

*Prototheca* spp. is a rare cause of pyogranulomatous colitis in dogs due to disseminated systemic infection (▶Chap. 7.3.1.5.3). Algae are unicellular, spherical to oval, with sporangia ranging from 7–13 µm (*P. wickerhamii*) to 14–25 µm (*P. zopfii*). Algae undergo endosporulation, exhibiting internal septations (▶Fig. 1-149). The organisms might be difficult to identify with routine stains but are revealed by PAS and GMS stains.[95]

**Granulomatous colitis and enteritis** are rarely associated with gastrointestinal and/or systemic mycobacterial infections in dogs and cats.[96,97]

In endemic areas for bovine tuberculosis, the gastrointestinal manifestation may be seen in cats that ingest raw bovine milk or viscera contaminated with *Mycobacterium*.

Mycobacterial lesions are typically nodular and transmural, corresponding to aggregates of epithelioid macrophages and multinucleated giant cells. In these cases, an involvement of the regional lymph nodes is common. A variable number of acid-fast bacilli are detectable with Ziehl-Neelsen or other acid-fast stains.[97] Sporadic intracellular bacilli are seen in infections with members of the tuberculosis complex (*M. tuberculosis, M. bovis, M. microti*). In contrast, numerous intracellular and/or extracellular bacilli are seen in infections with the non-tuberculous mycobacteria (e.g., *M. avium, M. malmoense, M. fortuitum, M. branderi/shimoidei*).[96,97]

In **canine schistosomiasis** (▶Chap. 7.3.1.4), caused by the trematode *Heterobilharzia americana*, multiple mineralized granulomas may be present throughout the large and small intestinal wall, sometimes concentrated in the submucosa.[98] These granulomas can also be seen in the liver and pancreas, among other organs.[99] The trematode eggs incite an inflammatory response while migrating from the venules to the intestinal lumen. The eggs vary from 50–75 µm in diameter, contain a yellow to brown, refractile eggshell with an internal miracidium (▶Fig. 1-150), and are often mineralized and degenerated.[98] Adult trematodes are rarely detected within the veins.[99]

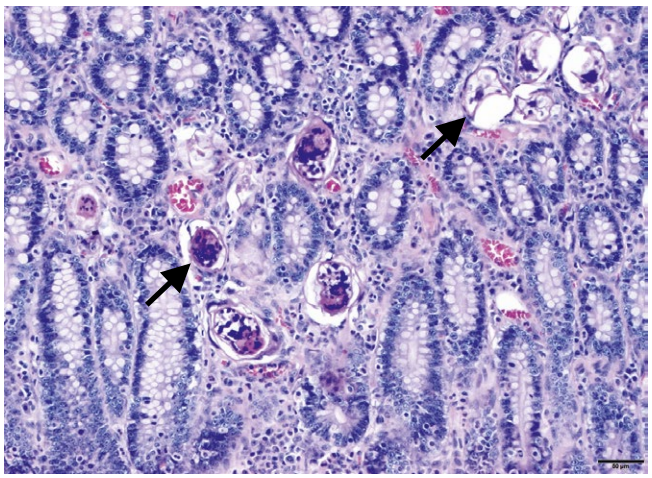


**Fig. 1-150** *Heterobilharzia americana* infection in the jejunum of a dog

Multiple 40–50 µm-diameter trematode eggs with refractile shells (**arrows**) are seen in the lamina propria and within the lumen of veins (H&E stain).

**Trichuriasis** (▶Chap. 8.3.1.1), caused by the whipworm *Trichuris* spp., can result in typhlitis or typhlocolitis in dogs and cats.[100,101] The severity and composition of the inflammatory infiltrate are variable and characterized by eosinophils, neutrophils, lymphocytes, and/or plasma cells with adult nematodes and larvae on the mucosal surface or embedded in the mucosa. Rarely, *Trichuris* spp. penetrate the submucosa and tunica muscularis. Adult nematodes contain coelomyarian musculature, bacillary bands, and stichosomes; eggs contain bipolar plugs.[101]

**In cats, the nematode *Strongyloides* spp.** can penetrate the colonic mucosa and produce nodular lesions ranging from 1–8 mm in diameter with a central depression. The nodules extend from the mucosa to the submucosa and consist of adenomatous hyperplasia of the glands associated with a lymphoplasmacytic and eosinophilic inflammatory response to the nematode adults, rhabditiform larvae, and eggs. Adult females are approximately 100 µm in diameter with platymyarian musculature, paired genital tracts, and an intestine composed of uninucleate cells.[71]

**The protozoa *Tritrichomonas blagburni*** may cause lymphoplasmacytic and/or neutrophilic colitis in young cats, resulting in chronic large bowel diarrhea (▶Chap. 8.3.3). On histopathology, the trichomonads are elongate, teardrop- to crescent-shaped, ranging from 4–8 mm long with eosinophilic cytoplasm and a faint, hyperchromatic, round-to-oval nucleus. In a study including naturally infected cats, the organisms were histologically detected in approximately 50% of the examined tissue sections.[102] When present, the trichomonads are more frequently seen on the mucosal surface adjacent to the epithelium and occasionally in the lumen of the crypts or invading the lamina propria. On histopathology, the trophozoites cannot be differentiated from those of *Giardia* spp., requiring fecal culture or PCR analysis.[102]

**Amoebiasis** is a rare cause of ulcerative, fibrinonecrotizing typhlocolitis in dogs and cats.[103,104] The disease caused by *Entamoeba histolytica* appears to be more severe in animals with concurrent *Ancylostoma* spp. or *Trichuris vulpis* infection. Initial lesions are characterized by superficial mucosal erosions, while established colitis cases exhibit a characteristic flask-shaped, deep ulcer with a narrow neck through the mucosa and a broad base in the submucosa.[8] Amoebae may be seen at the margins of the lesions or admixed with cellular debris. The trophozoites are approximately 20 µm in diameter (ranging from 6–50 µm), spherical to oval-shaped, with a nucleus containing a central karyosome. The trophozoite cytoplasm stains with PAS.[103]

**Coccidiosis** is caused by *Cystoisospora* spp. in dogs and cats. Multiplication of the organism occurs mainly in the small intestinal epithelium but is occasionally seen in the large intestine.[76,77]

**Enteropathogenic *E. coli*** is a cause of enterocolitis in cats and dogs, especially in kittens (▶Chap. 7.3.1.2.5). The associated lesions described in kittens include lymphoplasmacytic or neutrophilic inflammation in the ileum and colon, with epithelial injury and occasional crypt dilation. Gram-negative bacterial rods can be seen attached to the superficial and cryptal epithelium.[66] Pathogenic *E. coli* must be differentiated from Gram-positive enterococci (*Enterococcus hirae*), are considered commensals, and are seen adherent to the intestinal epithelium of healthy kittens.[105] The definitive diagnosis of enteropathogenic *E. coli* requires fecal bacterial culture, with a selection of *E. coli* colonies and screening for pathogenicity determinants, because *E. coli* can be cultured both from healthy and diarrheic animals.[66] Other strains of attaching and effacing *E. coli* 0157:H7 can cause hemolytic-uremic syndrome. *E. coli* colonizing the intestinal tract can release Shiga-like toxins that circulate systemically, resulting in anemia, fibrinous glomerulonephritis, and skin lesions (Alabama rot).

**Tyzzer's disease** is caused by *Clostridium piliforme*. It is a condition of young animals (▶Chap. 9.5.2) and uncommonly affects immunosuppressed kittens and puppies.[106,107]

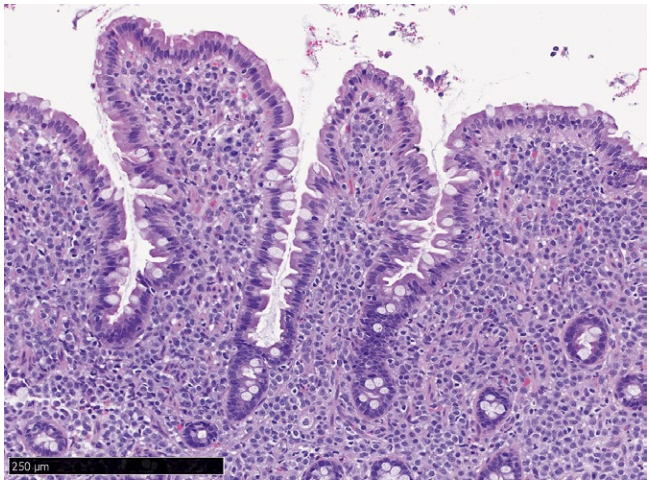



**Fig. 1-151** Large-cell lymphoma in the ileum of a cat
Large neoplastic lymphocytes diffusely infiltrate the lamina propria (H&E stain).

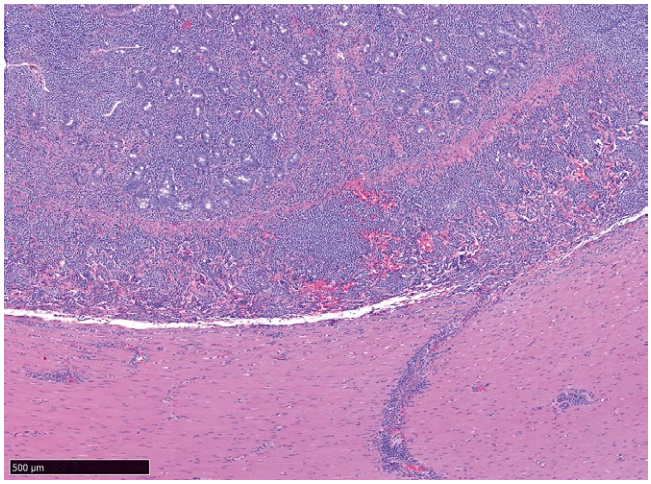



**Fig. 1-152** Small-cell lymphoma in the jejunum of a cat
Neoplastic lymphocytes with scant cytoplasm and small nuclei infiltrate into the submucosa and muscularis externa (H&E stain).

Colonic lesions include necrosis and distension of the crypts by neutrophils and cellular debris (crypt abscesses), with a mixed inflammatory infiltrate in the lamina propria.[108] Clusters of silver stain-positive (e.g., Warthin-Starry and Steiner's stain), Gram-negative, slender, 4–20 µm long bacilli arranged in crisscrossed stacks are seen within the cytoplasm of cryptal and superficial epithelial cells and goblet cells.[108] Necrotizing and neutrophilic lesions can also be found in the small intestine, liver, and myocardium.[106]

**Epithelial necrosis** with hemorrhage and large rod-shaped bacteria adhered to the epithelium is described in the small intestine and colon of dogs with acute hemorrhagic diarrhea associated with *Clostridium perfringens* type A infection.[59]

In some parvoviral enteritis cases of dogs and cats (▶Chap. 7.3.1.1), crypt necrosis can be seen in the large intestine. However, the lesions are less severe than those seen in the small intestine.

### 1.8.1.5 Proliferative and neoplastic lesions of the gastrointestinal tract

#### 1.8.1.5.1 Lymphoma

Lymphoma is a common gastrointestinal neoplasm of cats and dogs (▶Chap. 11.3) and, when primary, more frequently originates from T cells.[109,110] Of enteric T-cell lymphomas, enteropathy-associated T-cell lymphoma (EATL) type 1 (large-cell, ▶Fig. 1-151) is most common in dogs, whereas EATL type 2 (small-cell, ▶Fig. 1-152) is most common in cats.[110] Canine anaplastic large T-cell lymphomas express CD3 and sometimes CD30 and are often transmural with necrosis.[111] In dogs, EATL type 1 (large-cell) tumors have increased proliferation rates as determined by Ki67 compared with IBD and EATL type 2 (small-cell).[110] Dogs with small-cell T-cell lymphoma (SCL; EATL type 2) can have prolonged survival if treated with steroids and alkylating agents and if they lack anemia and weight loss.[112] However, some cases of SCL/EATL type 2 in dogs may transition into large-cell lymphoma.[113]

Differentiation of an emerging EATL type 2 from IBD based on morphology alone can be difficult, especially in cats, where both entities are frequent causes of chronic enteropathy. Lymphoid infiltration of the intestinal wall beyond the mucosa, epitheliotropism (i.e., intraepithelial nests and plaques; ▶Fig. 1-153), and homogeneity of the lymphocytic infiltrate are histologic features that favor a diagnosis of lymphoma.[114] The accuracy of a diagnosis of EATL type 2 is greatly improved when morphologic evaluation is combined with IHC for T- and B-cell markers and PCR to assess antigen receptor rearrangements and clonality (PARR) in a stepwise approach.[114] Dogs with intestinal lymphoma can have increased numbers of FoxP3 T regulatory cells and reduced survival compared with dogs with IBD.[115]

#### 1.8.1.5.2 Other neoplasias

The main mesenchymal intestinal tumors with nonangiogenic, non-lymphogenic origin include leiomyoma, leiomyosarcoma, and gastrointestinal stromal tumor (GIST; ▶Chap. 7.3.7 and ▶Chap. 7.3.9). Intestinal fibrosarcomas and neurogenic neoplasms are rare.

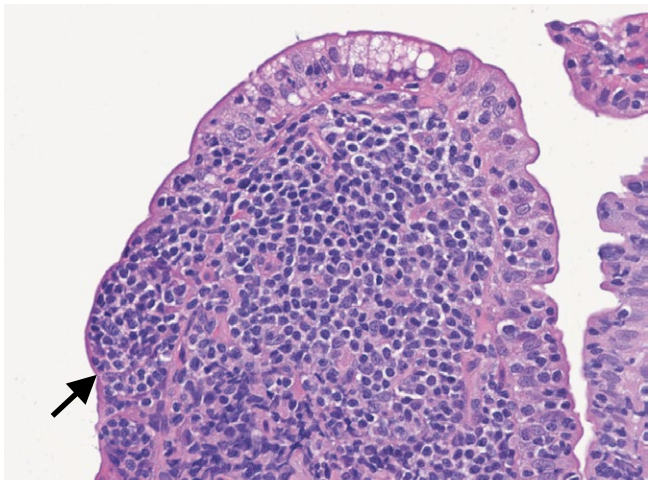


**Fig. 1-153** Small-cell lymphoma in the duodenum of a cat
A monomorphic population of small lymphocytes expands the villous lamina propria, and the formation of intraepithelial plaques (**arrow**) is seen (H&E stain).

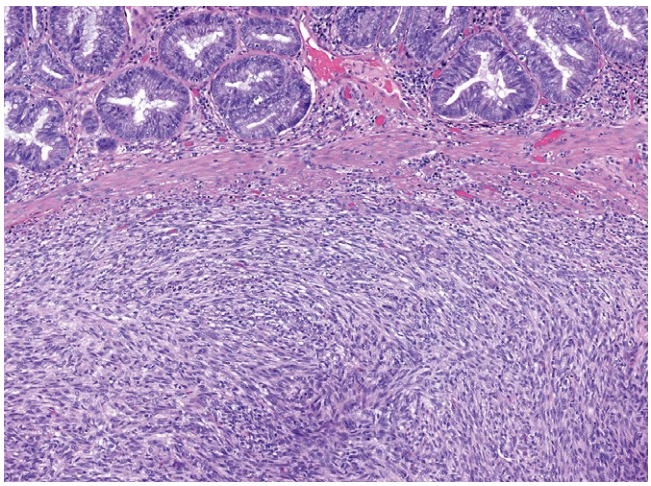


**Fig. 1-154** Gastrointestinal stromal tumor (GIST) in the colon of a dog
The submucosa and muscularis externa are infiltrated and effaced by a proliferation of spindle-shaped cells arranged in interlacing bundles (H&E stain).

**Leiomyomas** are benign, well-demarcated neoplasms from the muscularis layer and are common in the cardia of dogs. Interlacing bundles of spindle-shaped cells with abundant cytoplasm, a cigar-shaped nucleus, rare mitotic activity, and minimal atypia are characteristic of leiomyoma.[116] Leiomyosarcoma is a malignant neoplasm of leiomyocytes with variable degrees of differentiation and most often occurs in the small intestine.[117,118] Compared with leiomyomas, the malignant counterpart exhibits increased mitotic activity and atypia, reduced cytoplasm, and areas of necrosis. Leiomyosarcomas can be invasive, but metastasis is rare.[117] The main differential diagnosis for leiomyosarcoma is gastrointestinal stromal sarcoma tumor, which requires IHC for differentiation.

**Gastrointestinal stromal tumors** (GISTs; ▶Fig. 1-154) are tumors believed to be from Cajal cells. They have metastatic potential and occur mainly in the distal small intestine and cecum.[117] IHC detects the expression of KIT and DOG-1 only in GISTs.[119] On the other hand, leiomyomas, leiomyosarcomas, and GISTs can express smooth muscle actin, desmin, S100, and PGP 9.5, among other markers.[120]

**Hyperplastic polyps** are non-neoplastic growths and may occur in any part of the gastric and intestinal mucosa of dogs and cats, but they are more frequent in the rectum of dogs. Gastric hyperplastic polyps are usually incidental lesions, while rectal lesions may result in dyschezia, hematochezia, and/or diarrhea.[121] Hyperplastic polyps are characterized by areas of thickened, hyperplastic epithelium that forms papillomatous folds with cystic dilation supported by a fibrous stalk.[121] In contrast to an adenoma, the epithelial cells of a polyp are similar to the adjacent epithelium, with basilar nuclei, and have no evidence of cryptal branching, dysplasia, anisocytosis, or anisokaryosis.[121] The supporting fibrous stroma variably contains mixed inflammatory cells with granulation tissue, and these polypoid lesions are called inflammatory polyps.[121] Inflammatory polyps of miniature dachshunds are a specific entity with hyperplastic goblet cells and B cells in stage 1 lesions but neutrophils in stage 2 and 3 lesions.[121] Inflammatory colorectal polyps of miniature dachshunds can develop into adenomas and adenocarcinomas.[122] Osseous (osteoid) metaplasia and mucin accumulation may occur, especially in the rectal hyperplastic polyps.[121] The mitotic rate cannot differentiate a hyperplastic polyp from an adenoma.[121]

**Adenomas** are composed of neoplastic hyperchromatic epithelial cells that tend to lose their basilar arrangement and be organized in a pseudostratified pattern with decreased goblet cell differentiation (▶Fig. 1-155).[122] Nuclei are larger and darker and may contain prominent nucleoli. Rectal adenomas can be subdivided into tubular adenomas and villous adenomas. Tubular adenomas consist of proliferated epithelial cells arranged in branching and budding tubules surrounded by lamina propria. Villous adenomas form frond-like projections of the lamina propria covered by rectal epithelium. A lesion that combines features of both subtypes is called tubulovillous adenoma.[120]

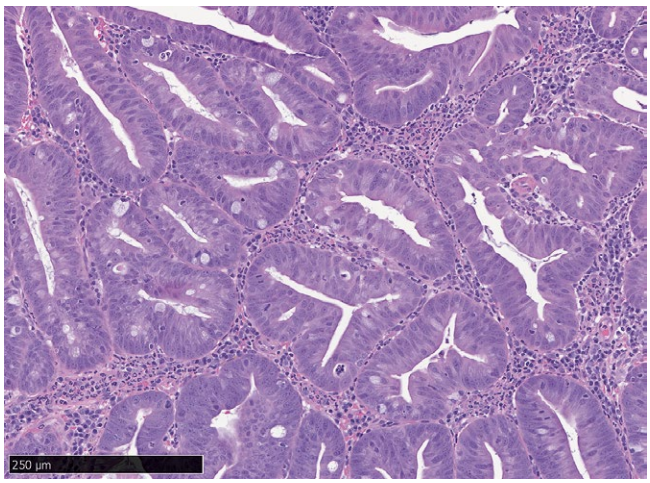



**Fig. 1-155** Rectal adenoma in a dog
Neoplastic epithelial cells are columnar and arranged in tubules or lining the crypts in a pseudostratified pattern. These cells have hyperchromatic cytoplasm, oval nuclei, and variably conspicuous nucleoli. The lamina propria is infiltrated by neutrophils (H&E stain).

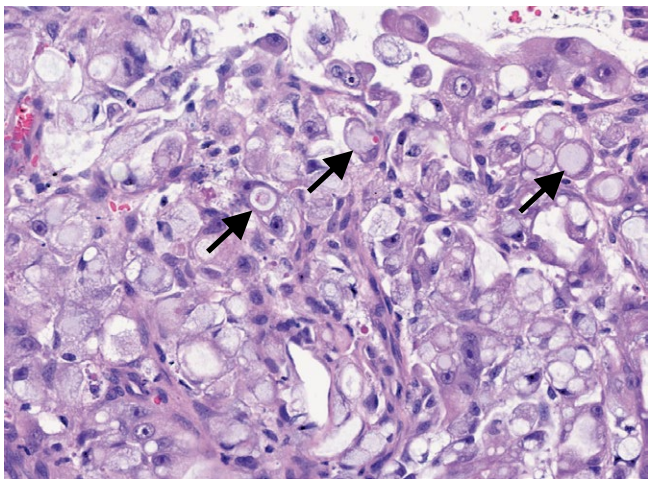


**Fig. 1-156** Gastric adenocarcinoma in a dog
The mucosa is infiltrated by polygonal to irregular neoplastic cells that often have a large cytoplasmic vacuole containing mucinous material (**arrows**) that often displaces the nucleus (signet-ring cells) (H&E stain).

**In situ carcinomas** are most common in the rectum (▶Chap. 8.4.4) and consist of neoplastic proliferation of epithelial cells, with malignancy features confined to the epithelium and without invading the basement membrane. Proliferated cells are characterized by marked dysplasia, formation of highly irregular glands with reduced numbers of goblet cells, loss of cellular polarity, and high mitotic activity.[123] Differentiating a rectal in situ carcinoma from an adenoma may be difficult because the degree of atypia allowed in a rectal adenoma is not standardized. Evaluation of dysplasia is subjective, and the cellular features may vary between different regions of the neoplasm.[120]

**Adenocarcinomas** are malignant epithelial tumors invading through the basement membrane. Adenocarcinomas of the stomach (▶Chap. 6.3.4) are not common but can be aggressive when occurring.[124] They typically affect middle-aged dogs of various breeds.[124] According to the World Health Organization (WHO) classification, gastric adenocarcinomas can be tubular, papillary, mucinous, signet-ring (▶Fig. 1-156), or undifferentiated.[125] An alternative system classifies gastric carcinomas as intestinal-type if neoplastic cells form glands, diffuse-type if cells have an individual or nest array, and mixed-type.[126] Gastric adenocarcinomas are often ulcerated; therefore, endoscopic biopsies might not represent the lesion, especially if few superficial tissue samples are obtained.

**Intestinal adenocarcinoma** is not common in dogs but is the second most common intestinal neoplasm of cats.[127] Dogs with adenocarcinoma of the small intestine (▶Chap. 7.3.9) can have a poor prognosis. However, one study indicates that with surgical excision, even with lymph node metastasis, some affected dogs have a fair prognosis.[128] In the rectum, these tumors can be classified as intramucosal adenocarcinomas when the cells are confined to the lamina propria or invasive carcinomas when the cells infiltrate the submucosa and other layers (▶Fig. 1-157).[120]

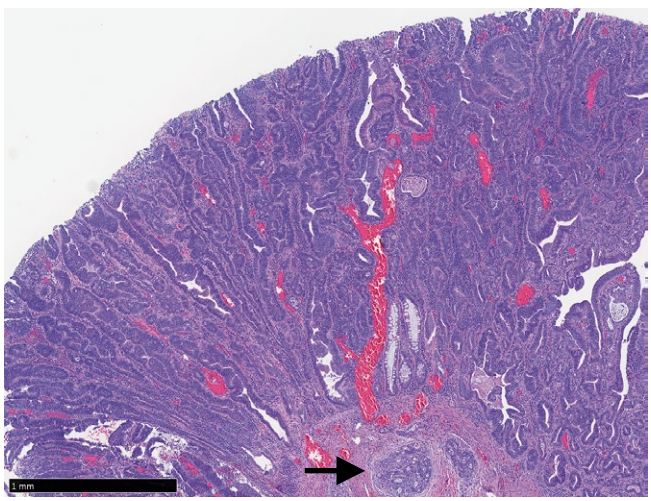



**Fig. 1-157** Rectal adenocarcinoma in a dog
Neoplastic epithelial cells infiltrate the muscularis mucosa and submucosa (**arrow**) (H&E stain).

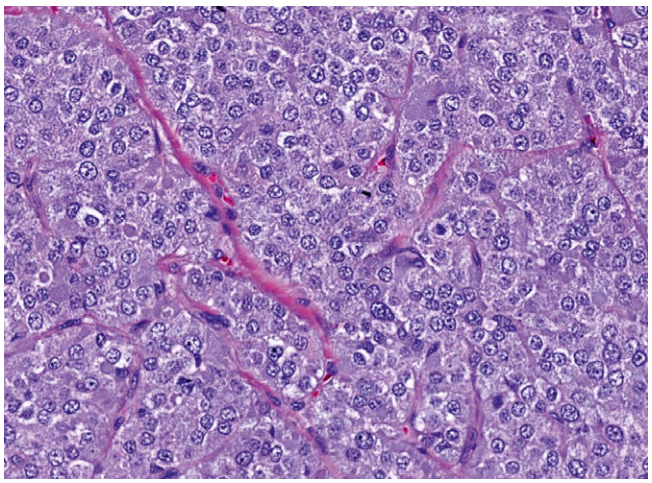


**Fig. 1-158** Neuroendocrine carcinoma in the jejunum of a dog
Neoplastic cells containing abundant, granular cytoplasm are arranged in packets supported by a fine fibrovascular stroma (H&E stain).

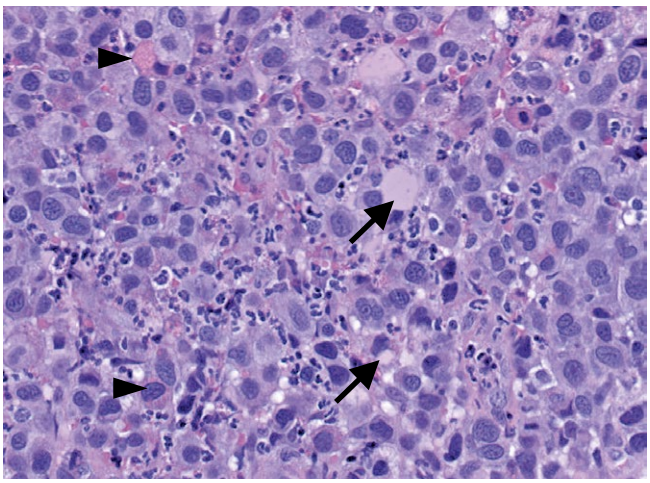


**Fig. 1-159** Plasma cell tumor in the rectum of a dog
Round neoplastic cells with abundant cytoplasm containing pale eosinophilic, amorphous material in the cytoplasm (**arrows**) and occasional bright eosinophilic cytoplasmic globules (**arrowhead**). Neutrophils infiltrate between the neoplastic cells (H&E stain).

**Neuroendocrine carcinomas (carcinoids)** are uncommon neoplasms of the GI tract arising from enteroendocrine cells and usually have an aggressive behavior with widespread metastasis in dogs.[123] These tumors may be functional and produce hormones (▶Chap. 11.4.5). Neoplastic cells are organized in palisading nests, solid sheets, or rosettes supported by a delicate fibrovascular stroma.[129] Cells are usually small, with a moderate amount of granular cytoplasm (▶Fig. 1-158).[129] Argyrophilic granules can be detected with Grimelius stain, while a modified Fontana-Masson stain reveals argentaffin granules. However, special stains are not specific. Therefore, definitive diagnosis requires electron microscopy or IHC for chromogranin, synaptophysin, or PGP 9.5.[120]

**Extramedullary plasma cell tumors** are uncommon in the GI tract.[130,131] Histologically, the cells are easily recognized as a round cell tumor, but differentiation from lymphoma might be challenging. Extramedullary plasma cell tumors in the GI tract are well-demarcated, unencapsulated nodules with cells located primarily in the submucosa that may extend to the mucosa. Well-differentiated cells have a perinuclear pale area with a central or eccentric nucleus (▶Fig. 1-159) with occasional binucleation and multinucleation.[130] The cytoplasm may contain eosinophilic globules (Russell bodies) and amyloid deposits, and chondroid and/or osseous metaplasia can be detected in some cases.[130] IHC for multiple myeloma oncogene-1 (MUM-1) or immunoglobulin light chains confirms the diagnosis.[120]

**Gastrointestinal mast cell tumors** are uncommon but more prevalent in cats than dogs. The neoplasm is frequently well-demarcated, located in the submucosa and muscularis layer, but transmural infiltration may occur.[132] Cells tend to be anaplastic, poorly granulated, and organized in sheets or grouped in packets resembling a carcinoid.[133] Few eosinophils infiltrate the neoplasm.[132] Typical mast cell granules are not observed in gastrointestinal mast cell tumors, often failing to stain with Giemsa and toluidine blue stains. In cats, only a third of intestinal mast cell tumors are positive for KIT, and about half are positive for histamine, posing a challenge to confirm the diagnosis.[134] Lymphocyte and plasma cell markers may be used to rule out tumors from this lineage. Gastrointestinal mast cell tumors tend to be more aggressive than those located in the skin.[133]

**Mesothelioma** is rare in dogs and cats, and when it occurs, mesothelial cells arise from pleural or peritoneal linings. These cells may differentiate into epithelial-like or mesenchymal-like cells on the peritoneal surface. There are epithelial, sarcomatoid, and biphasic types with numerous subcategories. Therefore, mesothelioma must be differentiated from reactive mesothelium, carcinomatosis, and metastatic sarcoma. With IHC, cytokeratin and vimentin are supportive of mesothelioma. Asbestos exposure is associated with mesothelioma in humans but less commonly with mesothelioma in dogs.[135]

### 1.8.1.6 Miscellaneous disorders

**Uremic gastropathy** is a lesion of dogs with renal failure. Histologically, mineralization occurs especially in the mid-portion of the mucosa (▶Fig. 1-160) and in blood vessels of the submucosa, in association with fibrinoid necrosis of the vessel walls, edema, and necrosis of the epithelium. The von Kossa histological stain highlights the mineralization.[136]

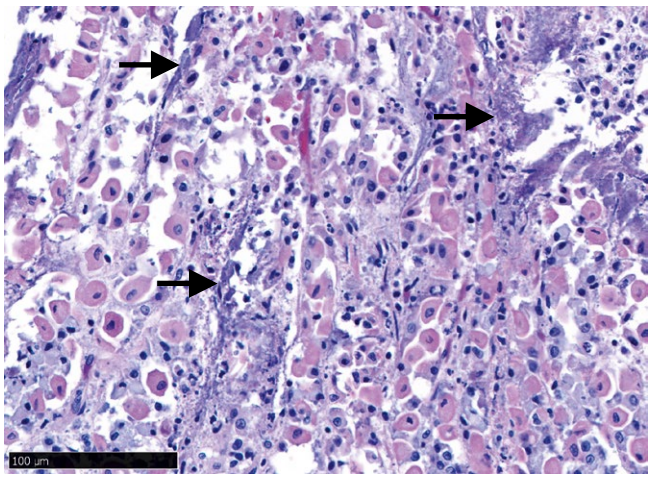



**Fig. 1-160** Uremic gastropathy, gastric fundus in a dog
Deposits of granular, deeply basophilic material (mineralization) in the mucosa are associated with degeneration and necrosis of epithelial cells (H&E stain).

**Intestinal lymphangiectasia** (▶Chap. 7.3.8) can be a primary process or secondary to inflammation, neoplasia, or impaired lymphatic drainage.[137] Primary lymphangiectasia is less common and occurs in certain dog breeds, including Yorkshire terriers, Maltese, Norwegian lundehunds, Chinese shar-peis, and soft-coated wheaten terriers.[137] The etiology of primary intestinal lymphangiectasia is unknown, and dogs have dilated lacteals that can rupture and leak into the lumen and interstitium, resulting in PLE.[137] Dilated crypts filled with cellular debris, mucus, and proteinaceous material are commonly seen in these cases.[137] Lipogranulomas associated with ruptured lacteals might be seen in the serosa and submucosa.[138] Lymphatic hypoplasia, where lacteals cannot be detected histologically, has been reported in dogs with PLE.[139] The dilated crypts are referred to as "crypt abscesses," but bacteria are not involved with the lesions.[140] Mild neutrophilic or lymphoplasmacytic inflammation in the lamina propria is common. Dilated lacteals and crypt abscesses can be associated with PLE.[51–53] Segmental lipogranulomatous lymphangitis and lymphangiectasia have been described in dogs' intestines without PLE, presenting as a mass-like lesion.[141]

**Deposition of amyloid** in the GI tract is reported in aging dogs, and dogs and cats with systemic amyloidosis and in association with extramedullary plasma cell tumors.[130,142,143] Amorphous, eosinophilic, Congo red-positive material is seen within the lamina propria and around vessels in the submucosa and muscularis externa and must be differentiated from fibrosis.[142,143]

**Intestinal vascular ectasia/angiodysplasia** is an uncommon cause of melena and hematochezia in dogs. The pathogenesis is not completely understood, and these lesions are reported in young to aged dogs.[144] Vascular ectasia occurs as multifocal red areas of venous and arterial dilation in the mucosa and submucosa.[144] Lesions are more frequently located in the colon and cecum, but involvement of the small intestine has been described.[145] Endoscopic evaluation (flexible endoscopy and/or video capsule endoscopy) is essential for the diagnosis because these lesions are not visible from the serosal surface (▶Chap. 1.5).[144]

**Intestinal pseudo-obstruction** is characterized by functional evidence of intestinal dysmotility without mechanical obstruction of the lumen. In veterinary medicine, it is associated with intestinal leiomyositis, dysautonomia, ganglionitis, and smooth muscle α-actin deficiency.[146] Intestinal leiomyositis is an uncommon disorder in dogs and cats, resulting in intestinal pseudo-obstruction characterized by impaired intestinal motility. The condition is believed to be immune-mediated with infiltration of lymphocytes targeting the external muscularis layer of the small intestine, especially in the jejunum and, to a lesser degree, the stomach and colon. The inflammation spares myenteric ganglia and plexuses. The myocytes in the muscularis externa degenerate, necrotize, or are replaced by a loose-to-dense fibrous stroma (▶Fig. 1-161). Full-thickness biopsies are essential for the diagnosis.[147] Dysautonomia is reported in dogs and cats, and lesions consist of degeneration of autonomic ganglia with neuronal vacuolation, loss of Nissl substance (chromatolysis), and a marked reduction in ganglionic neurons.[148] Myenteric ganglionitis, where inflammation may be accompanied by neuronal degeneration and loss, is rare in dogs and cats.[149,150] Deficiency of smooth muscle α-actin is rarely reported in cats with diffuse intestinal dila-

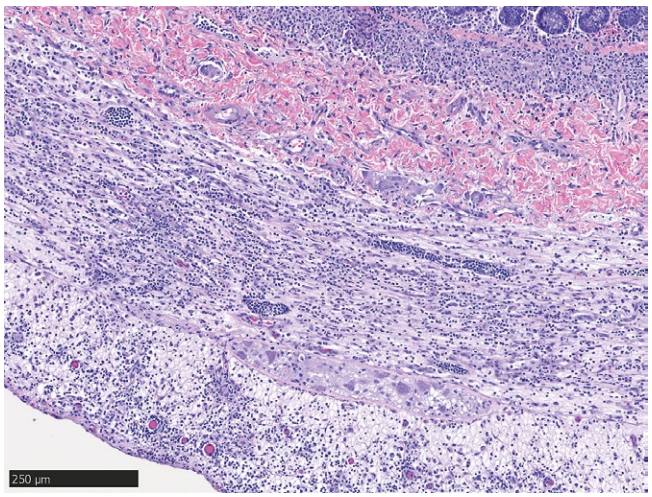



**Fig. 1-161** Intestinal leiomyositis in the jejunum of a dog
The leiomyocytes in the muscularis externa are diffusely degenerated and atrophied with dense infiltration of inflammatory cells (H&E stain).

tion and is histologically recognized as cytoplasmic basophilia of the external muscularis layer. IHC can demonstrate a loss of smooth muscle α-actin expression.[146]

**Ganglioneuromatosis** is a poorly demarcated, diffuse intramucosal to transmural proliferation of ganglion cells of the enteric autonomic nervous system. This condition is reported in young to aged dogs. Ganglioneuromatosis is considered a hamartomatous process, contrasting from ganglioneuroma or other neoplasms of neural origin that form well-demarcated-to-nodular lesions.[151]

**Intussusception** occurs when a portion of the intestine telescopes into an adjacent portion of the intestine. This can occur physiologically without consequence, but if persistent, the affected areas of the intestine can undergo venous infarction with necrosis and hemorrhage. In addition to the intestine and cecum, areas that can undergo intussusception include the gastroesophageal and pylorogastric regions. The most common sites in the intestine include the ileocecal junction and jejunum. Histologically, lesions include vascular congestion and dilation, hemorrhage, accumulation of seroproteinaceous fluid, fibrin deposition, and necrosis. Microscopic lesions may also identify an underlying cause such as, neoplasia, which tends to occur more commonly in cats, and inflammatory disease, which is more common in dogs.[152,153]

**KEY FACTS**

- Histopathologic assessment of gastrointestinal tissue can identify specific lesions that can help definitively diagnose some diseases.
- At the same time, histopathology and morphometry have limitations. Many enteric conditions cause alterations resulting in clinical signs but lack specific microscopic lesions.
- Also, the quality and number of endoscopic biopsies and histopathologic processing may impact the results.
- Reaching a final diagnosis requires communication between the clinician and the pathologist.

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
svg.to/9842-01-08-01

## 1.8.2 Liver and the gallbladder

John Cullen

### 1.8.2.1 Introduction

This chapter will provide a brief overview of the histologic appearance of the normal liver and the major disease processes affecting the canine and feline hepatobiliary systems. More detailed descriptions can be found in several references.[1–6]

### 1.8.2.2 Normal histology of the liver

The organization of the liver is composed of multiple repeating units, not unlike a cluster of grapes held firmly. There are several schemes for describing the functional units, and the main two are based on either blood flow or bile secretion. The most frequently used scheme refers to the hepatic lobule, which is based on blood flow, and this terminology will be used here. The hepatic lobule is a roughly hexagonal structure, 1–2 mm wide. At the center, the lobule has a terminal hepatic venule (also termed the central vein), which is a tributary of the hepatic vein. There are typically five or six portal tracts at the outer edges of the lobule. Within each portal tract, there are bile ducts, branches of the portal vein, the hepatic artery, autonomic nerves, and lymph vessels, all supported by an extracellular matrix containing abundant collagenous stroma. The limiting plate is defined as a dis-

continuous border of hepatocytes that abuts the edge of the portal tract connective tissue. Blood flows into the sinusoids from the terminal distributing branches of the hepatic artery and portal veins that leave the portal tracts and penetrate the limiting plate, draining into the sinusoids (▶Fig. 1-162). Portal blood and hepatic arterial blood mix in the sinusoids. Blood drains from the sinusoids into the central veins and to progressively larger sublobular veins and then into the hepatic veins and subsequently into the vena cava. The lobule is divided conceptually into three regions; periportal, surrounding the portal tract; centrilobular, surrounding the central vein; and between these two is the midzonal region.

Within the parenchyma of adult dogs and cats, hepatocytes are arranged in one-cell-thick branching plates, although in neonates and regenerating liver, the plates are typically two cells thick. Vascular sinusoids separate the hepatic plates. Hepatic sinusoids differ from capillaries in that they are lined by fenestrated endothelial cells that lack a typical basement membrane, whereas capillaries have a continuous endothelial lining and are ensheathed in the basement membrane. The sinusoidal endothelium is supported by a fine network of extracellular matrix containing collagen types III, IV, and XVIII and other extracellular matrix components beneath the endothelial cells. Collagen type I is not found in normal sinusoids. These elements collectively make up the "reticulin" of the liver that can be stained with special silver stains. This scaffolding supports the endothelial cells and allows for a thin space, the space of Disse, that occurs between the endothelial cells and the apical surface of the hepatocytes. Within the sinusoids, plasma constituents can readily access the surface of the hepatocytes via the fenestrations in the sinusoidal endothelium, although circulating cells are excluded. The sinusoidal-facing surface of the hepatocyte has a continuous arrangement of microvilli that facilitate the prodigious uptake and secretion of substances that are characteristic of the liver. Any disturbances of the microanatomy of the sinusoids can lead to a significant loss of hepatic function.

#### 1.8.2.2.1 Hepatocytes

Hepatocytes are polygonal with an abundant cytoplasm that can vary from densely eosinophilic to pale depending on the quantity of cytoplasmic glycogen. The size of the hepatocytes can vary based on the extent of vacuolation. The nucleus is centrally placed, and one or more nucleoli may be recognized; binucleated cells may occasionally be found. Mitoses are rarely seen in normal liver.

There is marked zonal heterogeneity of the hepatocytes' metabolic capabilities depending on their location within the lobule. The most important variation involves the metabolism

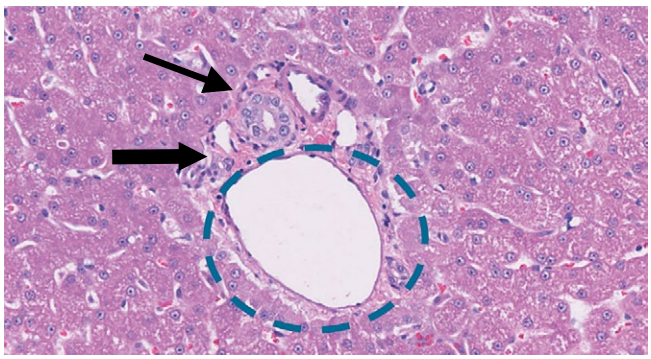


**Fig. 1-162** H&E stain: Normal portal tract

The portal vein is outlined in the **dashed line**, the bile duct has the **thin arrow,** and the hepatic artery is indicated by the **thicker arrow**.

of endogenous (steroid hormones) and exogenous substances (drugs, toxins). In the centrilobular region of the lobule, the cytochrome P450 enzymes (CYPs) are most abundant. This is significant because the CYPs metabolize these substances for excretion from the body via the bile or urine as water-soluble compounds. This process involves initial oxidation by the CYPs in preparation for conjugation to water-soluble molecules, such as glutathione, sulfates, and others. When there are excessive amounts of the parent compound or inadequate glutathione, the highly reactive CYP-oxidized molecules can form bonds with cellular proteins and lipids, leading to acute necrosis. It is for this reason that nearly all drug toxicities lead to centrilobular necrosis (▶Fig. 1-163).

#### 1.8.2.2.2 Kupffer cells

Hepatic macrophages, termed *Kupffer cells,* line the lumen of the sinusoids. These cells are components of the monocyte-macrophage system and have an important role in the immune functions of the liver. They remove a variety of infectious agents, as well as important inflammatory mediators, such as endotoxins, from the portal blood. Senescent cells, such as erythrocytes, immune complexes, and particulate material, are also removed by phagocytosis. Damage to the Kupffer cells or bypassing the hepatic sinusoidal circulation due to congenital or acquired shunting of portal blood leads to the abnormal entry of various infectious agents and inflammatory mediators into the systemic circulation.

#### 1.8.2.2.3 Hepatic stellate cells

Hepatic stellate cells, unlike the Kupffer cells, are found within the space of Disse, under the endothelium, and between hepatocytes. Hepatic stellate cells are primarily

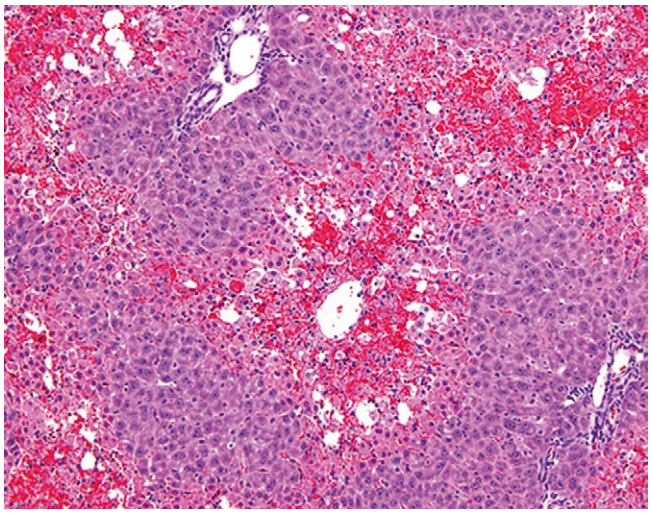


**Fig. 1-163** Acute centrilobular necrosis

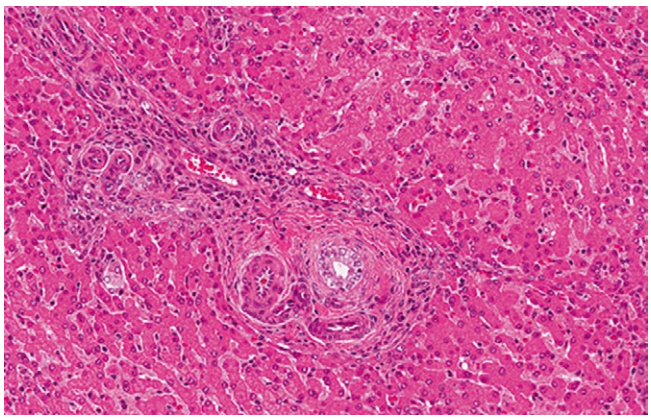


**Fig. 1-164** Portal tract with typical changes associated with portal vein hypoperfusion

Note that no portal vein is evident, and multiple small arterioles are present.

responsible for storing vitamin A in their characteristic cytoplasmic vacuoles. During hepatic injury, stellate cells are important contributors to hepatic fibrosis. Typically, cats have prominent, clear round vacuoles in their hepatic stellate cells and should not be confused with hepatic lipid vacuoles.

### 1.8.2.3 Vascular disorders of the liver

Most vascular disorders of the liver of primary clinical significance involve hypoperfusion by the portal vein (▶ box "Vascular disorders"). There is a stereotypical histologic pattern seen in liver in response to inadequate portal inflow that consists of proliferation and branching of the hepatic artery, loss or diminution of the portal vein profile, and hepatocellular atrophy (▶Fig. 1-164). Lymphatic dilation may also be present. Congenital portosystemic shunts are not associated with portal hypertension, but portal vein hypoplasia, portal vein obstruction, and hepatic arteriovenous malformations/fistulae all have the potential to cause portal hypertension. Clinical data is needed to separate the possible conditions leading to portal vein hypoperfusion. Imaging studies (especially CT angiography) are now most useful for detecting portosystemic shunts, intra- or extrahepatic arteriovenous malformations/fistulae, and portal vein obstructions.

*Peliosis hepatis* is the term applied to dilated vascular spaces, typically endothelial lined, found in the liver parenchyma of older animals. They are more frequent in the immediate subcapsular region of the parenchyma. Cats are affected more often than dogs. The cause is unknown but may involve loss of hepatocytes leading to distention of sinusoids. There is no clinical significance, but they should be differentiated from hemangiosarcoma metastasis.

**Vascular disorders of the liver**

- Congenital portosystemic shunts
- Vascular disorders associated with portal hypertension
  - Portal vein hypoplasia
  - Hepatic arteriovenous malformations/fistulae
  - Portal vein obstruction
- Incidental vascular disorders
  - Peliosis hepatis

### 1.8.2.4 Parenchymal disorders of the liver

Parenchymal disorders of the liver are listed in the ▶ box "Parenchymal disorders."

**Parenchymal disorders of the liver**

- Reversible injury
  - Cell swelling, lipid accumulation, steroid-induced hepatopathy
- Amyloidosis
- Hepatocellular death
  - Apoptosis
  - Necrosis
- Acute and chronic hepatitis
- Hepatic abscesses and granulomas
- Hepatic metabolic storage disorders

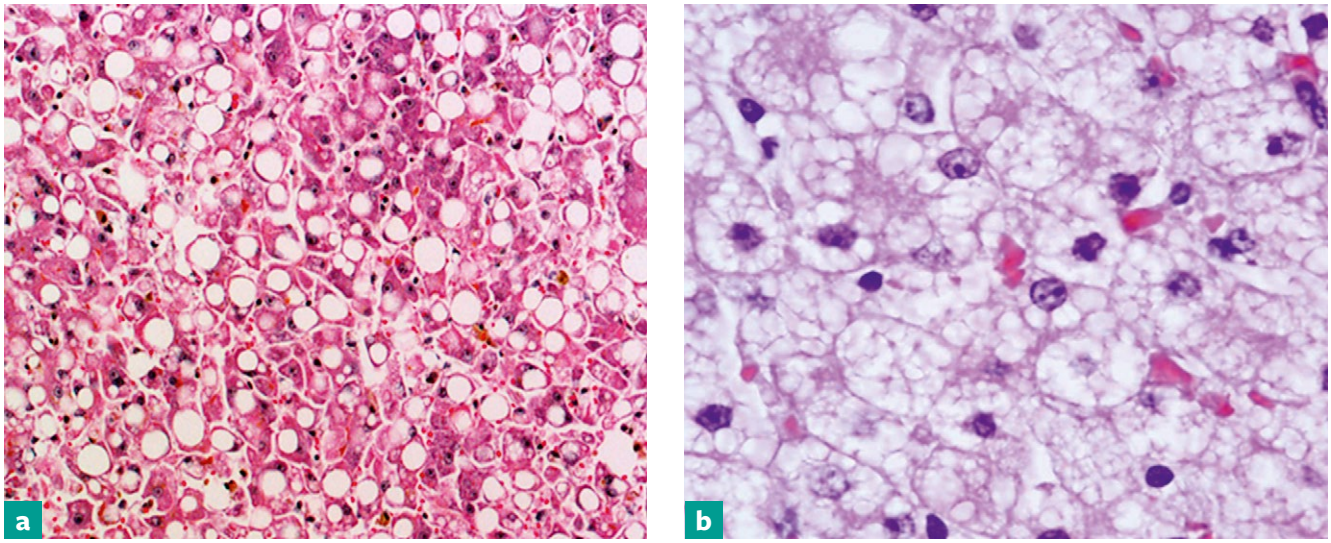



**Fig. 1-165** Lipid vacuoles in hepatocytes
Macrovesicular lipid (**a**) and microvesicular lipid (**b**) in hepatocytes

#### 1.8.2.4.1 Reversible hepatocellular injury

There are multiple changes in hepatocytes associated with reversible injury. Initial damage to a hepatocyte can manifest as cell swelling and increased pallor of the cytoplasm, however, even in biopsy specimens this change can be difficult to appreciate.

The accumulation of lipids in hepatocytes is readily appreciated as clear, round discrete cytoplasmic vacuoles. The term microvascular steatosis is used when vacuoles are smaller than hepatocyte nuclei, and the nucleus remains central (▶ Fig. 1-165a). This lesion may be associated with mitochondrial dysfunction and indicate serious hepatocyte injury. Macrovesicular lipid is characterized by vacuoles that are larger than a hepatocyte nucleus and tend to displace the nucleus (▶ Fig. 1-165b). In adults, hepatocellular lipid accumulation is more common in cats than in dogs.

Steroid-induced hepatopathy is limited to dogs and recognized as swelling of affected hepatocytes by abundant glycogen deposition leading to diaphanous strands of eosinophilic cytoplasm separated by clear, ragged vacuoles. Corticosteroids, either endogenous or exogenous, are the most frequent cause, but it is possible that other adrenal or ovarian steroids can produce similar but less dramatic swelling.

#### 1.8.2.4.2 Hepatic amyloidosis

Amyloid may occur in the liver, and a variety of sites can be affected. Amyloid within the space of Disse is a particular concern because it limits hepatic function considerably. Histologically, pale eosinophilic, glassy material is appreciated by routine staining with H&E.

#### 1.8.2.4.3 Hepatocellular death: apoptosis and necrosis

Hepatocytes, as well as other cells of the liver, can be destroyed by a wide variety of insults, including toxins, therapeutic drugs, infectious agents, hypoxia, immune mechanisms, and severe metabolic disturbances. There are two principal pathways of cell death.

**Apoptosis** or programmed cell death is an active process that results in cell shrinkage, retention of membrane integrity, and subsequent fragmentation of the cell into deeply eosinophilic apoptotic bodies that are phagocytosed by a variety of cell types (▶ Fig. 1-166).

**Necrosis** has two forms. Coagulative necrosis, in which sudden catastrophic denaturation of cytoplasmic proteins occurs; the affected cell may retain its outline while the nucleus undergoes pyknosis and eventual karyorrhexis and lytic necrosis. Oncosis, in which loss of membrane integrity leads to cell swelling and rupture. A series of changes occur following the death of hepatocytes. Typically, the reticulin

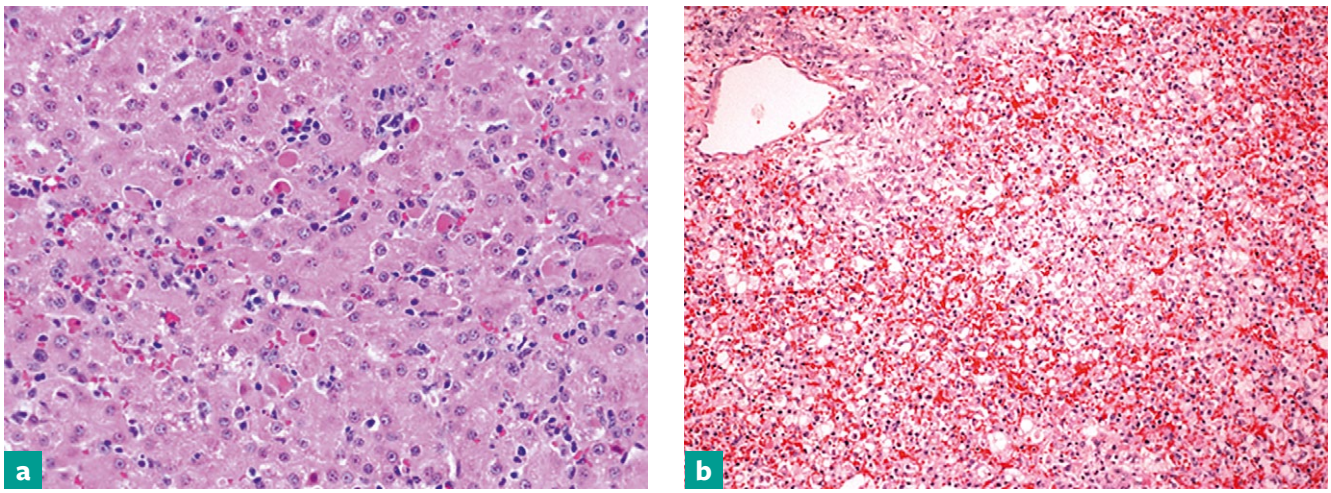



**Fig. 1-166** Hepatocyte apoptosis and necrosis

**a** Apoptotic hepatocytes are recognized as shrunken, deeply eosinophilic remnants.

**b** Necrosis is characterized by cell swelling and lysis.

framework is damaged, and there is a local influx of erythrocytes at the site of injury. Kupffer cells proliferate, and macrophages are recruited to the area to phagocytose the cellular debris, often leaving hemosiderin or lipofuscin-laded macrophages at the site of prior injury. The distribution of cell death should be recorded based on location and severity. Centrilobular necrosis, for example, is a common response to chemical or drug-induced injury and to acute severe hypoxia.

### 1.8.2.5 Acute and chronic hepatitis and cirrhosis

**Acute hepatitis** is characterized by a combination of inflammation and hepatocyte death. Depending on the time course, early regeneration may also be evident. The type of inflammation varies with the etiology, which neutrophils predominating in bacterial and protozoal infection, pyogranulomatous inflammation following fungal infections and granulomatous responses following mycobacterial infections.

**Chronic hepatitis** can have many causes and is far more common in dogs than cats. Histologically, there is hepatocyte damage with apoptosis or necrosis, fibrosis, and an influx of mononuclear inflammatory cells, lymphocytes, and plasma cells, although other cells types can also be found (▶Fig. 1-167). Evidence of regeneration may also be present depending on the severity and duration of the injury. The pattern and extent of inflammation and fibrosis should be included in the histologic description.

**Copper accumulation** is the most commonly known cause of chronic hepatitis in dogs, although many cases of chronic hepatitis are idiopathic. In addition to the typical changes seen with chronic hepatitis, copper-induced hepatitis also presents with pigmented macrophage aggregates that may be surrounded by mixed inflammatory cells. Individual hepatocyte necrosis can be common. Copper stains are very useful for identifying copper in the liver and can be used for semi-quantitative assessment of the copper content (▶Fig. 1-168).

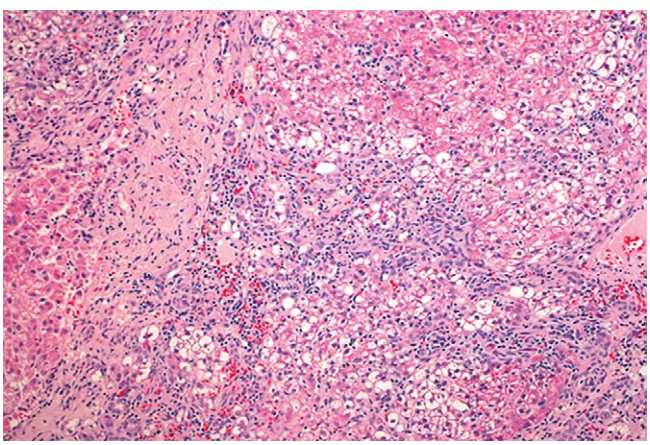


**Fig. 1-167** Chronic hepatitis

Inflammatory infiltrates, fibrosis, hepatocellular injury, and proliferated bile ducts are present in a canine liver.

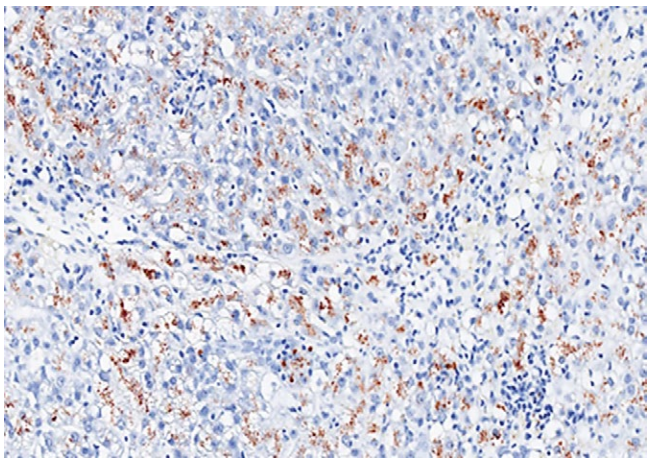


**Fig. 1-168** Hepatic copper accumulation is recognized as dark orange granules in a dog liver. Rhodanine stain

**Cirrhosis** is the end stage of chronic hepatitis and is defined as the presence of bridging fibrotic septa that often contain shunting vessels and the formation of regenerative nodules. Because of the extensive disruption of normal lobular architecture, portal vein inflow is often inhibited, leading to portal hypertension. While common in dogs, cirrhosis is rarely seen in cats.

#### 1.8.2.5.1 Hepatic abscesses and granulomas

Hepatic abscesses resemble those elsewhere in the body with a central region of necrosis and cell debris rimmed with an influx of neutrophils and a peripheral zone of mononuclear cells in older lesions.

Hepatic granulomas are aggregates of activated macrophages, typically with an epithelioid phenotype, and resemble granulomas in other tissues.

#### 1.8.2.5.2 Hepatic metabolic storage diseases

Metabolic storage disorders are usually inherited but can, in some circumstances, be acquired. Both hepatocytes and Kupffer cells can be involved depending on the type of disorder. There are many appearances possible with the variety of storage diseases, but most often, there are either vacuoles or pigments in the hepatocytes or Kupffer cells.

### 1.8.2.6 Normal histology of the biliary tree

#### 1.8.2.6.1 Biliary epithelium

The biliary system begins as canaliculi, spaces formed by specialized hepatocellular membranes between adjacent hepatocytes. The canalicular system begins in the centrilobular regions of the hepatic lobule and bile flows towards the portal tract via intermediary cholangioles that converge into interlobular bile ducts. Bile then flows into the lobar ducts lined with low columnar epithelium that unite to form the hepatic duct. The confluence of the common hepatic duct and the cystic duct from the gallbladder form the common bile duct by which bile is carried to the duodenum.

Bipotential progenitor cells that have the ability to differentiate into hepatocytes or biliary epithelium are believed to reside in the area immediately adjacent to the canals of Hering. These cells may proliferate in circumstances in which mature hepatocytes or bile duct epithelium cannot replicate, such as severe injury or nutritional deficits. When these cells proliferate, they form islands or crude tubules of small basophilic cells found initially at the margin of the limiting plate. This proliferation is regarded as one of the forms of the *ductular reaction* and is a hallmark of severe injury.

#### 1.8.2.6.2 Gallbladder epithelium

The epithelium of the gallbladder is typically columnar, and there are numerous mucus-producing goblet cells present.

### 1.8.2.7 Biliary disorders

Common biliary disorders are listed in the ▶ box "Biliary disorders."

**Common biliary disorders**
- Cholestasis and cholate stasis
- Congenital biliary cystic disorders
- Inflammation
  - Neutrophilic cholangitis
  - Lymphocytic cholangitis
  - Destructive cholangitis
  - Cholecystitis
- Gallbladder mucocele
- Gallbladder infarction

#### 1.8.2.7.1 Cholestasis

##### Intrahepatic cholestasis

The typical pattern of intrahepatic cholestasis involves the presence of bile plugs in the canaliculi (▶Fig. 1-169a). There are many possible causes ranging from disturbances of the function of the molecular pumps that transport bilirubin or

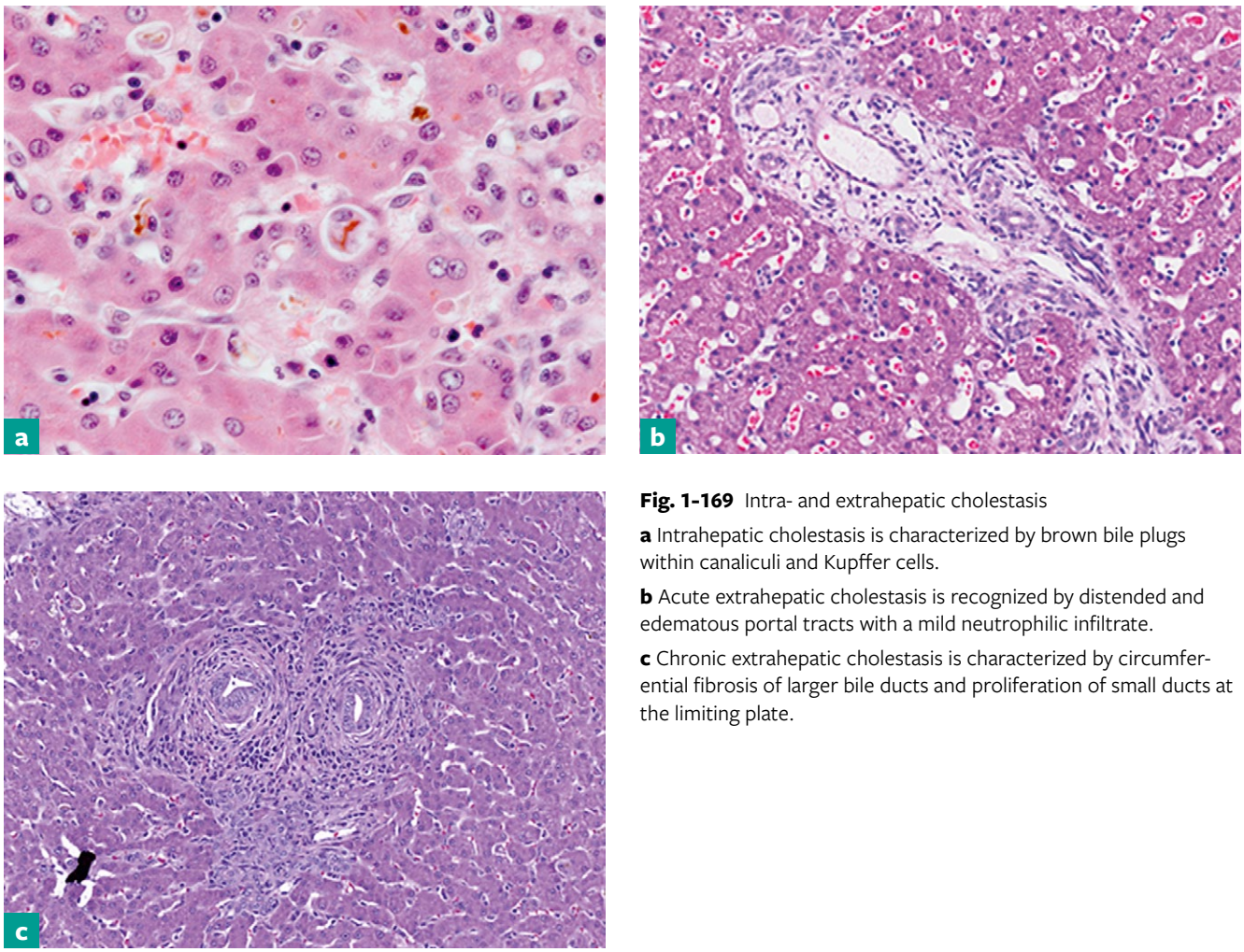


**Fig. 1-169** Intra- and extrahepatic cholestasis

**a** Intrahepatic cholestasis is characterized by brown bile plugs within canaliculi and Kupffer cells.

**b** Acute extrahepatic cholestasis is recognized by distended and edematous portal tracts with a mild neutrophilic infiltrate.

**c** Chronic extrahepatic cholestasis is characterized by circumferential fibrosis of larger bile ducts and proliferation of small ducts at the limiting plate.

bile acids, as caused by endotoxin and some antibiotics, or direct damage to hepatocytes from various toxins. Overload of the excretory pathways and concurrent hypoxia caused by acute hemolytic anemia can also lead to the formation of bile plugs. Regurgitated bile plugs can also be seen in macrophages.

### Extrahepatic cholestasis

**Acute extrahepatic cholestasis** has a characteristic pattern in the liver. Portal tracts develop edema, separating the elements of the connective tissue. A mild neutrophilic infiltrate is present, as well as small numbers of pigmented macrophages (▶ Fig. 1-169b). The bile ducts may be dilated and may contain mucus. The lining epithelial cells lose their uniform cuboidal or columnar shape and become mildly pleomorphic. With time, proliferations of small caliber bile ducts, one type of ductular reaction, usually form at the outer margins of the portal tract.

**Chronic extrahepatic cholestasis** develops with prolonged disruption of the bile flow. The edema of the portal tract resolves, and there is a characteristic proliferation of myofibroblasts that surround the ducts forming an "onion skin" appearance. Infiltrating inflammatory cells are most often a mix of mononuclear cell types, and pigmented macrophages are more numerous (▶ Fig. 1-169c). The proliferation of bile ducts becomes more prevalent as the newly formed bile ducts mature. With time, canalicular plugs tend to become less evident, but bile in Kupffer cells can persist. Special stains such as Hall's stain can be used to identify bile that may not be evident on H&E, but frozen sections are superior to paraffin-embedded for this purpose if detection of bile is essential.

## 1.8.2.7.2 Inflammation of the biliary tree

Inflammatory diseases of the bile ducts include two main categories, neutrophilic and lymphocytic cholangitis.

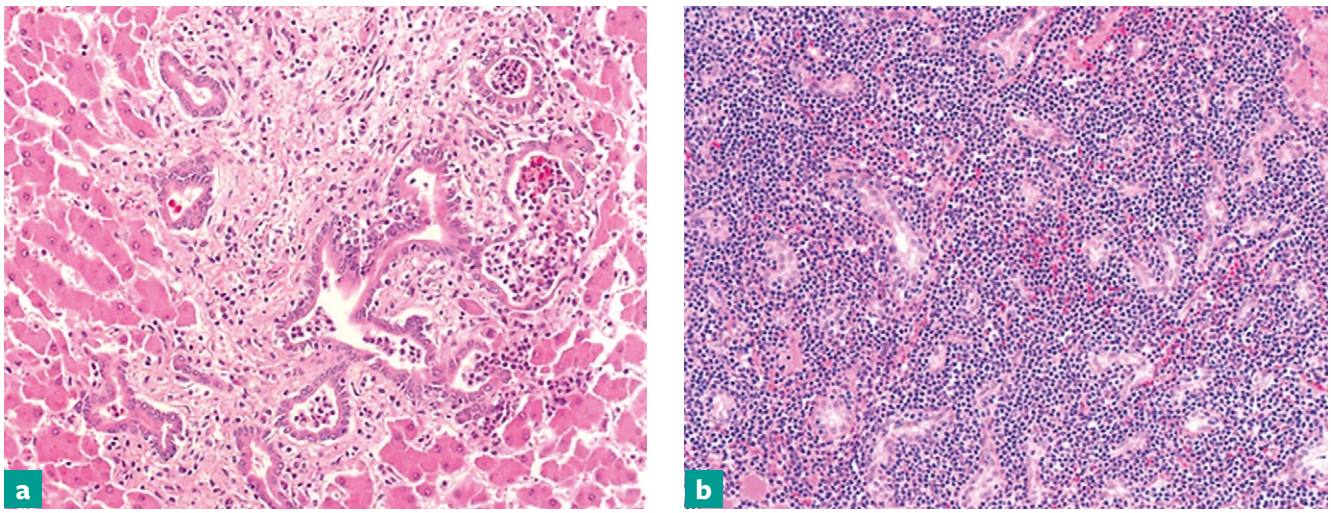


**Fig. 1-170** Cholangitis
**a** Neutrophilic cholangitis
**b** Lymphocytic cholangitis

### Acute neutrophilic cholangitis

Neutrophilic cholangitis is caused by bacterial infection of the biliary tree. This may be the result of intestinal bacteria inappropriately entering the common bile duct and extending to the liver and possibly the gallbladder but translocation across the intestinal wall and hematogenous spread in the portal circulation is another possible route of infection. Acute neutrophilic cholangitis is recognized by the presence of neutrophils within the lumen or within the lining of the bile duct. In some circumstances, there are only neutrophils, and in others, clear suppuration is evident. Because suppuration is not always present, the term neutrophilic cholangitis is preferred over suppurative cholangitis. In some instances, there can be necrosis of the bile duct wall with the release of bacteria into the adjacent parenchyma. In these instances, there is focal necrosis of hepatocytes and a primarily neutrophilic infiltrate with associated macrophages. In this circumstance, the term cholangiohepatitis is appropriate as both the biliary tree and the hepatic parenchyma are involved (▶Fig. 1-170a).

### Chronic neutrophilic cholangitis

With time, untreated or under-treated acute cholangitis evolves into chronic neutrophilic cholangitis. There are varied appearances of this condition depending on the presence or absence of concurrent obstruction. Typically, there is a mixed inflammatory infiltrate with lymphocytes and macrophages often predominating, but neutrophils are still evident in bile ducts and within the duct walls. Fibrosis of the portal tracts is typically evident as well. One form of ductular reaction (biliary hyperplasia) is also more extensive in the chronic form.

### Lymphocytic cholangitis

Lymphocytic cholangitis is a disease of cats, usually older cats. Histologically, there is a dense accumulation of mature lymphocytes with dense basophilic nuclei and scant cytoplasm centered on bile ducts (▶Fig. 1-170b). Plasma cells can be found in some instances as well. Typically, there is a proliferation of bile ducts and, in many cases, evidence of damage to the biliary epithelium. In some cases, this damage is sufficient to destroy the duct and leave a fibrous scar. The diagnostic challenge is ruling out lymphoma as both disorders lead to infiltrates of small, mature lymphocytes, and in both circumstances, T cells predominate. Lack of bile duct proliferation or damage and lymphoid infiltrates around the central veins suggest lymphoma. Ancillary diagnostics, such as PARR, and evaluation of other organ systems for signs of lymphoma can aid in a final diagnosis.

### Parasitic cholangitis

Dogs and cats can be infected with biliary flukes of a variety of species. The response of the bile ducts to the presence of flukes involves robust fibrosis and often distention of the affected ducts. Necrotic debris can be abundant. Inflammation is variable and likely reflects the effects of chronicity. Ductular reactions can be prominent. It is often difficult to find flukes in biopsy material.

#### Destructive cholangitis

Rare, idiosyncratic toxicity can lead to destructive cholangitis, a condition characterized by necrosis of the biliary epithelium and sudden dramatic increases in serum bilirubin (▶Chap. 1.3.3.5). Necrotic epithelial cells line ducts or, in some instances, the ducts are not apparent within the portal tracts, and only pigmented, foamy macrophages containing bile and debris remain. Trimethoprim-sulfamethoxazole is one of the drugs associated with this condition.

### 1.8.2.7.3 Disorders of the gallbladder

#### Cholecystitis

The gallbladder is susceptible to infections similar to those of the biliary tree. Consequently, the gallbladder can be infected with a variety of bacteria, most often of enteric origin, and, less often, other organisms, including fungi, protozoa, and parasites. Infection of the gallbladder leads to inflammatory infiltrates, typically neutrophilic in bacterial infections, and proliferation or focal ulceration of the mucosa. Chronic infection can lead to prominent proliferative response by the epithelium.

#### Gallbladder mucocele

Gallbladder mucocele is an increasingly common disorder. Histologically, dense laminated pale basophilic mucus fills the lumen of the gallbladder, and the affected mucosa forms "staghorn"-shaped projections into the dense mucus.

#### Gallbladder infarction

Gallbladder infarction can develop spontaneously or in concert with gallbladder mucocele. There is a characteristic full-thickness necrosis of the gallbladder. Often, thrombosis of a branch of the cystic artery is present. Rupture of the gallbladder wall may occur and can lead to bile peritonitis.

## 1.8.2.8 Hepatic hyperplasia and neoplasia

### 1.8.2.8.1 Nodular hyperplasia and regenerative nodules

In the liver of the dog almost exclusively, two types of hyperplastic lesions can occur. The first, nodular hyperplasia, is an idiopathic proliferation of mature hepatocytes that forms an expansile mass within the liver. Typically, the remainder of the liver is normal, and the masses retain lobular architecture with portal tracts present. They are of no clinical significance but should be distinguished from primary or metastatic lesions.

Regenerative nodules form in a background of significant parenchymal injury. These nodules differ from nodular hyperplasia as they typically lack normal portal tracts.

### 1.8.2.8.2 Hepatocellular adenoma

These benign lesions are formed by mature hepatocytes with little evidence of pleomorphism. As they grow, hepatic adenomas compress the adjacent parenchyma in a uniform fashion with a distinct line of demarcation between the neoplasm and the adjacent parenchyma. Normal lobular architecture is lost in adenomas, and portal tracts are rare or absent. Focal regions of necrosis and hemorrhage can be found. The histologic similarity between regenerative nodules and adenomas can cause diagnostic challenges in small biopsies.

### 1.8.2.8.3 Hepatocellular carcinoma

Hepatocellular carcinoma is a mass formed by malignant hepatocytes. Often, there is moderate to marked pleomorphism of the hepatocytes. Sinusoidal arrangements are typically distorted with a variability in the thickness of the hepatic plates. Mitotic figures may be frequent. The interface between the tumor and the adjacent parenchyma is not uniform, and projections of the tumor may extend irregularly into the adjacent parenchyma. Regions of necrosis and hemorrhage are common, leading to morbidity and mortality much more frequently than metastasis of the primary tumor.

### 1.8.2.8.4 Cholangiocellular adenoma (biliary adenoma)

Benign neoplasms of the biliary epithelium are quite uncommon and characterized as discrete nodules composed of well-differentiated cuboidal epithelial cells that form compact arrangements of tubules. Congenital biliary ductal plate malformations may form arrays of ducts, some cystic, that can be confused with cholangiocellular adenomas. This is particularly true in cats.

### 1.8.2.8.5 Cholangiocellular carcinoma (biliary carcinoma)

Cholangiocellular carcinomas are malignant tumors of the biliary epithelium, including the gallbladder. The affected biliary epithelium is typically pleomorphic, and cells may pile up within the lumens of the neoplastic ducts. Mucus

is frequently observed, rather than bile, in tubules. Mitotic figures are common. Prominent fibrosis, termed scirrhous response, is typical, as is an aggressive growth pattern with the invasion of adjacent parenchyma and lymphatics. Metastasis is common.

#### 1.8.2.8.6 Carcinoid

Carcinoids are uncommon malignant neoplasms derived most likely from the resident neuroendocrine cells of the intrahepatic or extrahepatic biliary tree, including the gallbladder. Cells are typically small, elongated, or spindle-shaped and form ribbons or rosettes. Necrosis and hemorrhage are common within these tumors. Carcinoids have an aggressive growth pattern and may spread within the liver or to other organs. It can be difficult to distinguish primary from metastatic lesions as they have a similar histologic appearance. IHC for neuroendocrine markers can assist in a final diagnosis.

#### 1.8.2.8.7 Mesenchymal tumors

A variety of rare tumors derived from mesenchymal elements can form primary tumors in the liver. They resemble similar tumors in other sites of the body.

**KEY FACTS**

- Understanding the basics of hepatic histopathology is essential to understand biopsy and postmortem reports.
- The histologic findings in biopsies offer an informed guide to appropriate therapy.

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
svg.to/9842-01-08-02

## 1.8.3 Pancreas

Katja Steiger

### 1.8.3.1 Introduction and tissue collection

Histopathology is the gold standard diagnostic tool for some pancreatic diseases (i.e., pancreatitis and pancreatic neoplasms) while others (i.e., exocrine pancreatic insufficiency [EPI] or diabetes mellitus) cannot be defined by specific histopathologic findings.

In general, histopathology can be performed on pancreatic biopsies or resected tissue specimens. The latter is most often obtained in patients with suspected pancreatic neoplasia (▶Chap. 10.3.3). Collection of a pancreatic biopsy should be considered if a laparotomy or laparoscopy is being performed in a patient with suspected pancreatic disease for another reason.[1]

Different techniques have been described to collect pancreatic biopsies in dogs and cats. Either suture fracture or surgical dissection and ligation techniques can be used, and care should be taken that neither the duct nor the vascular system is damaged during the biopsy procedure. Pancreatic biopsy per se is considered safe,[2,3] and if performed carefully, there is little risk for post-collection pancreatitis.[4] Nevertheless, the collection of a pancreatic biopsy requires invasive procedures that are expensive and potentially detrimental in patients that are hemodynamically unstable.[5] Thus, the procedure of collecting a pancreatic biopsy might be complicated by the sensitivity of the pancreas to hypoxemia, whether induced by hypotension during anesthesia or by pancreatic blood flow impairment following manipulations of other organs during the procedure.[4]

In cases with suspected diffuse pancreatic alterations, it has been suggested to collect a pancreatic biopsy at the distal right limb of the organ because of the distance from the duct system and easy surgical access.[6]

In cats, if only one biopsy can be collected, a biopsy from the left limb should be collected.[7]

Pancreatic alterations are often localized and not grossly identifiable; thus, a single biopsy may not be reliable for whole organ assessment. Multiple samples from a variety of locations within the pancreas will usually provide a greater diagnostic yield than a single-site biopsy.[3]

Because concurrent inflammation of the intestines and/or liver appears to be a common problem in cats and may

also occur in dogs, intestinal and hepatic biopsies should be considered in patients (especially cats) suspected of having pancreatitis that are undergoing exploratory laparotomy. Likewise, cats with inflammatory bowel disease and/or cholangitis that undergo laparotomy or laparoscopy should be considered for collection of a pancreatic biopsy.

### 1.8.3.2 Tissue handling and processing

Pancreatic biopsies or resection specimens should immediately be placed into 10% neutral buffered formalin (equivalent to 4% formaldehyde) at a ratio of 10:1 (fixative to tissue) and stored at room temperature until submission to the pathology laboratory. As for other organs, the size of the tissue specimen should not exceed 1 $cm^3$ to ensure proper fixation.[7] Larger tissue specimens can be cut into smaller pieces. Also, in cases of a suspected neoplasm, tissue marking dyes might be useful to help the pathologist identify the tissue orientation.

As is the case for histopathological assessment of other tissues, signalment, major clinical and laboratory findings, and, if possible, the suspected clinical diagnosis should be submitted with the tissue specimen to the pathologist.

The majority of histopathological diagnoses in pancreatic tissue can be achieved with standard hematoxylin-eosin staining (H&E staining); special stains or IHC are needed infrequently (i.e., specific infectious agents or complex classifications of neoplasms).

### 1.8.3.3 Histology of the pancreas

Histologically, the pancreas consists of the exocrine pancreas, which comprises about 98% of the pancreatic mass in dogs and the endocrine islets of Langerhans.[8] The distribution of the islets of Langerhans is not uniform in relation to the lobes or interstitial tissue.[9] The exocrine pancreas is a tubuloalveolar gland consisting of acinar cells arranged in lobules of acini and duct cells (▶Fig. 1-171). Acinar cells are columnar to triangular with basally oriented nuclei. In the apical portion of the cell, they are packed with membrane-bound secretory granules (zymogen granules), often clearly visible with H&E staining, which contains the digestive enzymes or their precursors (i.e., zymogens). The lumen of the acini is connected to intercalated ducts that are lined with a flattened cuboidal epithelium (centroacinar cells). These small ductules open into intralobular ducts that coalesce into interlobular ducts and are lined with cuboidal epithelium (▶Fig. 1-171). The interlobular ducts are located between the lobules and are embedded in fine septae of connective tissue. Small interlobular ducts are lined with cuboidal epithelium, while larger ducts have a columnar epithelium. Within the interlobular connective tissue, intrapancreatic vessels can also be identified (▶Fig. 1-171). The interlobular ducts open into the major pancreatic duct that penetrates through the wall of the duodenum.

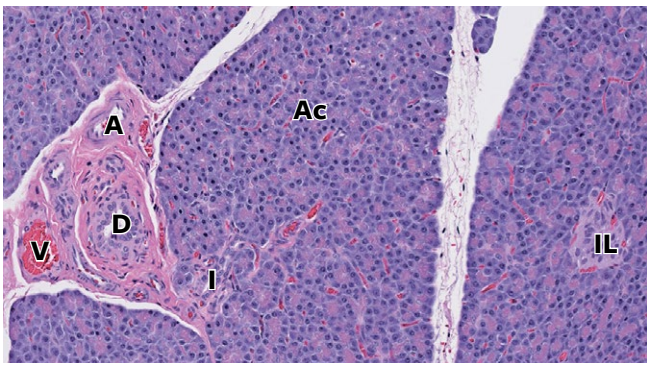



**Fig. 1-171** Normal histological appearance of the pancreas
Acini (**Ac**) are arranged in lobules. An intralobular duct with cuboidal epithelium (**I**) and a small interlobular duct (**D**) are also visible. The latter is embedded in a fine fibrillar connective tissue and is accompanied by small arteries (**A**) and a vein (**V**). A small islet of Langerhans (**IL**) represents the endocrine compartment of the pancreas.

Numerous Pacinian corpuscles are visible as 1–3 mm sized nodules within the interlobular connective tissue of the pancreas of cats. They represent a normal gross or histopathologic finding.[10]

### 1.8.3.4 Histopathology of the pancreas

As mentioned above, histopathology is an important diagnostic tool for some pancreatic diseases, while for others the histopathological changes are not specific, although there might be serious clinical consequences. Additionally, several microscopic lesions that can be identified in the pancreas should be considered incidental findings that may not be associated with clinical symptoms.

As a general rule, the pancreas has some regenerative capacity. After limited injury, acinar cells can replicate or precursor cells can arise (probably from centroacinar cells).[10] However, in patients with severe acute injury, where there has been sufficient tissue destruction and fibrosis, there is usually little evidence of regeneration of the exocrine pancreas. Sometimes proliferated ductules and atrophy of the exocrine lobules can be observed.[10] Depending on the amount of injury, only the endocrine compartment might be left in a background of complete atrophy of the exocrine pancreas.

#### 1.8.3.4.1 Pancreatitis

*Pancreatitis* is a broad term that includes all responses to acute and chronic damage to pancreatic acini and ducts associated with inflammation. The degree, distribution, and nature of histopathological changes depend on the underlying disease process and time course. Mild to moderate infiltration of the pancreas with inflammatory cells is common, and its clinical significance remains uncertain in both cats, [11] as well as in dogs.[12] Thus, the histopathological findings always have to be interpreted carefully with respect to the clinical findings. In general, the histological definitions of acute and chronic pancreatitis used in humans can be utilized in dogs and cats.[13] This means that acute pancreatitis is associated with varying degrees of neutrophilic infiltration, edema, and necrosis, but if the patient recovers, it is potentially completely reversible, both histopathologically and functionally.[13,14] Chronic pancreatitis is characterized by permanent, irreversible and typically progressive histopathological alterations, in particular fibrosis and acinar cell loss (▶ Chap. 10.3.1).[13–15]

At present, a definitive diagnosis of pancreatitis has only be made by histopathologic examination of pancreatic tissue in cats, which is due to considerable differences in the description of lesions and definition of severity.[4] Nevertheless, histopathology remains the only way to differentiate acute and chronic pancreatitis. Histopathologic scoring systems for the evaluation of severity of pancreatitis have been proposed for both dogs and cats.[7,11,12,16,17] However, histopathologic criteria for the classification of pancreatitis have not been universally standardized in veterinary medicine, and substantial confusion exists regarding both classification and terminology of canine and feline pancreatitis, underscoring the need for a universally accepted multidisciplinary classification system as is available for humans, integrating clinical findings, potential etiology, and histopathology.[18]

**Pancreatic biopsies from patients with moderate or severe acute pancreatitis** are not collected frequently. The majority of reports refer to findings observed during necropsy, i.e., from patients that have either died from the disease or have been euthanized because of the disease. Thus, as is the case in human patients, no systematic information about the histopathology of most clinical cases with acute pancreatitis is available. It can be suggested that the main histopathological findings in acute pancreatic necrosis start at the periphery of affected lobules with variably extensive involvement of adjacent adipose and other connective tissue. In cases with predominance of necrosis over acute inflammation, the lesion might also be termed "acute pancreatic necrosis".[10] Histopathologically, the alterations can be referred to the degradation of pancreatic and adjacent parenchyma, including vascular damage.[10] Thus, the lesion can also represent acute hemorrhagic pancreatitis with extensive areas of hemorrhage. Severe cases are characterized by extensive edema (i.e., accumulation of a fibrinous exudate in the interlobular septa) and coagulation necrosis of the pancreatic parenchyma. Interlobular septa can also be infiltrated by neutrophils and macrophages, depending on the time course of the alteration. Liquefactive necrosis and saponification, accompanied by the infiltration of neutrophils often occur in the mesentery adjacent to the affected portions of the pancreas. In severe cases, thrombi are often observed in small veins and arteries, leading to further ischemic damage of the pancreas. Thrombi may even extend from the pancreas and into the portal vein.[19]

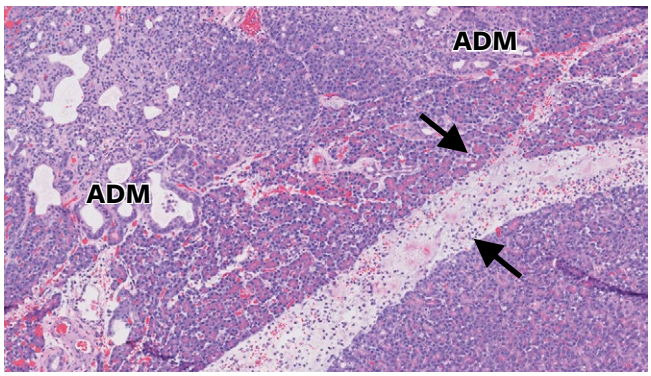



**Fig. 1-172** Histopathology of an acute to subacute suppurative pancreatitis in a cat with moderate interlobular edema, inter- and intralobular neutrophils (**arrows**), and reactive acinar-to-ductal metaplasia (**ADM**)

Occasionally, especially in cats, neutrophils may predominate in acute pancreatitis without extensive necrosis, which then is called acute interstitial or acute suppurative pancreatitis (▶ Fig. 1-172).[20] The neutrophils may be observed in the parenchyma, in the interlobular septa, or infiltrating the pancreatic ducts. It has been suggested that this distinct subtype of acute pancreatitis might be the consequence of ascending bacterial infection,[10] but this remains speculative as there is no etiological proof.

**Fluid accumulations** may occur following acute necrotizing or suppurative pancreatitis and may be found in the pancreas or adjacent to it.[21] Histopathologically, pseudocysts, as well as walled-off necrosis, are enclosed by a wall of granulation tissue. For further information on the pathophysiological differences of pancreatic and peripancreatic fluid collections, please refer to ▶ Chap. 10.3.1.

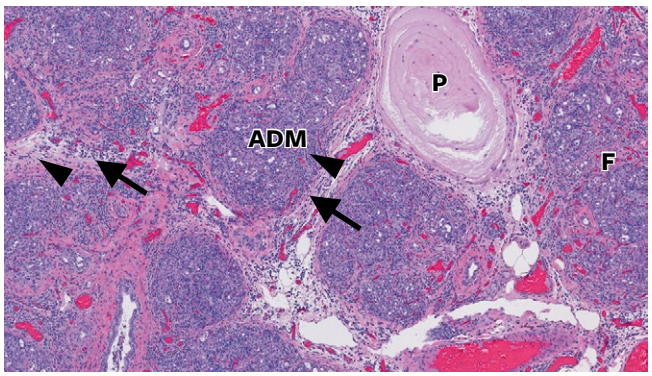



**Fig. 1-173** Chronic pancreatitis in a cat with inter- and intralobular infiltration by lymphocytes (**arrows**) and isolated neutrophils (**arrowheads**) as well as moderate inter- and intralobular fibrosis (**F**). Note the Pacini corpuscule (**P**). The acinar cells have undergone acinar-to-ductal metaplasia (**ADM**).

**Chronic pancreatitis** is characterized by fibrosis, inflammatory cell infiltration dominated by lymphocytes and plasma cells, and parenchymal atrophy (▶Fig. 1-173).[11,12] Hyperplasia of ducts is relatively common in patients with chronic pancreatitis. Lesions may be focal, multifocal, or regional. Mild to moderate lesions may occur in either dogs or cats without obvious clinical disease.[7,22] Thus, some degree of mononuclear cell infiltration of the pancreas seems to be common.[11,12,16] The occurrence of a few scattered lymphocytes within the pancreatic parenchyma might be considered normal, at least in cats, but this has been questioned by other authors.[11] The observation of mild signs of inflammation in a pancreatic biopsy can be a diagnostic challenge, as these lesions may represent ongoing pancreatitis but may not necessarily explain the clinical signs in a given patient.[4]

Cystic dilatation of acini, ectasia of the pancreatic ducts, or the development of large and multiple cysts is a common finding in cats with chronic pancreatitis[10,11] but is an infrequent finding in dogs.[17] In dogs with chronic pancreatitis, areas of acute necrosis and suppurative inflammation can be observed next to granulation tissue and fibrosis; this might then be diagnosed as "acute on chronic" inflammation.[17,23] In cats, the inflammatory component in chronic pancreatitis is often rather mild compared with the amount of fibrosis.[10,11]

The distribution of pancreatic fibrosis might be different between species and also between dog breeds. Watson et al.[17] described interlobular fibrosis being predominant in cavalier King Charles and cocker spaniels and an intralobular fibrotic phenotype in terriers and collies. Extensive periductal fibrosis, as described in cats and in boxers, may lead to localized stenosis and cystic dilatation with squamous metaplasia of the ductal epithelium.[9,17] Acinar-to-ductal metaplasia, a frequent finding in human patients with chronic pancreatitis and in mouse models, has also been described in cats with chronic pancreatitis (▶Fig. 1-173).[7]

Exclusion of pancreatitis based on histopathology is difficult because inflammatory lesions of the pancreas are often highly localized, multifocal, or not grossly visible and can thus easily be missed.[11,12,20] Therefore, it is recommended that multiple pancreatic biopsies be evaluated to increase the likelihood of finding microscopic lesions, although this is not always feasible in clinical practice. Thus, the absence of histopathologic findings of pancreatitis must be interpreted with caution, especially when only one section of the pancreas has been examined.[1,11,12]

Mild pancreatitis might also represent a response of the pancreas to concurrent disease.[4] The pancreas can also be involved in systemic granulomatous infections (e.g., zygote fungi, cryptococcosis, schistosomiasis, or FIP).

#### 1.8.3.4.2 Exocrine pancreatic insufficiency

Exocrine pancreatic insufficiency (EPI, ▶Chap. 10.3.2) is a functional and not a histopathologic diagnosis; therefore, histopathology is not indicated for the diagnosis of EPI. It has been estimated that more than 90% of the secretory capacity of the pancreatic parenchyma needs to be destroyed before clinical signs of EPI develop. Any pancreatic pathology of sufficient severity, aside from juvenile pancreatic atrophy, including pancreatitis, pancreatic necrosis, toxic injury, localized and systemic infections, ductal obstruction, and neoplasia, can lead to acquired EPI.[9] Thus, especially in breeds with a known predisposition of pancreatic atrophy, histopathology should only be performed if the cause of EPI needs to be definitively determined.[24]

#### 1.8.3.4.3 Pancreatic hyperplasia and neoplasia

**Hyperplasia of the exocrine pancreas** is a frequent finding, especially in older dogs and cats. In cats, atypical pancreatic nodules have been described histopathologically.[11] Hyperplastic foci are nodular to slightly compressed aggregates of acinar cells that may or may not contain zymogen granules (▶Fig. 1-174).[10,25] They can occur as solitary lesions, but in most cases, multiple hyperplastic nodules are observed. The lesion is not of clinical significance besides being a differential diagnosis to neoplastic lesions when observed during exploratory laparotomy.

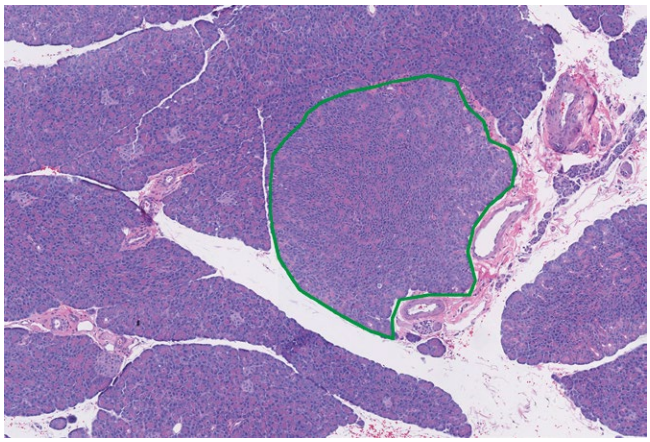


**Fig. 1-174** Nodular hyperplasia of the exocrine pancreas (area encircled by the **green line**) in an 11-year-old cat.

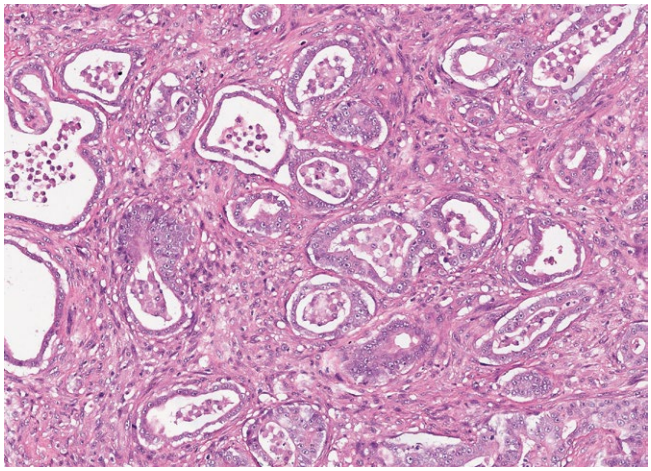


**Fig. 1-175** A tubular growth pattern in carcinoma of the pancreas in an 8-year-old cat (same neoplasm as in ▶Fig. 1-176).

**Islet hyperplasia** is often subtle, and its clinical significance is questionable. In dogs, **nesidioblastosis** has been reported as a non-neoplastic proliferation of islet and ductular tissue.[26] The histopathology of neoplastic diseases of the endocrine pancreas is better described in dogs than in cats. The endocrine origin of a neoplasm of the pancreas can often be determined by examination of ordinary H&E-stained sections. The neoplastic cells are usually characterized by nests of neoplastic cells with distinct cell borders, a faintly granular cytoplasm, and a finely stippled nucleus with one nucleolus.[27] In questionable cases, immunohistochemical expression of synaptophysin distinguishes these tumors from exocrine ones. Most often, they are functional neoplasms, with **insulinoma** being the most frequent one, but also other hormonal phenotypes can occur. Endocrine tumors of the pancreas in dogs and cats are classified into adenoma and carcinoma, the latter being the more frequent one. Mitotic figures are uncommon, thus, local invasiveness and the occurrence of metastases are the main criteria to distinguish benign from malignant tumors.

**Adenomas of the exocrine pancreas** are rare, but they have been described in both dogs and cats.[23,28] In a recent retrospective study of pancreatic neoplasms in cats, a high prevalence of cystic tumors was observed in cats in general, with a higher number of benign vs. malignant lesions.[28] Histopathologically, pancreatic adenomas are usually single, larger than normal pancreatic lobules; they compress the adjacent tissue and are separated by a thin fibrous capsule. They can consist of well-differentiated acinar cells (acinar type) or small ductular structures lined with cuboidal or columnar epithelium (tubular type).[9]

**Exocrine pancreatic adenocarcinomas** can occur as solitary or multiple masses. In dogs, they tend to occur more often in the right pancreatic limb than in the left.[29] Histopathologically, different growth patterns have been described, which might refer to the cell of origin of each individual neoplasia. Tubular forms (▶Fig. 1-175) have been considered to be derived from ductal epithelium, whereas tumors consisting of cells with distinctive zymogen granules have been interpreted of being of acinar origin (▶Fig. 1-176). The poorly differentiated solid acinar growth pattern seems to be the most frequent in dogs,[29] which stands in contrast to human patients, where ductal adenocarcinomas are by far the most important malignant pancreatic neoplasm.[30] A hyalinizing variant with abundant hyaline material between the neoplastic tumor cells has also been described in dogs.[31] Tumors with this morphology might be biologically less aggressive than conventional exocrine pancreatic carcinomas in the dog.[31] Also, clear cell variants[29] and undifferentiated neoplasms without acinar or ductular structures, sometimes with abundant fibrous stroma, can occur.[9] Very rarely, mixed exocrine-endocrine neoplasms have been described in dogs.[27,32] In cats, cystic growth patterns of malignant pancreatic neoplasms have been described; thus, cystic pancreatic tumors (both benign and malignant) should be considered as a differential diagnosis of intraabdominal cystic masses in cats.[28]

**Nonepithelial and secondary neoplasms** can also be found in the pancreas, and involvement of the pancreas in lymphoma has been described.[33]

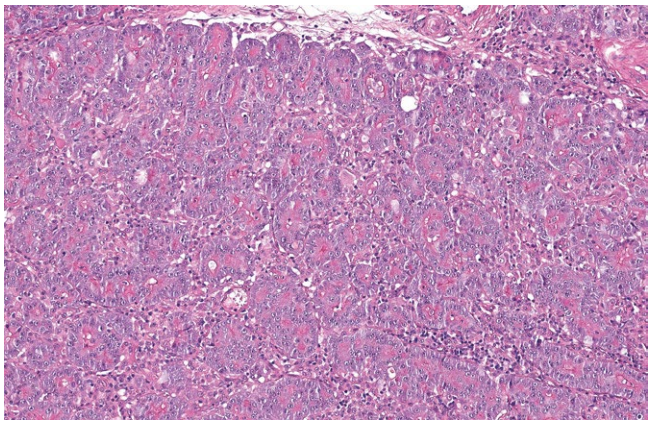


**Fig. 1-176** Carcinoma of the pancreas in an 8-year-old cat with an acinar growth pattern and distinct zymogen granules (same neoplasm as in ▶Fig. 1-175).

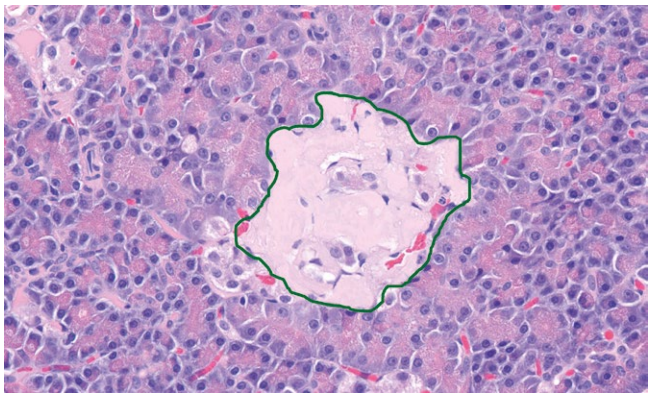


**Fig. 1-177** Extracellular accumulation of eosinophilic hyaline material (amyloid, **encircled by a green line**) in an islet of Langerhans in a 13-year-old cat.

#### 1.8.3.4.4 Other lesions

**Lipomatosis** of the pancreas occasionally occurs in cats, usually as part of generalized obesity, but it can also be restricted to the pancreas. Pancreatic lipomatosis is usually not functionally relevant.

**Necrosis of individual or small groups of acinar cells** sometimes occurs in the course of local and systemic disorders (i.e., viral infections with epitheliotropism, intoxications, or shock). These findings can be incidental in the course of the systemic disease – given that the associated inflammation is minimal and no self-perpetuating inflammatory vicious circle is induced.

It has been reported that loss of zymogen granules in the exocrine cells can be observed after starvation.[10] **Vacuolization** of acinar cells is sometimes detected in cats and might be a sign of degeneration or, especially in obese cats, accumulation of lipids in the acinar cytoplasm. Additionally, vacuolization of acinar cells has been described in patients with several types of lysosomal storage diseases.[10] Nodules of **ectopic splenic tissue** can be observed in the pancreas of both dogs and cats and are sometimes even grossly visible. This is an incidental finding that has to be differentiated from pancreatic neoplasia.[10]

**Pancreatic cysts** have been described in the pancreas as a component of congenital polycystic disease in dogs or cats. These lesions are 1–2 mm in diameter and lined with a cuboidal to cylindrical epithelium, surrounded by a thin fibrotic zone.[34] Pancreatic cysts, independent of congenital disease, are usually incidental, not functionally significant, and usually above 10 mm in diameter. Especially in cats, they have to be differentiated from cystic pancreatic lesions (see above).

Histopathologic lesions of the pancreas in the course of **diabetes mellitus** are often non-specific and secondary, although degeneration or necrosis of pancreatic islets or lymphoplasmacytic inflammation with associated selective islet cell destruction have been described.[10] Intracellular glycogen accumulation in islet cells and/or pancreatic ducts can occur as a result of a metabolic derangement.[9] In the cat, there might be a correlation between islet amyloidosis (▶Fig. 1-177) and diabetes mellitus, but almost half of older cats may display islet amyloidosis. Thus, such changes should be interpreted with caution.[9] Diabetes mellitus in dogs can occur if a significant portion of the pancreas is affected by chronic pancreatitis.[10]

**KEY FACTS**

- Histopathology is the gold standard for the diagnosis of pancreatitis and pancreatic neoplasms.
- Histopathology is not useful for the diagnosis of exocrine pancreatic insufficiency or diabetes mellitus.
- The collection of a pancreatic biopsy, if performed carefully, is a safe procedure in both dogs and cats.
- If there is no grossly visible localized alteration, multiple biopsies of the pancreas should be collected.
- Neoplastic diseases of the pancreas are often malignant, and cats have a higher prevalence of cystic neoplasms than do dogs.

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
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## 1.9 Assessment of gastrointestinal (GI) motility

Frédéric P. Gaschen

### 1.9.1 Introduction and physiology of GI motility

The scope of this chapter is limited to gastric, small, and large intestinal motility in dogs and cats. It is focused on non-obstructive disorders of GI motility which frequently occur in dogs and cats but may remain unrecognized. Often, they are secondary to acute or chronic inflammation of the GI tract, neighboring organs (e.g., pancreas), or the peritoneum. GI motility may also be perturbed by electrolyte disturbances (e.g., hypokalemia), drugs (e.g., opiates), or abdominal surgery and anesthesia. Finally, more rarely, primary disorders of GI motility may occur (e.g., dysautonomia). In addition, recent studies have shown that disturbances of the gut microbiome may negatively impact GI motility through their effects on the tryptophan pathway that generates serotonin, an essential neurotransmitter in the enteric nervous system.[1]

Gastrointestinal motility is a complex series of events that aims at

1. storing and
2. grinding ingested food into particles of a determined size in the stomach before they are propelled into the small intestine;
3. moving the ingesta through the small intestine while allowing the digestive and absorptive processes to take place;
4. optimizing conditions for fermentation and water reabsorption processes in the proximal colon; and
5. storing and coordinating the evacuation of fecal material from the distal colon and rectum.

GI motility is dependent on smooth muscle contractions that are regulated by a combination of myogenic, neural, and hormonal factors.[2–4] A detailed discussion of the physiology of gastric, small intestinal and large intestinal motility is beyond the scope of this chapter and can be found in the listed references.

### 1.9.2 Indications for assessment of GI motility

Abnormal GI motility may complicate the clinical presentation and compromise the outcome of diseases, such as acute or chronic gastric or intestinal inflammation, acute pancreatitis or critical illness and delay recovery from abdominal surgery. Clinical signs of decreased/absent GI motility are not specific and vary depending on the circumstances. They may include persisting hyporexia/anorexia, signs of nausea, vomiting, or regurgitation (e.g., following gastroesophageal reflux), cranial abdominal discomfort, abdominal distension, and bloated abdomen. Intestinal sounds are usually absent on abdominal auscultation. If dysmotility is suspected, a basic assessment of GI motility is recommended using widely available techniques, such as survey abdominal radiographs and abdominal ultrasonography (▶Chap. 1.9.3). If these initial investigations remain inconclusive, more advanced techniques can be used based on their availability.

### 1.9.3 Available methods for evaluation of GI motility

Various techniques can be used to assess GI motility in different segments of the GI tract, as described below and summarized in ▶Tab. 1-23. An ideal technique would be easily accessible in the clinical setting, would require minimal manipulations or blood samplings from the dog or cat, and would offer rapid analysis of biological samples as needed to

**Tab. 1-23** Characteristics of available methods for assessment of gastrointestinal motility in dogs and cats

| Method | Stomach | Small intestine | Colon |
|---|---|---|---|
| **Radiography** | | | |
| Survey radiography | + | + | + |
| Liquid barium | + | + | + |
| Barium meal | + | + | – |
| BIPS | + | + | + |
| **Ultrasonography** | | | |
| Qualitative | + | + | – |
| Quantitative | + | – | – |
| **Scintigraphy** | | | |
| Nuclear scintigraphy | + | + | + |
| **Tracer studies** | | | |
| Plasma | + | + | – |
| Breath | + | + | – |
| **Capsules** | | | |
| Wireless motility capsule | + | + | + |
| Videoendoscopy capsule | + | + | – |

**BIPS** = barium-impregnated polyethylene spheres

accurately assess transit times and motility in the GI segment of interest (stomach, small or large intestine). Not surprisingly, such a method is not available at this time; therefore, the strengths and weaknesses of existing methods are listed in ▶Tab. 1-24.

Transit times reported in the literature for the same technique vary widely because of a lack of standardization of the size and caloric content of administered meals as well as of the protocol applied. In addition, transit times may be prolonged because of hospital-associated stress and may also vary from day to day in the same animal.[5,6]

#### 1.9.3.1 Radiographs

Radiographic studies are easily accessible and can provide valuable information. Survey radiographs are required to rule out gastrointestinal obstruction. They may also reveal the presence of non-obstructive ileus (adynamic, functional, or paralytic ileus). A description of the radiologic features of ileus can be found in ▶Chap. 1.4.5.1.

Liquid barium has been widely used to assess GI transit times, and details of the procedure can be found in ▶Chap. 1.4.3. With the exception of mechanical obstructions due to foreign bodies or other space-occupying lesions obstructing the gastric or intestinal lumen, assessment of gastric emptying (GE) of liquids does not accurately reflect GE of solids. When barium is mixed with food, it can easily dissociate from the test meal and empty into the duodenum even though the solid food is still in the stomach, making the study unreliable.

Barium-impregnated polyethylene spheres (BIPS) have been used for the evaluation of GI transit times in dogs and cats. They come in two sizes (1.5 and 5 mm diameter) and can easily be used in practice. However, a correlation between the GE of BIPS and the reference method (radionuclide scintigraphy) has been disappointing in dogs and in cats.[7,8]

#### 1.9.3.2 Ultrasonography

Ultrasound machines are widely available, and transabdominal ultrasound examination of the GI tract is a routine exam in dogs and cats presented with GI signs. As described in ▶Chap. 1.4.4, ultrasound can be useful for detecting morphologic gastric wall abnormalities and qualitatively evaluat-

**Tab. 1-24** Strengths and weaknesses of available methods for assessment of GI motility in dogs and cats

| Method | Strengths | Weaknesses |
|---|---|---|
| Radiography | • Equipment widely available<br>• Survey and contrast studies allow the identification of mechanical GI obstructions.<br>• Survey films may allow diagnosis of severe adynamic ileus | • Survey films are insensitive for assessment of GI motility<br>• Barium contrast studies (liquid barium or barium meal) do not accurately reflect solid-phase GE<br>• GE emptying of BIPS correlates poorly with the gold standard |
| Ultrasonography | • Equipment widely available<br>• Qualitative: rapid assessment of gastric and small intestinal motility<br>• Quantitative: accurate, real-time assessment of actual GE and gastric motility | • Difficult to perform in obese, painful, or otherwise uncooperative patients or when gas is present in the GI tract<br>• Qualitative: operator needs to be familiar with abdominal ultrasonography<br>• Quantitative: skills are required for identification and observation of the antrum over time. Full studies are time-consuming |
| Nuclear scintigraphy | Reference method for GE evaluation | • Limited availability<br>• Strict radiation protection protocols must be implemented<br>• License may be required to handle radioactive isotopes |
| Tracer studies | Accurate assessment of gastric or orocecal transit times | • Repeated sampling of blood or breath air is required<br>• Blood or breath air analyses require specialized equipment that is not easily available in veterinary diagnostic labs<br>• Results are only valid if intestinal and liver functions are normal |
| Capsules | • Can be used in the home environment<br>• WMC: Pressure curves and motility index provide information on motility<br>• VEC: easily available | • Use limited to dogs > 15 kg<br>• WMC: Significant investment required to purchase equipment<br>• VEC: unsure how fasted transit times correlate with postprandial transit times |

**GI** = gastrointestinal; **BIPS** = barium-impregnated spheres; **GE** = gastric emptying; **VEC** = videoendoscopy capsule; **WMC** = wireless motility capsule

ing contractile activity. A normal stomach containing some food should contract 4–5 times per minute.[9] However, the frequency of antral contractions depends on the degree of filling and time since the last meal; an empty stomach can be in a resting state and show fewer and weaker contractions.[10]

Small intestinal luminal contents and peristalsis can also be evaluated. Reported normal rates of peristalsis are approximately five contractions/minute for proximal duodenum and 1–3 to 5.2 contractions/minute for the rest of the small intestine.[9] As noted for the stomach, these rates may vary depending on the timing of the last meal.[10]

Quantitative assessment of GE is performed using sequential evaluation of antral size after a meal and relies on the postprandial measurement of the cross-sectional area or estimated volume of the relaxed pyloric antrum over time. Animals are positioned in dorsal or right lateral recumbency. As the stomach empties, the size of the antrum decreases and ultimately returns to the fasted dimension. Values are plotted over time to obtain GE times (▶ Fig. 1-178). The technique allows determination of solid-phase gastric emptying time as well as the evaluation of motility parameters, including frequency and amplitude of antral contractions and motility index.[3] It was shown to correlate well with a breath tracer method in dogs[11] and with radionuclide scintigraphy in cats.[12] However, it cannot be reliably quantitatively evaluate small intestinal motility.

### 1.9.3.3 Radionuclide scintigraphy

Radionuclide scintigraphy is the reference technique for evaluating GE in people, dogs, and cats.[3] The animal is fed a solid meal mixed with radiolabeled technetium ($^{99m}$Tc) bound to albumin, colloid, disofenin, mebrofenin, or sulfur. Postprandial scans are performed at regular intervals with a gamma camera to allow quantification of the radioactivity present in the stomach. A time curve is drawn, and $t_{1/2}$ (time at which one half of the initial radioactivity remains in the stomach) and $t_{50\%}$ (time at 50% of the area under the curve) of GE can be calculated (▶ Fig. 1-178).[6,12] Another radioactive isotope, $^{111}$Indium bound to DTPA (diethylenetriamine pentaacetate), can be used for the assessment of colonic transit time. Unfortunately, scintigraphy is only available at academic institutions and select referral centers and is used mostly for research purposes.

GE $t_{1/2}$ (time at which the gastric radioactivity had decreased to 1/2 of the maximum) ranged from 100–182 minutes in six healthy purpose-bred dogs of approximately the same size fed 30% of their daily caloric requirements with dry kibbles and baby food.[6] It was 196 ± 45 minutes in eight healthy purpose-bred cats after a meal supplying approximately 20% of their daily caloric requirement.[12]

### 1.9.3.4 Tracers

These techniques use plasma or breath tracers. Markers are mixed with the meal and used for postprandial assessment of GE and/or intestinal transit.

In plasma tracer studies of GE, acetaminophen/paracetamol is rapidly absorbed in the proximal duodenum, and postprandial time plots of the serum concentrations are used to extrapolate GE times. The technique has been used successfully for the assessment of GE but has not yet been validated by comparison to other techniques in dogs.[13] In addition, the accuracy of the method for assessing solid-phase

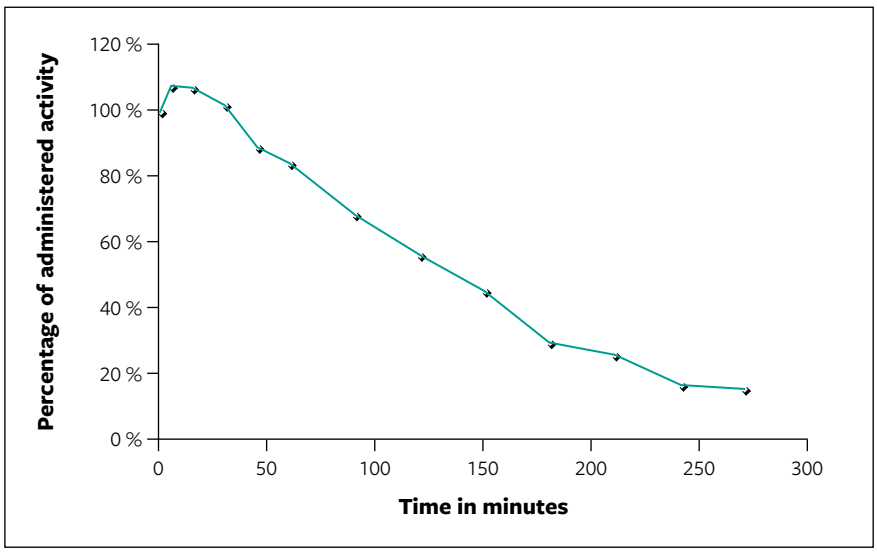



**Fig. 1-178** Gastric emptying curve obtained by radionuclide scintigraphy in a healthy dog

Cumulative scintigraphic residual radioactivity in the gastric area plotted against time after ingestion of a dry kibble meal providing 30% of the daily caloric requirements. Gastric half emptying time (GE $t_{1/2}$; time at which the gastric radioactivity had decreased to 1/2 of the maximum) was calculated to be 107.7 min.

GE has been questioned.[14] Sulfasalazine is a compound molecule of sulfapyridine and 5-aminosalicylate linked by an azochemical bond validated for orocecal transit time (OCTT) measurements in the dog.[15] After oral dosing, most of the sulfasalazine is transported unmetabolized to the distal GI tract, where cecal and colonic microbiota metabolize the drug to its component parts. Sulfapyridine is largely absorbed intact by the colonic mucosa, and its appearance in plasma, therefore, reflects the OCTT of sulfasalazine.

In breath tracer studies of GE, the marker (e.g., $^{13}$C-octanoic acid or $^{13}$C-sodium acetate) is absorbed in the duodenum and metabolized in the liver with the release of $^{13}$C, which is ultimately exhaled. Postprandial time plotting of $^{13}C/^{12}C$ ratios in the breath air is used to extrapolate GE times in dogs and cats.[16–18] OCTT can be assessed with the $H_2$ breath test, which reflects the production of hydrogen by the colonic microbiota after a carbohydrate meal and has been validated in both dogs and cats.[15,19] While these techniques are easier to access and not limited by radiation exposure, availability is still mostly limited to research facilities at this time.

### 1.9.3.5 Capsules

Two types of capsules can be used for the evaluation of GI motility. The wireless motility capsule (WMC, SmartPill® capsule, Medtronic, Minneapolis, MN) is specifically designed for this purpose. It can record temperature, pH, and pressure during its journey through the GI tract and transmits data to a receiver kept near or on the dog. It permits evaluation of gastric emptying and small intestinal and colonic transit times (▶Fig. 1-179). The frequency and amplitude of gastric and intestinal contractions can be determined, and a motility index calculated. The capsule exits the stomach after the whole meal has been propelled into the duodenum after the onset of an interprandial phase <3 migrating motor complexes. WMC is the only technique that allows evaluation of GI motility in the home environment, and it has been validated for use in dogs in comparison to radionuclide scintigraphy.[6] Equipment is relatively expensive and mostly used in the research setting. Due to the capsule size and the risk of gastric retention, use is limited to dogs >15 kg body weight.

In 31 healthy pet dogs weighing between 19.6 and 81.2 kg and fed a dry kibble meal providing 25% of their daily energy requirements, GE times ranged from 405–897 minutes, small bowel transit lasted from 96–224 minutes, and large bowel transit times varied from 427–2573 minutes.[20]

The ALICAM® capsule is an easy-to-use gastrointestinal imaging modality (ALICAM, Infinity Medical, Palo Alto, CA). The fully automated capsule-sized camera device is administered orally to fasted dogs and propelled by natural peristalsis. Images are stored in the capsule and downloaded after it is defecated. The times required for passage of the capsule through the stomach and small intestine can be determined based on the correlation of images with an internal clock.[21] Use of this capsule is limited to fasted dogs, and the correlation of fasted with postprandial transit times has not been investigated. Body size limitations are similar to those for the WMC.

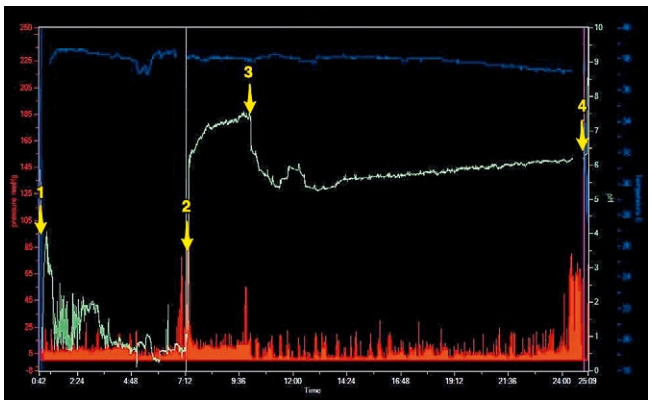



**Fig. 1-179** Evaluation of gastric emptying time (GET) by wireless motility capsule (WMC) in a healthy dog

The WMC was administered with a dry kibble test meal, which provided approximately 30% of the daily estimated energy requirement. The dark blue line shows temperature (in °C), the green line shows pH, and the red line shows intraluminal pressure. The X-axis represents time (hh:min).

**1:** Capsule enters the stomach (low pH)

**2:** Capsule exits the stomach (rise in pH by >3 units)

**3:** Capsule enters large bowel (drop in pH by ≧1 unit)

**4:** Capsule exits the rectum (drop in the temperature curve).

The GET (time 2 minus time 1) is 6 h 28 min. Small bowel transit time (time 3 minus time 2) is approx. 2 h 30 min. Large bowel transit time (time 4 minus time 3) is approx. 15 h 15 min. Total transit time (time 4 minus time 1) is a little longer than 24 h.

(From Husnik and Gaschen 2021[3] with permission.)

## 1.9.4 Clinical evaluation of GI motility

Numerous studies have investigated the effects of various drugs on healthy dogs and cats and in animals with experimentally altered GI motility, and how their results can be translated to clinical situations affecting dogs and cats is unknown. Few publications pertain to dogs and cats with spontaneous diseases or undergoing interventions commonly performed in small animals that might affect GI motility.

### CLINICAL PEARLS

Recent studies using the wireless motility capsule in healthy dogs have documented that hospitalization resulted in delayed GE when compared with evaluation in the home environment[5] and that general anesthesia significantly impacted GI transit times.[22]

In addition, the benefits of metoclopramide to restore GI motility following abdominal surgery were shown in instrumentalized research dogs.[23] Finally, delayed GE was documented in dogs that had undergone abdominal surgery for gastric dilatation-volvulus or exploratory laparotomy using the Na-acetate breath test.[24]

There is a need for validated, clinically applicable techniques for the evaluation of GI transit times that are accessible in the clinical setting and affordable. Ultimately, well-designed prospective studies investigating the effect of various treatment strategies for optimizing GI motility in sick dogs and cats will be necessary to allow an evidence-based approach to GI motility disorders in dogs and cats.

### KEY FACTS

- Gastrointestinal (GI) motility is a complex series of events dependent on smooth muscle contractions that are regulated by a combination of myogenic, neural, and hormonal factors.
- Abnormal GI motility may complicate the clinical presentation and may impact disease management.
- Various modalities can be used to assess GI motility of different segments of the GI tract, all of which are associated with various advantages and disadvantages.

### References

The complete list of references for this chapter can be downloaded from vetline.de:
svg.to/9842-01-09

# 2 Clinical evaluation of dogs and cats with specific clinical signs

## 2.1 Clinical evaluation of patients with acute signs of gastrointestinal disease

Emily N. Gould

### 2.1.1 Introduction

Acute onset gastrointestinal (GI) signs are a primary reason that owners seek emergent veterinary care for their cats and dogs. The severity of disorders responsible for GI signs can range from mild and self-limiting to severe and life-threatening. A definitive diagnosis is not always possible, but it is important to recognize patients that require intensive hospitalization vs. outpatient care. Identifying if a clinical problem is primary GI vs. extra-GI in origin is crucial in developing the best diagnostic and therapeutic plan. Because these signs are often non-specific, a thorough but targeted case history, physical examination, and initial diagnostic plan are key to localizing the affected part of the GI tract and successfully prioritizing differentials. The following chapter provides a stepwise approach to the diagnostic evaluation of companion animals with acute onset GI signs. The most common of these are vomiting, regurgitation, and diarrhea with or without appetite changes (hyporexia, dysrexia, or anorexia).

### 2.1.2 Clinical signs consistent with acute gastrointestinal disease

#### 2.1.2.1 Vomiting

Of importance is the differentiation between vomiting and regurgitation because these clinical signs localize disease to different parts of the GI tract, and owners commonly use both terms interchangeably. Vomiting is an **active event with prodromal signs**, with the vomiting reflex initiated via humoral and neural pathways.[1] If vomiting is present, the most common abnormalities noted are ptyalism, lip-smacking, and/or exaggerated/difficult swallowing paired with active abdominal contractions before vomiting. A combination of all or only one of the above prodromal signs might be noted and vary from patient to patient. The origin of the vomited material can be localized to either the stomach or small intestines but does not differentiate primary GI vs. extra-GI causes. Other characteristics, such as hematemesis, vomiting frequency, and overall patient attitude, are important in determining how aggressive a diagnostic and treatment plan is warranted.

#### 2.1.2.2 Regurgitation

Regurgitation is a **passive event without any prodromal signs**. The most important difference between regurgitation and vomiting is that the material is brought up passively in regurgitation. Regurgitation implies esophageal dysfunction, and dogs develop clinical evidence of regurgitation much more commonly than cats. Patients often exhibit lip-smacking, an extension of the neck while swallowing, odynophagia (painful swallowing), and/or appetite changes. Some animals develop rhinitis secondary to the reflux of regurgitant material into the nasopharynx, which can manifest as reverse sneezing, stertor, and/or nasal discharge.

Criteria that do not distinguish regurgitation from vomiting are the timing of the event in relation to eating or drinking and the volume or character (e.g., solid, liquid, digested, or undigested) of the material. It is a common misconception that regurgitant material is undigested and occurs immediately after eating or drinking. Regurgitation can occur either at rest or during physical activity, so this is not a discriminating criterion.

#### 2.1.2.3 Diarrhea

Diarrhea should be categorized as either small intestinal (**SI**), large intestinal (**LI**), or mixed bowel diarrhea before formulating differentials and an appropriate diagnostic plan.

Animals with strictly **SI diarrhea** typically have **normal to increased stool volumes and defecation frequencies**. If blood is present, it is exclusively melena. Mucus is usually absent, but if present, it is located within the fecal ball (as opposed to coating the outside of the feces as with LI dis-

ease). Pets with SI disease might also have **additional clinical signs** (e.g., lethargy, changes in appetite, vomiting, and/or neurologic abnormalities) related to the underlying etiology. These are absent in most causes of LI diarrhea because many systemic diseases with alimentary involvement target the SI rather than the colon. Exceptions to this are pancreatitis (due to proximity of the colon and pancreas) and granulomatous colitis, which can cause LI diarrhea and significant weight loss.

Hallmark features of **LI diarrhea** include an **increased frequency and urgency of defecation** but **smaller fecal volumes**. Concurrent **tenesmus**, **dyschezia**, **mucus** (coating the feces), and/or **hematochezia** are common. The presence of systemic disease and LI diarrhea can help the clinician narrow down the differential diagnosis list to certain infectious or breed-specific disorders.

### 2.1.3 Differentials for acute gastrointestinal disease

The differentials for acute GI disease, encompassing all the clinical signs mentioned, are extremely broad. The most common reasons companion animals present for acute onset GI signs are dietary indiscretion, foreign body ingestion, worsening clinical signs in chronic enteropathy (CE) cases, or infectious (e.g., parasitic, viral) etiologies. The following section will cover these and other differentials, in addition to the clinical signs predominantly seen with specific diseases.

#### 2.1.3.1 Differentials for vomiting

Vomiting as a sole clinical sign localizes disease to the stomach and small intestines but does not differentiate a mechanical from a functional problem.

**Gastritis** is a common cause of vomiting, which can be due to infectious, inflammatory, neoplastic, parasitic, or toxic etiologies. Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most important drug classes causing gastritis and GI ulceration.

**Mechanical obstructions** secondary to a foreign body (FB) or mass in the upper GI tract are common in young or very old cats and dogs or those with a lifelong history of dietary indiscretion. Failing to rule these out early in the diagnostic workup may result in unnecessary diagnostics, a delay in critical therapy (e.g., endoscopic procedures), and an increase in mortality if the pet develops GI perforation or hemodynamically decompensates. Acute onset or intermittent vomiting can result from either a partially obstructive FB, mass, or thickening of tissue (i.e., hypertrophic gastropathy)[2,3] acting as a barrier to pyloric outflow. Pyloroduodenal adenomatous polyps in cats can cause a ball-valve effect with obstruction at the pyloric sphincter or proximal duodenum.[4,5] Intussusception is a top differential for young animals with vomiting and is often caused by GI parasites and/or viral enteritis. Cats develop intussusception infrequently compared with dogs, though it is reported as bimodal in age distribution and more likely to occur secondary to GI neoplasia in older cats.[6]



Dogs with acute onset, often non-productive retching, gagging, and/or vomiting, should be quickly assessed for gastric dilatation-volvulus (**GDV**, ▶Chap. 6.3.3).

Both **parvovirus** and **distemper virus infections** should be differentials for puppies that present with vomiting or clinical signs of gastroenteritis (with or without accompanying diarrhea). Distemper should be especially high on the list for young dogs with concurrent respiratory or neurologic signs.

**Stomach worms** (*Ollulanus* and *Physaloptera* spp.) are the most common parasitic cause of gastritis, with vomiting as a sole complaint in dogs and cats. These patients might present with concurrent hematemesis or melena. Other GI helminths are more likely to cause diarrhea.



**NOTE**

Cats with heartworm-associated respiratory disease can present with true vomiting or coughing that is mistaken for vomiting,[7] and distinguishing these is critical in guiding the diagnostic workup.

Common **gastric neoplasms** in the dog and cat are adenocarcinoma and lymphoma, respectively.[8] Less commonly seen malignancies are mast cell tumors, plasma cell tumors, and leiomyosarcomas.[8] These would rarely present without other chronic clinical signs (i.e., weight loss, dysrexia), but sometimes vomiting can be the only apparent clinical sign. Accompanying hematemesis should alert the clinician to the possibility of an upper GI neoplasm, administration of ulcerogenic drugs, or coagulopathy.

The most common **extra-GI causes** of acute vomiting in dogs and cats include acute kidney injury (AKI), diabetic ketoacidosis, endocrinopathies (e.g., hyperthyroidism in cats, hypoadrenocorticism in dogs), pancreatitis, and cholangiohepatitis in cats. Because the dog's shock organ is the

GI tract, anaphylactic patients commonly present with acute vomiting. Gallbladder mucoceles (▶Chap. 9.6.2) and biliary tract rupture can cause vomiting and often require emergent medical attention. In dogs, severe stranguria secondary to partial or complete urethral obstruction can elicit vomiting, as well as AKI secondary to urethral or ureteral obstruction in cats. Acute onset vestibular abnormalities (e.g., old-dog vestibular disease) can trigger emesis via activation of the vomiting center from the vestibular nuclei.[1] These pets typically have clinical signs of vestibular dysfunction. Most animals with vomiting secondary to hepatic or renal failure will have evidence of more chronic systemic disease.

#### 2.1.3.2 Differentials for regurgitation

Distinguishing regurgitation from vomiting is imperative as the diagnostic workup is usually markedly different.

As with vomiting, primary GI causes of regurgitation can be either functional or mechanical pathologies. Esophageal strictures (▶Chap. 5.3.5) and FBs (▶Chap. 5.3.4) are frequently recognized **mechanical causes** of regurgitation; both are frequently present acutely. Other common more chronic causes of regurgitation include brachycephalic airway syndrome, hiatal hernias (▶Chap. 5.3.9),[9,10] and esophageal neoplasms (▶Chap. 5.3.12).[8] Although uncommon, persistent right aortic arch (PRAA) is an important differential for puppies that develop regurgitation during transition from liquid to solid food (▶Chap. 5.3.11). German shepherd dogs are overrepresented, but this can occur in any breed. Regurgitation is rarely recognized in cats, but congenital anomalies such as PRAA have been noted in purebred kittens.[11]

Common **functional problems** causing regurgitation include esophagitis (▶Chap. 5.3.2) and megaesophagus (▶Chap. 5.3.8). Megaesophagus is a condition that can arise from idiopathic, congenital, autoimmune (myasthenia gravis), or toxic (lead, other heavy metals) etiologies. While it can present acutely, many animals display chronic clinical signs. Gastroesophageal reflux disease (GERD, ▶Chap. 5.3.3) is poorly defined in veterinary medicine but is likely a leading cause of esophagitis. GERD is associated with acute or chronic regurgitation, ptyalism, gagging, coughing,[12] and/or changes in phonation (from laryngitis secondary to reflux);[13] however, confirming the occurrence of clinical signs secondary to reflux events is challenging.[12] Many GERD patients exhibit meal-associated lip-smacking and soft coughing after eating or drinking. After ruling out an esophageal FB or stricture, GERD is a differential for animals with these presenting complaints.

Important **extra-GI causes** of regurgitation include hormonal deficiencies (e.g., hypoadrenocorticism, hypothyroidism in dogs) and megaesophagus caused by myasthenia gravis, polyneuropathy, or lead toxicity. Myasthenia gravis and/or polyneuropathy should be suspected with concurrent neurologic abnormalities.

#### 2.1.3.3 Differentials for diarrhea

Formulating a diagnostic and therapeutic plan for patients with diarrhea demands that the veterinarian first localizes it, determines how clinically affected the patient is and identifies if signs of concurrent systemic disease exist.

Commonly seen primary GI causes of **acute onset SI diarrhea** include parasites, dietary indiscretion, and an acute manifestation of a CE. Coccidia, *Giardia* spp., roundworms, and tapeworms are common SI parasites and typically cause SI diarrhea. Many dogs with CE will present as acute cases because either the owner never perceived their pet's slightly softer stools as diarrhea or a truly acute presentation was present. These dogs are often suspected of having dietary indiscretion because neither physical examination nor clinicopathologic abnormalities predict which dogs have CE vs. a dietary indiscretion and will never develop signs of chronic disease.

**LI diarrhea** is often primary GI in origin and in dogs, is commonly caused by irritable bowel syndrome (▶Chap. 8.3.4), dietary indiscretion, or endoparasites. Intestinal parasites preferentially affecting the LI include whipworms (▶Chap. 8.3.1.1), *Tritrichomonas blagburni* (formerly named *T. foetus*) in cats (▶Chap. 8.3.3), and hookworms (can also inhabit the SI). Granulomatous colitis is a differential in young to middle-aged dogs with LI diarrhea and concurrent weight loss (▶Chap. 8.3.1.2), particularly in French bulldogs and boxers.[14]

**Extra-GI causes** of diarrhea that must be ruled out include endocrinopathies (e.g., hyperthyroidism in cats, hypoadrenocorticism in dogs), hepatic or renal dysfunction, pancreatitis (▶Chap. 10.3.1), exocrine pancreatic insufficiency(▶Chap. 10.3.2), and systemic infectious diseases. Diarrhea seen with pancreatitis tends to be more LI due to the proximity of the pancreas to the ascending and transverse colon. Histoplasmosis is often systemic in the cat but mostly manifests as SI diarrhea and/or evidence of protein-losing enteropathy (PLE) in dogs (▶Chap. 7.3.8). Other considerations for SI diarrhea are *Heterobilharzia americana* (▶Chap. 7.3.1.4) in Gulf Coast areas and salmon poisoning, *Neorickettsia helminthoeca*, in the Pacific Northwest of the US. All of these organisms can cause vomiting with acute or chronic SI diarrhea. Dogs affected by salmon poisoning are usually febrile and often thrombocytopenic.[15–17] While hypercalcemia is a feature of heterobilharziosis, a recent

study found this in <10% of dogs,[18] but almost 50% of them had eosinophilia. In severe heterobilharziosis cases, hepatic involvement can also be seen. Dogs with any of these infections can have PLE with or without hyperglobulinemia. Protothecosis is a consideration for LI diarrhea with systemic disease in dogs.

**NOTE**
It is a common misconception that GI foreign bodies cause vomiting but not diarrhea. Especially animals with chronic or partially obstructive (i.e., linear or ball-valve effect) foreign bodies can have concurrent vomiting, but some animals present with diarrhea as the sole complaint.

### 2.1.4 Patient history

Essential questions about the patient history include those that successfully establish the chronicity of illness and paint a clear picture of the pet's lifestyle (e.g., single or multi-pet household, introduction of new pets, similar clinical signs in other pets, shelter or cattery environment, neuter status). Vaccine and preventative status are also important, as well as the indoor/outdoor status for cats. Any previous or recent history of dietary indiscretion, raw food feeding, or episodes of pancreatitis must be determined for animals with hematemesis, melena, and/or hematochezia. Initiation of any new diet, therapies, or changes to existing drug formulation or frequency is key, as many medications or drug interactions can cause GI signs. This includes the ingestion of any human medications the pet might have access to. Establishing the involvement of other body systems allows clinicians to prioritize differentials (e.g., viral disease in a young, unvaccinated puppy with concurrent respiratory and neurologic signs) and/or rule in or out extra-GI etiologies (e.g., concurrent neurologic abnormalities, especially after protein intake, with a portosystemic shunt).

#### 2.1.4.1 Patient history regarding vomiting and regurgitation

The clinician must differentiate if the animal shows vomiting, regurgitation, or a combination of both. If the owner has witnessed episodes, acting out of the events for the owner or viewing a video sequence provided by the owner can help discern the two. An allergic or anaphylactic reaction is a differential in an acutely vomiting dog (▶ Chap. 2.1.3). The owner should be asked about the possibility of an insect bite or sting, including vocalization shortly before the onset of vomiting. A gastric, SI, or esophageal FB are top differentials for patients with acute onset vomiting or regurgitation, regardless of the pet's age.

A GDV is a likely cause for retching, gagging, and/or abdominal bloating in a large breed dog, and determining gastropexy status is critical.

Careful questioning about any recent anesthesia or administration of specific medications (i.e., clindamycin or doxycycline tablets) is important in cats with acute onset vomiting, regurgitation, and/or dysphagia as esophageal strictures are common with these clinical presentations.[11]

Questioning about the timing of regurgitation to eating or drinking and concurrent weakness or neurologic signs is also important.

#### 2.1.4.2 Patient history regarding diarrhea

Successfully localizing diarrhea requires questions that allow the veterinarian to be confident about the volume, frequency, and character (e.g., presence and type of blood, presence of mucus) of the feces and to identify if tenesmus, dyschezia, and/or clinical signs of systemic disease are present. Hemorrhagic diarrhea should alert to the possibility of hookworms, whipworms, gastrointestinal ulceration, atypical hypoadrenocorticism (dogs), or neoplasia. Concurrent weight loss is concerning for either a malabsorptive or maldigestive process or endocrinopathy (e.g., hyperthyroidism or diabetes mellitus in cats).

Owners of cats with particularly foul-smelling, predominantly LI diarrhea should be asked if the cat originated from a shelter or cattery. Cats with *T. blagburni* often have a history of giardiasis refractory to metronidazole therapy.

### 2.1.5 Physical examination

The first goal is to establish if the patient is clinically stable. Animals with acute GI signs can present in hypovolemic or vasodilatory shock due to insensible fluid losses from vomiting and diarrhea, anaphylaxis, and/or septicemia. Assessment of hydration, capillary refill time, pulse rate and quality, and overall mentation should be prioritized as part of the triage examination. Assessing hydration status is imperative to determine if a patient requires inpatient care. A complete physical examination includes a basic neurologic and rectal examination. Muscle wasting or cachexia is indicative of a more chronic process (▶Chap. 2.4).

#### 2.1.5.1 Physical examination for vomiting

If an allergic (i.e., anaphylactic) reaction is suspected in a dog, careful inspection for any localized swelling indicating a sting or bite is necessary.

Crackles or wheezes noted on thoracic auscultation can indicate aspiration pneumonia. Pain elicited on abdominal palpation, along with SI thickening, might represent a FB or abdominal mass. Cranial abdominal pain raises suspicion of pancreatitis, but this clinical presentation varies from patient to patient. A palpable fluid wave alerts for the possibility of an acute abdomen (e.g., bile peritonitis, hemoabdomen) or a more chronic disease process with ascites (e.g., PLE or hepatic failure).

In cats, the tongue must be assessed for attachment or anchoring of a linear FB (▶Chap. 7.3.6).

#### 2.1.5.2 Physical examination for regurgitation

Dogs with an esophageal FB will often present quiet or lethargic with ptyalism and guarding or discomfort upon palpation of the neck. Halitosis might be noted with foreign material present in the esophagus for a prolonged period of time.

#### 2.1.5.3 Physical examination for diarrhea

Careful attention should be paid to abdominal palpation for masses, thickenings, or a fluid wave. Rectal palpation allows for the detection of melena, hematochezia, mass lesions, or pain (spinal or prostatic).

**CLINICAL PEARLS**

- Acting out vomiting and regurgitation for clients or encouraging the videotaping of events at home often elicits the most accurate clinical picture.
- Cats should always have the base of the tongue inspected for the presence of linear foreign bodies.
- Regurgitation is uncommon in cats, and this presentation demands an investigation for an esophageal foreign body or stricture (including questioning about recent anesthesia or oral medications).
- Atypical hypoadrenocorticism can manifest as acute gastrointestinal signs (with or without hemorrhagic diarrhea) without electrolyte abnormalities and should be ruled out early in the diagnostic process.
- The presence of solely large intestinal diarrhea with profound weight loss in a dog should prompt the consideration of granulomatous colitis or LI parasites, even if the diarrhea is acute.

### 2.1.6 Diagnostic testing

The extensiveness of the diagnostic plan depends upon how severely clinically affected the patient is and what information is gleaned from the history. Most patients warrant a minimum database consisting of a complete blood count (CBC), serum biochemistry panel, urinalysis, and routine fecal testing. The remainder of the plan depends on physical examination, minimum database, and/or diagnostic imaging findings. Clinically unstable or decompensated patients require immediate blood pressure, packed cell volume, total solids, lactate, and blood glucose measurements, and an abdominal FAST (focused assessment with sonography for trauma)[19,20] scan.

#### 2.1.6.1 Diagnostic testing for vomiting and regurgitation

A **CBC and serum biochemistry panel** can identify organ dysfunction and electrolyte and acid-base abnormalities (e.g., hypochloremic metabolic alkalosis). Although previously seen as pathognomonic for a pyloric outflow obstruction, hypochloremic metabolic alkalosis can occur with a small intestinal FB or severe vomiting.[21] Even acute (<24 hours) vomiting or ptyalism can result in profound electrolyte abnormalities. Hypoproteinemia might indicate GI bleeding or a protein-losing process (e.g., PLE).

**Abdominal radiographs** are necessary if a GI FB or mass is suspected, and thoracic radiographs if aspiration pneumonia is of concern. If a FB is suspected but not definitively diagnosed via radiographs, abdominal ultrasonography (**AUS**) is indicated as FBs can remain undetected when only one imaging modality is used. Intussusception requires AUS for definitive diagnosis. Indications for AUS generally depend on the clinical signs and stability of the patient. **Thoracic radiographs** are needed to detect an esophageal FB or megaesophagus in patients with acute onset regurgitation or odynophagia.

**Endoscopy** is rarely indicated as a first-line diagnostic unless a gastric FB or GI ulceration is suspected and should be considered emergent for patients with esophageal FBs as delays in procedure times following diagnosis have a worse outcome.[22,23]

**NOTE**

Any GDV suspect requires emergent abdominal radiographs following patient stabilization, as a delay in therapy affects survival. Serum lactate is indicated for GDV cases, as persistently increased (i.e., <40% decrease) lactate concentrations following fluid resuscitation has a greater chance of gastric necrosis and worse outcome.[24]

Once primary GI causes have been ruled out, **endocrine testing** (e.g., serum total T4 concentration in cats, baseline cortisol concentration in dogs) should be considered. A Spec PL (specific pancreas lipase concentration) is warranted in suspect pancreatitis cases. However, a definitive diagnosis of pancreatitis requires a combination of clinical signs and several diagnostics (i.e., consistent minimum database, increased Spec PL concentrations, compatible ultrasonographic findings).

### 2.1.6.2 Diagnostic testing for diarrhea

For stable and well-hydrated animals with an unremarkable physical examination and laboratory findings, it is reasonable to perform **fecal testing**, hold off on further diagnostics, and initiate supportive therapy (i.e., bland diet, probiotics, dietary fiber). Even with appropriate monthly preventatives, a fecal examination is recommended. When *Giardia* spp., coccidia, or other common GI parasites are suspected, a direct fecal examination (smear or wet mount)[25] and zinc centrifugation fecal float are recommended. Direct immunofluorescence assays (IFA) are the gold standard diagnostic for *Giardia duodenalis* and *Cryptosporidium* spp. Pairing IFA with zinc centrifugation will increase the diagnostic sensitivity[26] and is considered the gold standard for detecting *Giardia* spp. and coccidia (▶Chap. 7.3.1.3). Many parasites are shed intermittently, requiring multiple fecal examinations for a definitive diagnosis.[25]

In puppies or unvaccinated dogs suspected of having parvovirus (CPV) enteritis, the gold standard diagnostic test is the **fecal antigen test** (▶Chap. 7.3.1.1). Several commercial ELISAs detecting CPV antigen are available, and although specificity for all assays is very high, sensitivity is low.[27] Pairing the ELISA with fecal PCR (or immunoelectron microscopy, which is not routinely available) might reduce false negatives. False positives are uncommon but possible 4–8 days after vaccination with attenuated live vaccines.[27]

**AUS** is warranted in patients with suspected FB, mass, peritonitis, or fungal or protozoal infections. Dogs with heterobilharziosis can have pinpoint hyperechoic foci in the liver, small intestines, and/or mesenteric lymph nodes.[18]

Acute hemorrhagic diarrhea syndrome (AHDS) can cause marked hemoconcentration, hypoproteinemia, and hemorrhagic diarrhea with or without hypovolemic shock (▶Chap. 7.3.3). **Fecal enteropathogen testing** is only recommended with a known history of raw food ingestion, criteria consistent with sepsis, and/or the presence of similarly affected pets in the same household (▶Chap. 7.3.1.2).[28] Dogs with AHDS are more likely to test positive for *Clostridium perfringens netE* and *netF* pore-forming toxin genes than healthy dogs,[29] but the significance of a positive test is currently unknown. The *netF* gene has been associated with fatal necrotizing gastroenteritis in dogs,[30,31] but the prognostic or therapeutic importance of this test in non-septic AHDS needs further study.

**Blood cultures** are recommended in suspect septicemic cases, and treatment should not be withheld while awaiting the culture results. Rectal scrapings (using a cotton tip applicator or the tip of a gloved finger) provide an inexpensive, in-house diagnostic for identifying patients with infectious etiologies (e.g., histoplasmosis) or bacterial translocation (showing white blood cells and/or intracellular bacteria).[25]

When **histoplasmosis** is a differential, the gold standard test is a **urine ELISA** detecting *Histoplasma capsulatum* antigen (MiraVista Laboratories, Indianapolis, IN; Niche Diagnostics, Scarborough, ME).[17,33] Urine is preferred to plasma due to a higher sensitivity (▶Chap. 7.3.1.5.2).[34] *Heterobilharzia americana* can be diagnosed in fecal samples or biopsies (e.g., hepatic, intestinal) by **PCR** (▶Chap. 7.3.1.4).

In cats suspected to have **tritrichomoniasis**, the diagnostic test of choice to detect *T. blagburni* includes **fecal culture** (InPouch® TF-Feline culture) and **PCR** of a freshly voided fecal sample (▶Chap. 8.3.3).

For dogs with clinicopathologic abnormalities suspicious of **hypoadrenocorticism** (i.e., lack of stress leukogram, eosinophilia, hyponatremia, hyperkalemia, hypoalbuminemia, hypocholesterolemia, hypoglycemia, hypercalcemia), with or without signs of hypovolemic shock, **baseline cortisol** is necessary. An **ACTH stimulation test** (for adrenocorticotrophic hormone) is indicated for dogs with a baseline cortisol that does not exclude hypoadrenocorticism (Addison's disease). Dogs with atypical hypoadrenocorticism will present with similar clinical signs but normal electrolytes.[32] Concurrent polyuria/polydipsia, azotemia, and/or evidence of PLE, in addition to any clinicopathologic abnormalities noted above, should raise suspicion for Addison's disease.[32]

**KEY FACTS**

- The duration of clinical signs and clinical stability of the patient must be considered when formulating an individual diagnostic and therapeutic plan.
- Differentiating between vomiting and regurgitation is imperative prior to performing any further diagnostics.
- Discerning between small, large, and mixed bowel diarrhea is imperative to narrow down the differential diagnosis list.
- Esophageal foreign bodies and strictures must be ruled out for patients with acute onset regurgitation, as these require immediate intervention.
- A fecal enteropathogen panel should only be considered for patients with acute hemorrhagic diarrhea syndrome (AHDS) or gastrointestinal signs with
  1. evidence of septicemia,
  2. recent raw food ingestion, and/or
  3. other sick pets in the same household.

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
svg.to/9842-02-01

## 2.2 Clinical evaluation of patients with chronic vomiting

Panagiotis G. Xenoulis

### 2.2.1 Introduction

Vomiting is one of the most common problems in small animal practice. Vomiting is a complex physiological mechanism mediated by the emetic center located in the medulla. The emetic center can be triggered by stimuli originating from one or more of the following:

**a)** Receptors in the abdominal viscera (e.g., stimulated secondary to inflammation, organ distension, chemical irritation, or osmolality shifts)
**b)** Chemoreceptor trigger zone (e.g., secondary to chemical substances or toxins in the blood)
**c)** Semicircular canals of the vestibular apparatus
**d)** Cerebral cortex (e.g., secondary to excitement, stress, fear, or increased intracranial pressure)

Stimulation of the vomiting center by one or more of the above pathways results in vomiting, which is a coordinated event of abdominal and visceral muscle contractions, leading to the expulsion of material from the stomach and/or proximal small intestine.

Chronic vomiting is defined as vomiting that persists for >2 weeks and can be intermittent or continuous. Although patients with acute vomiting often do not require extensive diagnostic workup and vomiting often spontaneously resolves without or with only basic treatment, chronic vomiting almost always requires more extensive diagnostic investigation and specific treatment. Chronic vomiting as a clinical sign can result from a wide variety of clinical conditions, and the clinical approach to patients with chronic vomiting can be difficult and demanding (▶Fig. 2-1).

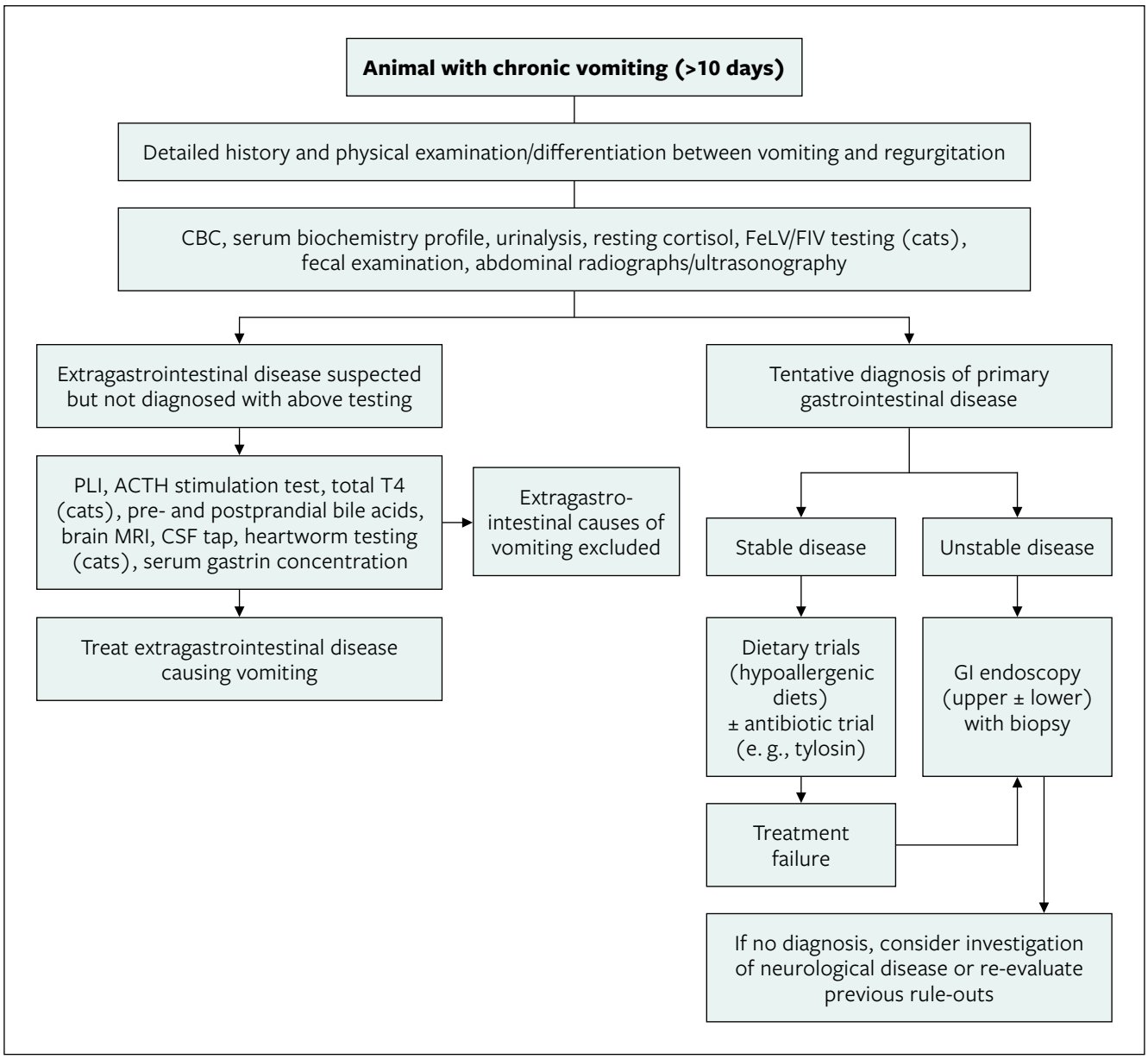



**Fig. 2-1** Diagnostic approach to dogs and cats with chronic vomiting

**CBC** = complete blood count, **FeLV** = feline leukemia virus, **FIV** = feline immunodeficiency virus, **PLI** = pancreatic lipase immunoreactivity, **ACTH** = adrenocorticotrophic hormone, **MRI** = magnetic resonance imaging, **CSF** = cerebrospinal fluid, **GI** = gastrointestinal

### 2.2.2 Causes of chronic vomiting

Vomiting, including chronic vomiting, can result from primary gastrointestinal (GI) disease but also extra-GI disorders (e.g., metabolic, inflammatory, and toxic conditions). Many vomiting patients have extra GI conditions (▶Tab. 2-1).

#### 2.2.2.1 Extragastrointestinal causes of chronic vomiting

Many extra-GI diseases can lead to chronic vomiting through several mechanisms. Most of these diseases can be ruled in or out based on the initial diagnostics described below. If a diagnosis still has not been made, further diagnostics may be needed to identify the cause of vomiting.

**Hepatobiliary diseases**, such as chronic hepatitis (▶Chap. 9.5.5.4), hepatic insufficiency or hepatic failure, gall bladder mucoceles (▶Chap. 9.6.2), hepatic lipidosis (▶Chap. 9.5.4.1.1), cholangiohepatitis (▶Chap. 9.6.3), neoplasia (▶Chap. 9.5.7, ▶Chap. 9.6.6), and portosystemic shunts (▶Chap. 9.5.3.2), can cause chronic vomiting.[1,2] Dogs and cats with hepatic failure most commonly have additional clinical signs, such as anorexia, diarrhea, weight loss, ascites, and possibly neurological signs (hepatic encephalopathy). In dogs and cats with hepatic disease, a serum biochemistry profile may reveal different combinations (depending on the specific disease) of increased serum hepatic enzyme activities and hyperbilirubinemia, while hypoalbuminemia, hypocholesterolemia, hypoglycemia, and low BUN (blood urea nitrogen) may be present with decreased functional capacity of the liver.[1,2] Hepatobiliary disease can be ruled out in most but not all cases by the absence of these clinicopathological abnormalities. Some diseases of the liver (e.g., neoplasia) often do not cause clinicopathologic abnormalities. If suspicion remains, other diagnostic tests, such as measurement of pre- and postprandial serum bile acid concentrations, abdominal radiographs, ultrasonography, and computed tomography may be required. Ultimately, hepatic biopsy is often necessary to obtain a definitive diagnosis.[1,2]

**Chronic kidney disease (CKD)** may lead to chronic vomiting in both dogs and cats through activation of the chemoreceptor trigger zone by uremic toxins and causing uremic gastritis. The most important parameters for diagnosing CKD are serum creatinine, BUN, and SDMA (symmetric dimethylarginine) concentrations, and urine specific gravity.[3] If suspected, renal ultrasound may provide further information about structural renal changes and help determine

**Tab. 2-1** Causes of chronic vomiting

| Gastrointestinal causes | Extra-intestinal causes |
|---|---|
| **GI tract obstruction**<br>• Gastric outflow obstruction<br>– Benign pyloric stenosis<br>– Foreign body<br>– Gastric antral mucosal hypertrophy<br>– Neoplasia<br>• Intestinal obstruction<br>– Foreign body<br>– Neoplasia<br>– Cicatrix<br>– Non-neoplastic infiltrative disease<br>– Intussusception<br><br>**Gastrointestinal inflammation**<br>• Inflammatory bowel disease<br>• Food hypersensitivity<br>• Food intolerance<br>• Intestinal dysbiosis<br>• Gastrointestinal ulceration<br>• Bilious vomiting syndrome<br>• *Helicobacter* spp.<br>• Parasites<br>– *Physaloptera* spp.<br>– *Ollulanus tricuspis*<br>– Ascarids<br>– *Giardia* spp.<br>• Viruses<br>– CPV/FPV<br>– FIV<br>– FeLV<br>– FIP<br>• Chronic colitis<br><br>**Miscellaneous**<br>• Idiopathic GI hypomotility<br>• Hiatal hernia<br>• Mast cell tumors<br>• Obstipation | **Drugs**<br>• NSAIDs<br>• Antimicrobials<br>• Chemotherapy<br>• Others<br><br>**Toxins**<br>• Heavy metals (lead, zinc)<br>• Plant toxins<br>• Grapes and raisins<br>• Ethylene glycol<br><br>**Abdominal inflammation/ Inflammation of abdominal organs**<br>• Chronic peritonitis<br>• Chronic hepatobiliary disease (e.g., chronic hepatitis, chronic cholangitis)<br>• Chronic pancreatitis<br>• Cholecystitis<br><br>**Nutrition**<br>• Food hypersensitivity<br>• Food intolerance<br>• Overeating/fast eating<br>• Dietary indiscretion<br><br>**Endocrine disorders**<br>• Hypoadrenocorticism (dogs)<br>• Hyperthyroidism (cats)<br>• Diabetes mellitus (diabetic ketoacidosis)<br><br>**Metabolic disorders**<br>• Chronic kidney disease<br>• Hepatic insufficiency/failure<br>• Hypercalcemia<br><br>**Neurological**<br>• Neoplasia<br>• Meningitis/encephalitis<br>• Increased intracranial pressure<br>• Hydrocephalus<br>• Psychogenic<br>• Vestibular disease<br>• Limbic epilepsy<br><br>**Miscellaneous**<br>• Dysautonomia<br>• Heartworms (cats)<br>• Pyometra<br>• Splenic disorders (e.g., splenitis)<br>• Others |

**NSAID** = non-steroidal anti-inflammatory drugs, **CPV** = canine parvovirus, **FPV** = feline parvovirus, **FeLV** = feline leukemia virus, **FIV** = feline immunodeficiency virus

prognosis. It needs to be pointed out that early stages of CKD (i.e., International Renal Interest Society [IRIS] stages I and II) are rarely associated with vomiting. Therefore, one should look for other causes of vomiting in those cases.

**Chronic pancreatitis** can also lead to chronic vomiting (▶Chap. 10.3.1). Chronic pancreatitis occurs commonly in both dogs and cats, and in addition to vomiting, it can be associated with other clinical signs, such as abdominal pain, anorexia, and diarrhea. In one study, vomiting was reported in 88% of 40 dogs with chronic clinical pancreatitis.[4] In cats, vomiting has been reported in 31–35% of cases, and most are considered to have chronic pancreatitis.[5] If chronic pancreatitis is suspected, a combination of abdominal ultrasonography and serum pancreatic lipase immunoreactivity concentration (Spec PL®) is currently the most accurate means for its diagnosis. However, clinical diagnosis is quite challenging, and the sensitivity of these diagnostic methods is lower for chronic than for acute pancreatitis.[5]

**Hypoadrenocorticism** is another potential cause of chronic vomiting in dogs (rarely in cats) and is commonly missed due to its ability to mimic other diseases. Dogs with hypoadrenocorticism may have intermittent anorexia, lethargy, vomiting, diarrhea, and/or weakness.[6] Hyperkalemia and hyponatremia may be evident on a serum biochemistry profile with the sodium:potassium ratio usually less than 27:1. However, in dogs with a sole glucocorticoid deficiency (atypical hypoadrenocorticism), serum electrolyte concentrations are normal.[6] The lack of a stress leukogram in an ill animal or a less commonly found "reverse" stress leukogram (i.e., lymphocytosis and eosinophil count in the upper reference interval or rarely eosinophilia) on a complete blood count (CBC) should raise suspicion that glucocorticoid deficiency may be present.[6] Measurement of baseline serum cortisol concentration is useful for excluding hypoadrenocorticism (if >2 µg/dL or >55 nmol/L). If hypoadrenocorticism is still suspected, an ACTH stimulation test should be performed.[6]

**Hyperthyroidism** is a common and important cause of chronic vomiting in older cats. Approximately 40% of hyperthyroid cats have chronic vomiting.[7] Hyperthyroidism in cats usually is diagnosed or ruled out after careful palpation of the neck to detect goiter, detection of concurrent clinical signs (e.g., weight loss, polyphagia, hyperactivity, and irritability), and measurement of serum total T4 concentrations. An increase in serum total T4 concentration is sensitive and almost 100% specific for hyperthyroidism.[7] In a small subset of cats (about 10%), non-thyroidal illness may suppress the total T4 concentration into the upper third of the reference interval. Repeat testing after several weeks or measurement of a serum-free T4 concentration by equilibrium dialysis can help in patients still suspected of having hyperthyroidism, whereas a normal serum TSH concentration can help rule out hyperthyroidism.[7]

**Heartworm disease** is an uncommon cause of chronic vomiting in cats. In one study of cats diagnosed with *Dirofilaria immitis* infections, 34% had a history of vomiting, and 10% had vomiting as the main clinical sign without any concurrent signs of respiratory disease.[8] A combination of antibody and antigen testing is usually necessary to assess exposure and the likelihood of heartworm infection given the overall low worm burden and the consequently low number of antigen-shedding female worms in cats.[8]

#### 2.2.2.2 Gastrointestinal causes of chronic vomiting

Primary GI causes of chronic vomiting typically include gastric diseases. However, it is important to note that chronic vomiting is also commonly caused by small intestinal disease.[9,10] This is especially common in cats.[10] Therefore, even if vomiting is the only clinical sign, small intestinal disease should always be on the differential diagnosis list.

**Dietary causes** of chronic vomiting are very common in both dogs and cats (▶Chap. 11.1). Dietary causes are commonly termed adverse reactions to food and include bad quality diets, dietary indiscretion, food allergy, and food intolerance.[9,11] Vomiting might be the only clinical sign, or there might also be diarrhea. Other clinical signs are uncommon. Concurrent vomiting or diarrhea and dermatologic signs might occur in food allergies. A detailed dietary history is crucial in cases where an adverse food reaction is suspected. Changing to a high-quality, bland, or hypoallergenic (novel or hydrolyzed protein) diet, depending on the underlying cause, will usually solve the clinical signs. However, multiple dietary trials are required in some cases, especially if a food allergy is present.[12] Continued vomiting is an indication for further laboratory tests, diagnostic imaging, and/or GI biopsy.

**Parasite infestations** also commonly cause chronic vomiting (▶Chap. 7.3.1.3). In addition to the stomach worm *Physaloptera* spp., which can cause severe and persistent vomiting,[13] roundworms, tapeworms, and *Giardia* spp. may also cause vomiting in some cases. Diagnosis is typically made by fecal examination, but broad-spectrum anthelminthic

therapy (e.g., fenbendazole, pyrantel) is also a reasonable initial choice in patients not suspected of having clinically severe disease.

**Antibiotic-responsive enteropathy** (ARE) appears to be more common in dogs than in cats.[14] It is more commonly associated with diarrhea and/or weight loss, but vomiting might also be present in some cases.

**Infiltrative GI disease** is a common and important cause of chronic vomiting in both dogs and cats. This includes different forms of inflammatory bowel disease (IBD) (▶Chap. 11.2), GI neoplasia (e.g., carcinoma, leiomyosarcoma, or lymphoma; ▶Chap. 6.3.4, ▶Chap. 7.3.9, ▶Chap. 8.3.7, ▶Chap. 11.3), and infections such as pythiosis and histoplasmosis (▶Chap. 7.3.1.5). IBD is a common cause of vomiting in dogs and cats and might be missed if only gastric causes are explored.[9,10,15] Especially in cats, in many cases with IBD or small-cell alimentary lymphoma, vomiting is the predominant clinical sign, with diarrhea being a minor disease component. In a recent study investigating cats with chronic enteropathies (IBD or lymphoma), 40% were presented for vomiting alone and 32% for vomiting and weight loss, as opposed to 4% and 7% for diarrhea and diarrhea plus weight loss, respectively.[10]

**Gastric emptying disorders** are fairly common causes of chronic vomiting and can result from either a mechanical obstruction (e. g., neoplasia, hyperplasia, or foreign bodies) or functional disorder.[16] Gastric or intestinal obstruction usually causes acute disease, but partial obstruction may lead to chronic vomiting. If a partial obstruction is suspected, abdominal radiographs and ultrasonography are the best initial tests. Gastrointestinal motility disorders may be secondary to other diseases (e.g., IBD, electrolyte disturbances, pancreatitis) or be primary.[16] The diagnosis of a primary gastrointestinal motility disorder is one of exclusion (▶Chap. 6.3.2, ▶Chap. 7.3.5). Accurate determination of abnormal gastric emptying is challenging (▶Chap. 1.9), and several techniques have been described.[16]

The role of **Helicobacter spp.** in gastritis and chronic vomiting is still uncertain in dogs and cats.[17] However, if organisms are present in a chronically vomiting animal, where no other cause can be identified, specific therapy for eradicating *Helicobacter* spp. may be indicated.[17] Gastric brush cytology is an effective way of detecting *Helicobacter* spp. and is more sensitive than the rapid urease test of biopsy samples (▶Chap. 6.3.1.3.1). Ultimately, a diagnosis of spiral bacteria is best made by histological evaluation of gastric biopsy samples. Given the still unclear pathogenicity of the organism, no consensus exists on what treatment, if any, should be initiated if these organisms are identified.[18]

## 2.2.3 Initial database

### 2.2.3.1 Differentiating vomiting from regurgitation and characteristics of vomited material

When an animal is presented with a complaint of chronic vomiting, it is essential to determine if it is, in fact, vomiting or regurgitating. Vomiting may occur any time after eating or drinking (seconds to hours). In most cases, vomiting is preceded by nausea, which may manifest by pacing, depression, lip licking, swallowing, salivation, and occasionally vocalization (cats). Retching, non-productive, rhythmic abdominal contractions usually follow, culminating in the act of vomiting. In contrast, regurgitation occurs passively, with animals expelling tubular undigested food or foamy white liquid with little or no effort. When the above findings are present, they are suggestive of vomiting. However, although absence of those signs usually indicates regurgitation, this is not always the case because sometimes vomiting can look almost exactly like regurgitation. Vomitus may contain bile pigment, while regurgitation should not. Both may look "digested", especially if regurgitated food has been retained in the esophagus for a prolonged period of time, rendering this an unreliable distinguishing characteristic.

A patient may vomit food, water, fresh blood, or mucus indistinguishable from regurgitated material. Blood in vomitus may be fresh (i.e., red) or digested to varying degrees (i.e., "coffee grounds" or "dregs" appearance), or there might be a mixture of those, depending on whether bleeding occurred immediately before vomiting or not. Hematemesis strongly suggests gastrointestinal ulceration. Clinicians should distinguish vomiting that produces specks of blood from vomiting in which there is substantial blood present (▶Fig. 2-2). The former may be caused by gastric mucosal trauma secondary to vigorous vomiting from any cause, while patients that produce more substantial amounts of blood generally should be approached differently.



Cat owners often tend to ignore trichobezoars or vomiting that contains hair because they consider it normal. However, in most cases, this is not the case. When vomiting occurs relatively frequently (i.e., ≥3 times per month), this should be considered potentially abnormal and should be further investigated.[10] The presence of hair in the vomiting material can result from a primary motility disorder or GI hypomotility secondary to another primary GI disease.

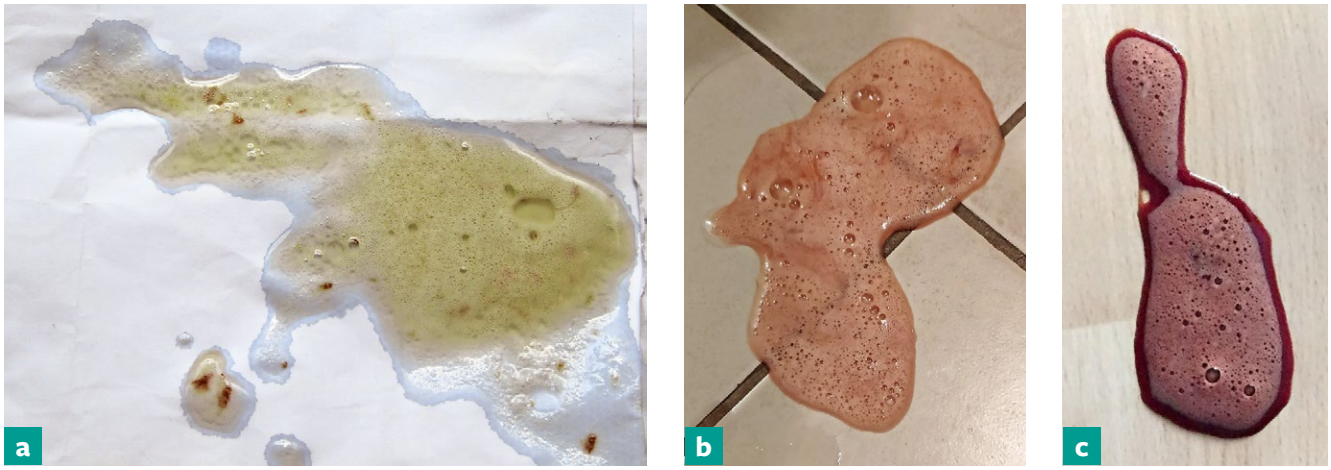



**Fig. 2-2** Different kinds of vomiting material

**a** Vomiting material that contains mainly fluid and some specs of blood. This is usually a clinically insignificant amount of blood and is not considered typical hematemesis.

**b** Vomiting material containing mainly fluid and some blood resulting in a uniform pink appearance.

**c** Vomiting material containing fluid and significant amounts of blood resulting in a red appearance (hematemesis).

It should be noted that eating grass is a common habit in some dogs and cats, and grass is a gastric irritant and, therefore, commonly leads to vomiting without necessarily indicating an underlying pathology.

#### 2.2.3.2 Patient history

First, the owner needs to understand what is considered an abnormal frequency of vomiting. In many cases, vomiting 3–4 times per month is considered normal by the owner. Although this might hold true for some cases, it is certainly not the case in others. In one study including 300 cats, of which 214 had chronic vomiting and vomiting ≥3 times per month was an inclusion criterion (in conjunction with increased intestinal wall thickness on ultrasonography), 96% were diagnosed with either IBD or lymphoma.[10]

A thorough patient history (including a detailed dietary history and questions about the animal's current diet or any dietary changes) should be obtained, and the clinician should search for historical evidence of ingested foreign objects, toxins, inappropriate food, or drugs. Owners may often be unaware of chronic foreign objects present in the stomach and, therefore, foreign bodies should not be excluded based on history alone (▶ Fig. 2-3).

Certain medications can cause vomiting that often is chronic if the medication is being administered for long periods. Such medications include but are not limited to antibiotics, chemotherapeutics, cyclosporin, and methimazole. Non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids (especially dexamethasone), when used chronically, can lead to chronic vomiting and hematemesis secondary to gastritis and gastrointestinal erosion or ulceration.

#### 2.2.3.3 Physical examination

Physical examination should also be thorough and can identify evidence of both GI and extra-GI disease. These include abdominal masses, pain, a distended colon (especially in

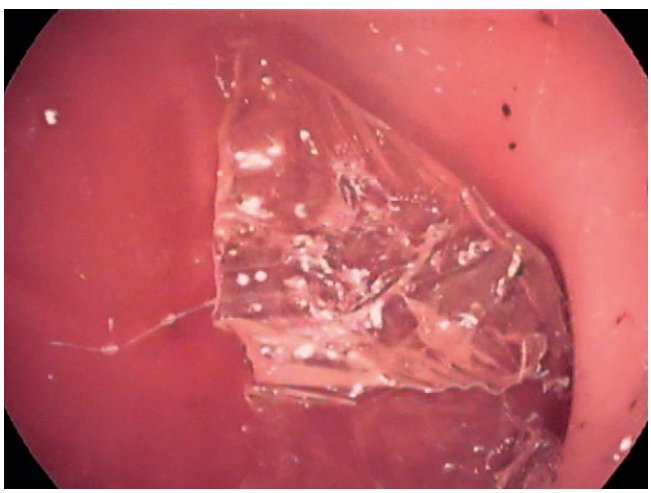


**Fig. 2-3** Endoscopic appearance of a foreign body (plastic material) causing chronic intermittent vomiting in a young cat that was not picked up on abdominal ultrasonography. Vomiting resolved after endoscopic removal of the foreign body.

cats), irregular or painful kidneys, organomegaly, thyroid nodules, uremic ulcers of the mouth, and other signs of systemic disease such as evidence of weight loss, dehydration, altered mentation, icterus, cardiac arrhythmias, mucous membrane pallor, and pyrexia. Vomiting cats should be investigated for linear foreign bodies at the base of the tongue. Parasites can also cause vomiting and, therefore, fecal examination for parasites should be performed.

Chronically vomiting dogs and cats are most often well hydrated; if the animal is vomiting frequently enough to become significantly dehydrated, the patient will usually present acutely. A digital rectal examination, especially to evaluate the feces for consistency and signs of occult bleeding, is also crucial. Neurological disease may lead to chronic vomiting, and clinical signs of vestibular disease, such as a head tilt, ataxia, or nystagmus, may be present. A complete neurological examination may be needed to detect more subtle central nervous system abnormalities. The combined findings from signalment, history, and physical examination allow the clinician to develop a complete clinical picture that will aid in formulating a list of differential diagnoses and necessary diagnostics.

### 2.2.4 Diagnostic approach

The diagnostic approach (▶Fig. 2-1) to patients with chronic vomiting can be either staged or aggressive, depending mainly on the severity of the clinical state of the animal. The diagnostic approach may be staged if the animal has been vomiting a few times per week with no concurrent clinical signs. If the patient has been vomiting more frequently and/or has concurrent hematemesis, weight loss, anorexia, pyrexia, or dehydration, a more aggressive approach is warranted so that a targeted treatment plan can be instituted as soon as possible. Furthermore, animals with additional findings on physical examination, routine diagnostic testing, and/or diagnostic imaging, associated with more severe disease or poorer prognosis, need to be investigated more aggressively.

The diagnostic approach to patients with chronic vomiting also varies greatly depending on the information obtained by signalment and patient history. For example, if an animal has been receiving NSAIDs and now is vomiting blood, gastric erosion and/or ulceration is by far the most likely diagnosis, and further diagnostics may be indicated to aid in determining the severity of disease and guiding the therapeutic approach.

Many extra-GI causes of vomiting are often associated with specific clinicopathologic changes. Therefore, a **minimum database** should be obtained for all patients with chronic vomiting, including a CBC, serum biochemistry profile with electrolytes, urinalysis, fecal analysis, abdominal radiographs, and FeLV/FIV (feline leukemia virus/feline immunodeficiency virus), and total T4 testing in cats. With this initial approach, a basic screen for secondary causes of vomiting (e.g., endocrine, metabolic, toxic, infectious) and complications of vomiting (e.g., acid-base and electrolyte abnormalities) is achieved. It may be necessary (based on the general clinical picture and initial clinicopathologic abnormalities) to measure serum bile acid concentrations (and/or blood ammonia concentrations) or resting serum cortisol concentrations (and/or perform an ACTH stimulation test) to screen for hepatic (▶Chap. 1.3.3) or adrenal insufficiency, respectively. Serum PLI (pancreatic lipase immunoreactivity) concentrations are useful for the diagnosis of pancreatitis in both dogs and cats (▶Chap. 1.3.4).

If the animal is systemically well with only mild intermittent vomiting, it is reasonable to stage the diagnostic workup and treat empirically (e.g., easily digestible diet ± gastroprotectants and antiemetics) pending the results of the initial diagnostic tests. A more aggressive approach is warranted in those patients in which vomiting has not resolved or that present systemically ill. It needs to be pointed out that clinicopathological findings are often normal in animals with primary GI disease. A coagulation profile should be done in animals with hematemesis to screen for coagulation abnormalities, although these are an uncommon cause of hematemesis.

After secondary causes of vomiting have been reliably ruled out, primary GI causes of chronic vomiting should be highly suspected. Endoparasites and dietary causes should be ruled out first.

A **fecal examination**, especially in patients with concurrent diarrhea, can also be useful in diagnosing gastrointestinal parasitism, such as ascarids and *Giardia* spp. A direct fecal smear and flotation should be performed for possible evidence of parasite eggs and protozoan cysts or organisms. However, it is important to note that standard flotation methods are rarely useful in identifying the presence of stomach worms (e.g., *Physaloptera* spp. and *Ollulanus tricuspis*). Diagnosis of these nematodes is most commonly accomplished using Baermann concentration of vomitus or gastroscopy. Diagnosis of giardiasis can also be difficult with direct fecal microscopy or standard flotation alone. The gold standard for giardiasis is performing at least three zinc sulfate concentration centrifugations on feces collected over 3–5 days.[19] Commercial ELISA kits to detect *Giardia* antigen in feces are also useful.[19]

**Therapeutic trials** are an important diagnostic tool for chronic vomiting. These typically include anthelminthic trials with a broad spectrum anthelminthic (e.g., fenbendazole, pyrantel) to exclude many common endoparasites, dietary tri-

als, and antibiotic trials. These can be performed sequentially in clinically well animals or combined in patients that need to be worked up more rapidly. Dietary trials with an easily digestible or preferably a hypoallergenic diet (exclusion or hydrolyzed protein) help diagnose or rule out adverse reactions to food.[12] Finally, some dogs with antibiotic-responsive enteropathy (ARE) may have vomiting as a predominant clinical sign, and a therapeutic trial with tylosin or metronidazole might prove helpful.

**Diagnostic imaging** can be useful in the workup of patients with chronic vomiting. Dogs and cats should first be screened by survey abdominal radiographs to evaluate for intestinal obstruction, constipation (especially in cats), foreign objects, masses, visceral displacement, and free abdominal fluid or gas.[20] In most patients with inflammatory GI diseases such as gastritis and inflammatory bowel disease (IBD), routine abdominal radiographs are normal. Abdominal ultrasonography is generally more sensitive than radiographs if performed correctly, but radiographs are more sensitive for revealing free air and some foreign bodies. Abdominal ultrasonography, alone or in combination with abdominal radiography, ideally should be performed in all cases where other diagnostics have failed to determine an underlying cause for the vomiting or for which further investigation of abdominal viscera is indicated (e.g., abdominal mass visualized on radiographs, renal azotemia, increased liver enzymes).[21] Ultrasonography may allow detection of hepatobiliary and pancreatic disease, evaluation of GI wall thickness and peristaltic activity, characterization of obstructive lesions, and an investigation for abdominal masses.[21] It may also facilitate fine-needle aspiration to aid in the definitive diagnosis of abdominal masses, cystic lesions, and lymphadenopathy.

If extensive clinical pathology testing and abdominal imaging are not diagnostic in a patient with chronic vomiting, the next diagnostic step is usually **upper GI endoscopy**. Endoscopy is one of the most reliable and cost-effective tools currently available for evaluating chronic vomiting when secondary GI diseases have been ruled out. Endoscopy is fast, safe, and minimally invasive. It allows visualization of mucosal lesions and the acquisition of gastric and intestinal biopsies. Endoscopy may reveal a cause of gastric outflow obstruction, such as antral pyloric mucosal hypertrophy, foreign bodies, or neoplasia. Erosive/ulcerative lesions, hemorrhage (▶Fig. 2-4), lymphoid follicular hyperplasia, gastric fluid retention, and mucosal friability throughout the stomach may also be discovered. Gastric neoplasia, pythiosis, or *Physaloptera* spp. may be associated with irregular masses or mucosal thickening, which should be biopsied for a definitive diagnosis.

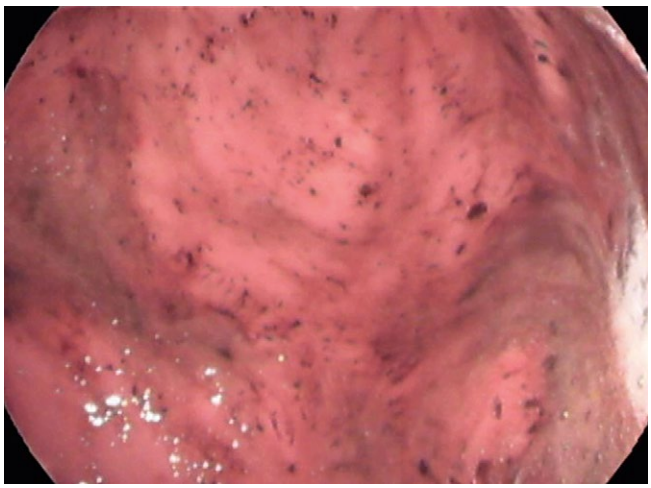


**Fig. 2-4** The endoscopic appearance of the stomach of a dog that presented with chronic vomiting, diarrhea, and weight loss.

Note the extensive hemorrhage of the gastric mucosa. Despite that, this dog did not display hematemesis. The dog was diagnosed with severe inflammatory bowel disease and intestinal lymphangiectasia.

If endoscopy is performed, biopsies should always be obtained from both the stomach and duodenum because both gastritis and duodenitis can cause vomiting.[22,23] Duodenitis (IBD) is a significant cause of vomiting without diarrhea in dogs and cats.[9,10] Additionally, biopsies of the ileum and sometimes ascending colon are often required (especially in cats) because the primary disease process, such as GI lymphoma, may be localized in these segments with only mild to moderate inflammatory infiltration of the remainder of the GI mucosa.[22] During endoscopy, the GI tract should always be biopsied regardless of normal gross mucosal appearance.[23]

If a definitive diagnosis is still not made after endoscopy and histopathology results, or if endoscopy is not available, an **exploratory laparotomy** should be considered, especially when serosal disease or potentially surgically curable lesions are suspected. However, surgery can miss gastric or intestinal mucosal lesions that will be picked up endoscopically.

Alternatively, if the cause of vomiting is undiagnosed after biopsy, some pathologic conditions may not have been investigated or inappropriately been ruled out. For example, common errors in ruling out certain diseases include ruling out hypoadrenocorticism because the animal has normal electrolyte concentrations; ruling out hyperthyroidism in a cat that has upper normal serum total T4 concentrations; ruling out liver disease (such as cirrhosis or neoplasia) in animals that have normal serum hepatic enzyme activities; or ruling out pancreatitis based on a normal ultrasonographic appearance of the pancreas. Finally, the clinician may con-

sider uncommon diseases that are more difficult to diagnose (e.g., idiopathic gastric hypomotility, occult CNS disease).

**Capsule endoscopy** (▶Chap. 1.5.6) has recently become available for dogs and can be used to evaluate patients for lesions throughout the GI tract.[24] It can be used when endoscopy is not available or when a lesion is suspected to be beyond the reach of the endoscope (e.g., mid-jejunum).

### KEY FACTS

- Detailed patient history and physical examination are important for the assessment of patients with chronic vomiting.
- Extragastrointestinal causes of vomiting (e.g., hyperthyroidism in cats, hypoadrenocorticism in dogs, pancreatitis, liver disease) are common and important, and should be excluded first.
- Chronic pancreatitis might be difficult to diagnose or rule out as a cause of chronic vomiting.
- Gastrointestinal endoscopy is useful for evaluating chronic vomiting after secondary causes of vomiting have been ruled out.
- Chronic or intermittent vomiting is commonly the predominant clinical sign of inflammatory bowel disease (IBD), especially in cats.

### References

The complete list of references for this chapter can be downloaded from vetline.de:
svg.to/9842-02-02

## 2.3 Clinical evaluation of patients with chronic diarrhea

Barbara Kohn, Christiane Weingart

### 2.3.1 Definition and differentials

Diarrhea is defined as the defecation of feces with reduced consistency due to increased water content. If diarrhea persists for more than 2–3 weeks, it is considered chronic. Both gastrointestinal (GI) and extra-gastrointestinal (extra-GI) diseases may be the cause (▶Tab. 2-2). In an evaluation of 136 dogs, chronic inflammatory enteropathies were the most frequent cause of chronic diarrhea, while 10% had extra-GI diseases (▶Tab. 2-3). In dogs and cats with extra-GI diseases, other clinical signs such as vomiting (▶Chap. 2.2) may predominate. Since many differential diagnoses for chronic diarrhea can be considered, a systematic approach is important (▶Fig. 2-5).

**Tab. 2-2** Differential diagnoses for chronic diarrhea in dogs and cats

| Primary disease location | Possible causes | Classification of diarrhea | Species |
|---|---|---|---|
| Extra-gastrointestinal disorders | **Exocrine pancreas** | | |
| | Pancreatitis | SB, LB | D/C |
| | Exocrine pancreatic insufficiency | SB | D/C |
| | Neoplasia | SB | D/C |
| | **Metabolic** | | |
| | Hepatopathy, portosystemic shunt | SB | D/C |
| | Cholangitis, cholecystitis | SB | D/C |
| | Nephropathy | SB | D/C |
| | **Endocrine** | | |
| | Hypoadrenocorticism | SB | D/C |
| | Hyperthyroidism | SB | C |
| | Hypothyroidism (rare) | SB | D |
| | **Other** | | |
| | Heart failure (rare) | SB | D/C |
| | Drugs (e.g., omeprazole) | SB | D/C |

▶▶

**Tab. 2-2** Differential diagnoses for chronic diarrhea in dogs and cats (Continuation)

| Primary disease location | Possible causes | Classification of diarrhea | Species |
|---|---|---|---|
| Gastrointestinal disorders | **Infectious** | | |
| | **Parasites** | | |
| | Ascarids, hookworms | SB, LB | D/C |
| | *Taenia* spp., *Dipylidium caninum* | SB | D/C |
| | *Ecchinococcus, Trichuris vulpis* | SB, LB | D/C |
| | *Giardia* spp., *Cystoisospora* spp. | SB | D/C |
| | *Cryptosporidium* spp. | SB | D/C |
| | *Tritrichomonas blagburni* | LB | C |
| | Leishmaniasis | SB, LB | D |
| | **Other infections** | | |
| | Feline infectious peritonitis | SB, LB | C |
| | Prototheca infection | LB | D |
| | Mycosis (histoplasmosis, phytiosis) | SB, LB | D/C |
| | **Inflammatory/idiopathic** | | |
| | Food-responsive enteropathy | SB, LB | D/C |
| | Antibiotic-responsive enteropathy | SB | D |
| | Probiotic-responsive enteropathy | SB, LB | D/C |
| | Inflammatory bowel disease | SB, LB | D/C |
| | Lymphangiectasia | SB | D |
| | Histiocytic ulcerative colitis | LB | D |
| | Feline gastrointestinal eosinophilic sclerosing fibroplasia | SB, LB | C |
| | Gluten-sensitive dyskinesia in border terriers | SB | D |
| | **Other** | | |
| | Neoplasia | SB, LB | D/C |
| | Vasculitis (immune-mediated) | SB, LB | D |
| | Chronic intussusception | SB, LB | D/C |

**D** = dog, **C** = cat, **SB** = small bowel diarrhea, **LB** = large bowel diarrhea

**Tab. 2-3** Primary and secondary causes for chronic diarrhea in 136 dogs[2]

| Primary causes: 123/136 dogs | Secondary causes: 13/136 dogs |
|---|---|
| **Inflammatory:** 97 dogs<br>• Food-responsive enteropathy: 64<br>• Inflammatory bowel disease: 15<br>• Antibiotic-responsive enteropathy: 11<br>• Steroid/Immunosuppressant-responsive enteropathy: 4<br>• Protein-losing enteropathy: 3<br>**Infectious:** 18 dogs<br>• Parasites: 15<br>• Protothecosis: 2<br>• Leishmaniasis: 1<br>**Neoplastic:** 6 dogs<br>• Lymphoma: 5<br>• Colorectal adenocarcinoma: 1<br>**Mechanical**: 1 dog<br>• Intussusception: 1<br>**Other**: 1 dog<br>• Vasculitis: 1 | **Exocrine pancreas**: 8 dogs<br>• Exocrine pancreatic insufficiency: 4<br>• Chronic Pancreatitis: 3<br>• Adenocarcinoma: 1<br>**Endocrine**: 2 dogs<br>• Hypoadrenocorticism: 1<br>• Hypothyroidism: 1<br>**Liver**: 1 dog<br>• Portosystemic shunt<br>**Kidney:** 1 dog<br>• Chronic kidney disease<br>**Cardiovascular**: 1 dog<br>• Chronic heart failure |

Inclusion criteria: diarrhea for ≥ 3 weeks and a complete diagnostic workup

### 2.3.2 Signalment

Certain breeds have a predisposition to particular forms of chronic enteropathies (▶Chap. 1.1). Young dogs are more prone to infectious diseases (such as parasites) and food-responsive diarrhea (FRD). In one study, the mean age of dogs with FRD (3.5 years; range 0.6–7.6 years) was significantly lower compared with dogs with steroid-/immunosuppressant-responsive diarrhea (IRD) (6.5 years; 2.1–13.0 years).[1] Neoplasms, such as adenocarcinomas, mast cell tumors, and spindle cell tumors, are more likely to occur in middle-aged to older patients, while lymphoma may also occur at a young age.

### 2.3.3 Medical history

The patient's medical history should include the duration of the clinical signs, fecal consistency, defecation frequency, behavior when defecating (e.g., tenesmus), body weight history, and the occurrence of borborygmi and flatulence. Diarrhea can contain mucus, fresh (hematochezia) or digested (melena) blood.

With this information, a distinction can be made between small bowel and large bowel diarrhea. Watery feces with the presence of undigested components, steatorrhea, melena, flatulence, or borborygmi indicate small intestinal disease, while patients with large bowel diarrhea usually have a high frequency of defecation (>3 times per day), tenesmus, mucus admixture, and possibly hematochezia.

Weight loss is a typical feature of small bowel diseases but can also occur occasionally in *Escherichia coli* associated granulomatous colitis (▶Chap. 8.3.1.2) of the boxer (and other breeds, e.g., Bulldogs). Vomiting can occur in diseases of both the small and large intestine. While appetite is usually normal in patients with large bowel disease, patients with small bowel diarrhea can have a normal appetite, polyphagia (due to malabsorption, possibly pica, coprophagia), or inappetence (due to nausea or abdominal pain). In small animals, the entire GI tract is often affected, which can manifest itself in either a mixed clinical picture or clinical signs consistent with a disease of either the large or small intestine.

The presence of findings such as icterus, polyuria/polydipsia, and vomiting can be an indication of an extraintestinal disease (e.g., pancreatitis, hepatopathy, cholangitis, hyperthyroidism, nephropathy). In an evaluation of 136 dogs with chronic diarrhea, vomiting was a common finding in GI (71%) and extra-GI (73%) diseases. However, moderate to severe vomiting was identified to be significantly more frequent in dogs with extra-GI (64%) disease compared with dogs with GI (28%) diseases.[2] Pruritic patients with dermatological and GI signs are more likely to have FRD.

Other important information includes the deworming status and the travel history. In addition, a detailed dietary history, which should include food composition (commercial, self-prepared) including the proteins and carbohydrates contained, the feeding of raw meat, and previous dietary changes, is important.

Furthermore, any prior treatment and response to therapy should be recorded.

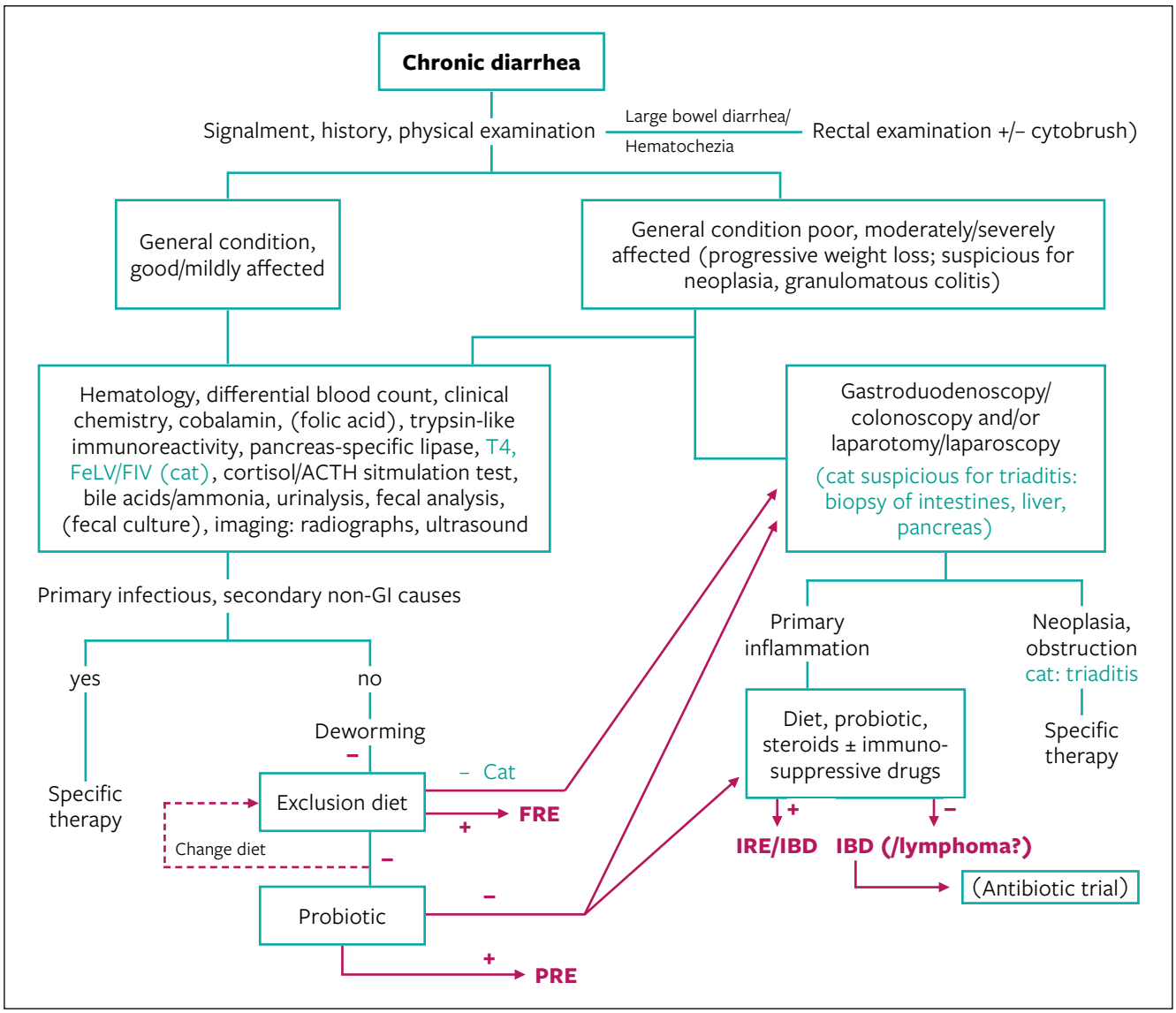



**Fig. 2-5** Diagnostic approach to chronic diarrhea in dogs and cats

**FRE** = food-responsive enteropathy, **PRE** = probiotic-responsive enteropathy, **IRE** = immunosuppressant-responsive enteropathy, **IBD** = inflammatory bowel disease, **FeLV** = feline leukemia virus, **FIV** = feline immunodeficiency virus, **ACTH** = adrenocorticotrophic hormone, **GI** = gastrointestinal

### 2.3.4 Clinical examination

The patient's body weight, body condition score (BCS), and muscle condition score (MCS) can provide information about the disease severity and can also be assessed serially to track the course of disease (▶Chap. 1.2). In addition to the general physical examination, special attention must be paid to the abdomen. By means of abdominal palpation, increased abdominal wall tension, thickened intestinal loops, and possibly even intraabdominal masses can be detected. Patients with severe protein-losing enteropathy (PLE) may develop peripheral edema and ascites (abdominal distension with a fluid wave).

For cats > 6 years old, thyroid palpation and blood pressure measurements should be performed. Patients with decompensated right heart failure may show clinical signs associated with abdominal effusion in addition to a heart murmur. Respiratory signs may occur in patients with PLE (thoracic effusion or pulmonary thromboembolism). Digital palpation of the rectum is important for the evaluation of the anal tone and detection of irregular thickening of the rectal mucosa and of rectal masses.

Clinical scoring systems (canine inflammatory bowel disease activity index [**CIBDAI**], canine chronic enteropathy clinical activity index [**CCECAI**], and feline chronic enteropathy activity index [**FCEAI**]) can be helpful for assessing the severity of a chronic enteropathy and can also be used to monitor its progress (▶Chap. 11.2). These scoring systems classify the severity of the enteropathy into mild, moderate, or severe based on the clinical signs of activity, appetite, vomiting, stool consistency, stool frequency, and weight loss. For the CCECAI score, pruritus, the occurrence of ascites/peripheral edema, and serum albumin concentrations are also included. The FCEAI includes GI signs (appetite, activity, vomiting, diarrhea, weight loss), the occurrence/absence of endoscopic lesions, and abnormalities in certain laboratory parameters (total protein, ALT/ALP activity, phosphorous).

### 2.3.5 Laboratory tests

A **complete blood count** does not usually lead to a diagnosis in patients with chronic diarrhea, but it can rule in or out various extra-GI diseases (e.g., hypoadrenocorticism) and determine if the patient is suffering from systemic complications of GI disease (e.g., hypoalbuminemia). Leukocytosis is non-specific, but the absence of a stress leukogram and the presence of eosinophilia and lymphocytosis may indicate hypoadrenocorticism. Other reasons for eosinophilia are allergic and parasitic diseases, eosinophilic chronic enteropathy, and rarely, feline gastrointestinal eosinophilic sclerosing fibroplasia. Lymphopenia is a common finding in dogs with intestinal lymphangiectasia. Non-regenerative, normocytic-normochromic anemia can result from anemia of inflammatory/neoplastic disease. Intestinal blood loss and hemolysis (e.g., secondary immune-mediated hemolysis) usually lead to a regenerative, macrocytic, possibly hypochromic anemia. In the presence of chronic anemia due to gastrointestinal blood loss, microcytosis, hypochromasia, a reduced reticulocyte hemoglobin content, and thrombocytosis may be present. Blood smear evaluation can provide valuable information on iron-deficient erythropoiesis (e.g., hypochromic erythrocytes, target cells, microcytic erythrocytes, poikilocytes).

Cats with chronic diarrhea should be screened for **feline leukemia virus** (FeLV-antigen test) and **feline immunodeficiency virus** (FIV-antibody test).

**Azotemia** can be prerenal or renal in patients with chronic diarrhea. The urine specific gravity is used to confirm renal azotemia. It should be noted that in patients with hypoadrenocorticism and concomitant (mostly prerenal) azotemia, the specific gravity is lower than expected due to hyponatremia. Increased urea concentrations may also indicate gastrointestinal bleeding. In patients with hypoalbuminemia or panhypoteinemia, urinalysis is important to exclude renal protein loss (increased urine protein to creatinine ratio). Once protein-losing nephropathy (PLN), hepatopathy, and hemorrhage have been excluded, intestinal protein loss can be assumed.

Patients with chronic enteropathies often show mild elevations in **liver enzyme activities** due to reactive hepatitis. Cats with hyperthyroidism may have a mild to moderate increases in ALT (alanine aminotransferase) and/or ALP (alkaline phosphatase) activities. In individual cases, the differentiation of GI from primary liver disease can be difficult. The determination of total serum bile acid concentrations (pre- and 2 hours postprandial), the use of laboratory parameters (such as albumin, urea, glucose, ammonia), and, if necessary, histological examination of a liver biopsy can help make this distinction. Hypocholesterolemia can occur with hepatopathy, hypoadrenocorticism, or lymphangiectasia. Rarely, patients with chronic enteropathy may develop clinically relevant hypocalcemia, hypomagnesemia, and coagulopathy due to malabsorption.

**Serum total T4** concentrations should be determined in any cat older than 6 years as a screening test for hyperthyroidism. Patients with chronic diarrhea, and panhypoproteinemia (reduced albumin and globulin concentration) due to PLE often require intensive care and an aggressive diagnostic workup. For causes of PLE, ▶Chap. 7.3.8.

Some dogs with PLE will have **serum globulin** concentrations within the reference interval. In exceptional cases of chronic diarrhea, hyperglobulinemia may be present (e.g., in basenji enteropathy). In contrast, only hypoalbuminemia usually occurs with PLN.

Measurement of the fecal **$\alpha_1$-proteinase inhibitor** ($\alpha_1$-PI) can be used as a confirmatory test in dogs with suspicion of albumin loss via the intestine and is helpful in diagnosing concomitant PLE in patients with PLN. This test may also be useful in dogs with PLE without diarrhea. The $\alpha_1$-PI protein has the same molecular size as albumin, but unlike albumin, it is not degraded in the gut. Fecal samples for the measurement of $\alpha_1$-PI should be frozen promptly and must not be collected rectally (measurement available at the Gastrointestinal Laboratory, Texas A&M University, TX, USA).

Dogs with PLE lose **antithrombin** as well as albumin via the intestine. Antithrombin is a natural anticoagulant that, if lost, can predispose the patient to thrombosis. While the determination of coagulation times via PT (prothrombin time) and aPTT (activated partial thromboplastin time) are not helpful, antithrombin measurement and, if available, thromboelastography may help diagnose hypercoagulopathy.[3]

Most patients with hypoadrenocorticism have **electrolyte abnormalities** (hyperkalemia, hyponatremia [Na:K

ratio <27], hypochloremia). Dogs with chronic signs usually present with the atypical type of hypoadrenocorticism (with normal electrolytes). It should be considered that other diseases (e.g., renal insufficiency, GI diseases, effusions, whipworm infection) can also lead to hyperkalemia and hyponatremia (pseudohypoadrenocorticism). A serum basal cortisol concentration >2 µg/dL excludes the presence of this disease, while a confirmatory ACTH stimulation test must be performed when the baseline value is <2 µg/dL.[4] Pre-treatment with glucocorticoids (systemic or topical in the form of ointments or drops) confounds the assessment of serum cortisol.

Whenever pancreatitis is suspected, the **serum pancreas-specific lipase** concentration should be measured. For this purpose, a point-of-care screening test can be used (SNAP® cPL or fPL for dogs and cats, respectively). An abnormal result should be followed by quantitative pancreas-specific lipase determination (Spec cPL® or Spec fPL® for dogs and cats, respectively) (▶Chap. 1.3.4.1). The sensitivity of this test is lower in chronic pancreatitis (e.g., mild inflammation, fibrosis) compared with acute pancreatitis. The DGGR (1,2-o-dilauryl-rac-glycero-3-glutaric acid-[6′-methylresorufin] ester) lipase activity is marketed as being more specific for pancreatic lipase than traditional lipase activity assays. It produces similar but not completely equivalent results compared with the Spec cPL/fPL assays.[5]

Exocrine pancreatic insufficiency (▶Chap. 10.3.2) is diagnosed by determining the **species-specific serum TLI** concentration after withholding food for a minimum of 8 hours.

**C-reactive protein** (CRP) is an acute-phase protein and a helpful biomarker in dogs for the detection and especially for the monitoring of inflammatory processes. There are various reports describing increased serum CRP concentrations in dogs with chronic enteropathy. While a correlation between CIBDAI and CRP concentration was demonstrated in a study involving 58 dogs, another study demonstrated increased serum CRP concentrations in only six of 21 dogs.[1,6] Furthermore, it should be considered that other inflammatory diseases, such as pancreatitis, are also associated with an increase in serum CRP concentration. The response of the major acute-phase proteins serum amyloid A (SAA) and $\alpha_1$-acid glycoprotein (AGP) in cats with chronic diarrhea has not been studied.

Low serum **cobalamin** (vitamin $B_{12}$) concentrations can be seen with chronic small bowel disease (absorption takes place in the ileum) but also in cases with exocrine pancreatic insufficiency. Further reasons for hypocobalaminemia are neoplasms with ileal involvement, small intestinal dysbiosis, and a hereditary cobalamin deficiency (Imerslund-Gräsbeck syndrome). The measurement of serum cobalamin is also useful from a therapeutic point of view, as this vitamin is involved in many metabolic processes (e.g., citric acid cycle, nucleic acid synthesis) and is important for enterocyte function, meaning it must therefore be supplemented in case of deficiency. The measurement of cobalamin concentration alone is not sufficient to fully assess intracellular cobalamin status. Increased methylmalonic acid and homocysteine are markers for cobalamin deficiency on a cellular level because the cobalamin-dependent methyl-malonyl-CoA mutase and methionine synthase are inhibited in cobalamin deficiency. However, the measurement of methylmalonic acid (in urine or serum) and homocysteine are not routinely performed in clinical practice (▶Chap. 1.3.2).

The significance of the finding of a low or high serum **folic acid** concentration is currently unclear. Some authors recommend folic acid supplementation in dogs with hypofolatemia.[7]

A **fecal parasitological examination** (preferably using three pooled fecal samples) is recommended in all patients with chronic diarrhea (▶Chap. 7.3.1.3). In addition to fecal flotation for detection of nematodes, a screening test for *Giardia* spp. must be carried out. Even if the result is negative, deworming with a broad-spectrum anthelminthic (e.g., fenbendazole) is advisable, as parasites can be excreted intermittently. In cats with large bowel diarrhea, a fecal PCR assay for the detection of *Tritrichomonas blagburni* (formerly named *T. foetus*) should be performed (if possible, the feces should be collected via colonic flush or with a fecal loop to increase sensitivity). In cases of severe infestation, the unicellular organisms can also be seen microscopically on direct smears (fresh feces diluted with saline). In young animals and immunocompromised patients, *Cryptosporidia* spp. can be a cause of chronic diarrhea and an ELISA, IFA, or PCR assay may be diagnostic. In endemic regions, a fecal PCR test for *Heterobilharzia americana* should be performed in dogs. In dogs with signs of colitis, an algal infection (*Prototheca zopfii*) can be diagnosed in rare cases by cytological examination of a **rectal scrape**. A **microbiological fecal analysis** using PCR testing for pathogenic bacteria (e.g., *Campylobacter* spp., *Salmonella* spp.) is indicated in select cases (e.g., in cases with concurrent fever or if multiple animals or people in the household are affected). However, it should be considered that many of the organisms isolated in fecal cultures or detected by fecal PCR are also found in the feces of healthy dogs and cats (▶Chap. 7.3.1.2).

### 2.3.6 Imaging techniques

Abdominal radiography usually does not lead to a diagnosis in patients with chronic diarrhea (▶Chap. 1.4). However, large intraabdominal masses and moderate to severe body

cavity effusions can be detected. Abdominal ultrasonography enables the assessment of the abdominal structures such as the intestine, stomach, lymph nodes, and extra-GI organs. Loss of intestinal wall layering may be consistent with neoplastic disease (e.g., lymphoma; ▶Chap. 11.3) or feline eosinophilic sclerosing fibroplasia. Patients with chronic enteropathies may have a thickened mucosal layer. The presence of hyperechoic striations (vertical hyperechoic stripes in the mucosa) is suggestive of lymphangiectasia and can be pronounced in dogs with PLE. Speckles (hyperechoic points in the mucosa) are non-specific.[8] Cats with chronic enteropathy are more likely to show muscularis layer thickening than dogs. In an evaluation of 300 cats with chronic small bowel disease and concurrent ultrasonographic evidence of thickening of the small intestinal wall, 150 cats had chronic enteritis, and 124 had intestinal lymphoma.[9] Enlarged lymph nodes may be reactive or neoplastic. In dogs, reduced thickness of the adrenal gland may support the suspicion of primary hypoadrenocorticism. Ultrasound-guided aspiration and biopsy are diagnostic techniques used to evaluate free fluid, masses, and structurally altered organs.

### 2.3.7 Additional testing

**Colonoscopy with biopsy** is indicated in boxer dogs, French/English bulldogs, mastiffs, and Alaskan malamutes with clinical signs of colitis and suspected *E. coli*-associated granulomatous colitis (formerly called histiocytic ulcerative colitis). The diagnosis can be confirmed via bacterial culture of a colonic biopsy (including an **antibiogram**) and histological documentation of invasive *E. coli* in the colonic mucosa, ideally using fluorescence-in situ-hybridization (FISH).

In dogs and cats with chronic diarrhea, after exclusion of extra-GI disease, infectious disease, intestinal tumors, or mechanical disease (e.g., intussusception), a **chronic enteropathy** can be confirmed. This is a disease complex that includes various chronic inflammatory bowel diseases that are classified by a response to therapy (i.e., food-responsive diarrhea, probiotic-responsive diarrhea, antibiotic-responsive diarrhea, IBD/IRD). In severe cases, the pronounced infiltration of the intestinal wall with inflammatory cells can result in PLE.

For further differentiation of chronic enteropathy, a stepwise approach is applied (▶Fig. 2-5). In patients with moderate to severe clinical signs and/or panhypoproteinemia, an aggressive diagnostic approach with simultaneous initiation of treatment is indicated. In patients with milder signs, the stepwise diagnostic approach usually starts with dietary trial(s). Options include highly digestible, low/moderate-fat diets (often containing prebiotics), a hydrolyzed protein diet, or a novel protein diet. Hydrolyzed diets contain proteins (e.g., poultry, soya, feather protein) that have been enzymatically split into polypeptides. The novel protein diet consists of a protein (e.g., horse, kangaroo, buffalo) and carbohydrate source (e.g., potatoes, cassava, millet) that is new to the patient and is commercially available or is home-prepared by the owner. A home-cooked diet must be adapted to the requirements of long-term feeding (e.g., the addition of vitamins and minerals). After 1–2 weeks, patients with a **food-responsive enteropathy** (**FRE**) should show a significant improvement in clinical signs. Additionally, dogs with large bowel diarrhea may occasionally respond to diets rich in fiber (e.g., added psyllium) (**fiber-responsive diarrhea**). If there is no response, an additional dietary trial (e.g., with a different protein source) is often attempted. The administration of probiotics can also lead to the resolution of clinical signs (so-called **probiotic-responsive enteropathy, PRE**). Moreover, an immunomodulatory effect, probiotics may also protect the host from pathogenic microorganisms or lead to an improvement of the intestinal mucosal barrier function. Data on the optimal composition, dosage, and duration of probiotic administration are currently lacking in veterinary medicine.

If the clinical signs do not improve satisfactorily with the diet change or probiotics, the diagnosis is most likely **idiopathic inflammatory bowel disease** (**IBD**) or intestinal **neoplasia**. To exclude a neoplastic disease, histological examination of the stomach and intestinal biopsies may be necessary, in addition to ultrasonography.

The decision regarding the technique of biopsy collection depends on several factors (▶Chap. 1.5.3). Endoscopic biopsy is less invasive but has the disadvantage that only mucosal samples can be collected (partial thickness). Samples must be taken from the stomach, duodenum and, if possible, the proximal jejunum (even if the findings are macroscopically inconspicuous) and, by means of colonoscopy, from the colon, and, if possible, the ileum (especially if small-cell lymphoma is suspected). In unclear cases, samples containing all layers of the bowel may have to be collected surgically (full-thickness, particularly important in the case of changes in the muscularis). In patients with severe hypoproteinemia, however, wound healing disorders may occur. Due to the increased risk of dehiscence, colonic biopsies should only be collected endoscopically.

Depending on the type of infiltrates, lymphoplasmacytic and eosinophilic enteritis can be diagnosed by histological examination using standardized World Small Animal Veterinary Association (WSAVA) guidelines (▶Chap. 1.8), although this distinction has little clinical relevance. To differentiate between small-cell lymphoma and lymphoplasmacytic enteri-

tis, additional investigations (i.e., immunohistochemistry, clonality tests) may be helpful. Granulomatous infiltrates occur in *E. coli*-associated granulomatous colitis or may be associated with leishmaniasis and in cats with *Campylobacter* spp. and FIP infection. Patients that do not have FRE or PRE, in which intestinal biopsy is omitted (e.g., due to an increased risk of anesthesia) and that respond to immunosuppressive medication are classified as having **immunosuppressant-responsive enteropathy** (**IRE**).

Response to treatment with metronidazole (or tylosin) indicates the presence of so-called **antibiotic-responsive enteropathy** (**ARE**). However, due to the frequent recurrence of clinical signs once they have been stopped and the risk of inducing microbial resistance, the routine administration of antibiotics is no longer recommended. According to recently published recommendations, treatment with an antibiotic should only be considered if dietary trials and administration of probiotics and anti-inflammatory drugs have been unsuccessful and only after histopathological examination of biopsies.[10]

### KEY FACTS

- Chronic diarrhea may be caused by numerous extra-GI diseases but is more often caused by primary GI diseases in dogs and cats.
- Inflammatory enteropathies (particularly food-responsive enteropathy) are the most common causes of chronic diarrhea in dogs.
- In cats, there are few studies evaluating the differential diagnoses of chronic diarrhea.
- A systematic workup including a detailed history, physical examination, complete blood count, clinical chemistry, specific laboratory parameters and tests (e.g., cobalamin, cortisol, TLI, PLI, T4), fecal parasitology, diagnostic imaging, dietary trials, and sometimes the histology/cytology of intestinal biopsies is essential for diagnosis, treatment, and prognosis.

### References

The complete list of references for this chapter can be downloaded from vetline.de:
svg.to/9842-02-03

## 2.4 Clinical evaluation of patients with chronic weight loss

Aarti Kathrani

### 2.4.1 Definition

There is no formal consensus for the definition of weight loss in veterinary medicine. However, in human medicine, it is defined as unintentional weight loss of at least 5% of the patient's usual body weight that occurs within the preceding 6–12 months, and that is not the expected consequence of treatment for a known illness.[1] The clinical disease activity indices used for canine and feline chronic enteropathy (CE) characterize weight loss of less than 5% body weight as mild, between 5–10% as moderate, and above 10% as severe.[2–4] Syndromes related to unintentional weight loss include cachexia and sarcopenia.

**Cachexia** is defined as a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass.[5] Cachexia has been described in dogs and cats with cancer, congestive heart failure, and renal disease and has been anecdotally described in dogs and cats with chronic respiratory diseases. In one study in dogs with protein-losing enteropathy (PLE) due to chronic enteropathy (CE) or lymphangiectasia (▶Chap. 7.3.8), 75% of dogs had low serum creatinine concentrations, suggesting muscle atrophy is likely prevalent in this disease.[6]

**Sarcopenia** is an age-related disease characterized by low muscle mass, muscle strength, and physical performance.[7] Although sarcopenia refers to the loss of muscle mass, it differs from cachexia, as it is a syndrome associated with aging in the absence of disease.[8] In sarcopenia, the loss of lean body mass is often accompanied by an increase in fat mass so that the total body weight may not change or may even increase. Significant loss of lean body mass was shown to occur during aging in dogs.[9]

**Malnutrition** is defined by the World Health Organization as a deficiency, excess, or imbalance in a person's intake of energy and/or nutrients. The European Society for Clinical Nutrition and Metabolism (ESPEN) states that the diagnosis of malnutrition in humans should be based on either a body mass index (BMI) of <18.5 or a combined finding of unintentional weight loss with either reduced BMI or a low fat-free mass.[10] There is currently no consensus for the definition of malnutrition in veterinary medicine.

### 2.4.2 Epidemiology

Sixty-one out of 71 dogs (88%) with PLE due to CE or lymphangiectasia had documented weight loss, with 30 dogs (43%) having severe loss (≥10%) at the time of diagnosis.[6] Interestingly, two studies examining dogs with PLE documented that body condition score (BCS) at the time of diagnosis was not associated with treatment outcome.[6,11]

Weight loss can also be significant with liver disease, particularly in cats with hepatic lipidosis, where most cats present with a history of anorexia and weight loss following a stressful event,[12] and with pancreatic disease, especially exocrine pancreatic insufficiency, where the most common clinical sign in cats was weight loss, which was reported in 91% of cats.[13]

### 2.4.3 Pathophysiology

The pathophysiology of unintentional weight loss varies depending on the underlying cause. Homeostasis of body weight is complex and involves caloric input, exercise, environmental exposures, and hormonal control. Unintentional weight loss due to cachexia involves pro-inflammatory cytokines that suppress appetite, promote the breakdown of muscle and fat, and increase energy expenditure. Cachexia is distinct from starvation and age-related loss of muscle mass. In a healthy animal deprived of sufficient calories to meet its daily energy needs, metabolic adaptations allow fat to be used as the primary energy source, thereby preserving lean body mass. However, in cachexia, various inflammatory mediators from the underlying disease decrease the ability to switch from fat utilization. Instead, amino acids continue to be used as the primary source of energy, leading to a loss of lean muscle mass.

### 2.4.4 Historical assessment

Historical assessment should include evaluating the age of the animal, social factors that may be apparent (e.g., access to food, neglect, or abuse), and a comprehensive diet history. Diet history should include all food currently offered and consumed by the animal, including treats, table foods, and any foods administered with medication. Any recent diet changes and timelines should be queried. The quality of the diet should be assessed to ensure that the animal is consuming a diet that meets the recommendations made by the WSAVA Global Nutrition Committee (https://wsava.org/wp-content/uploads/2020/01/Selecting-the-Best-Food-for-your-Pet.pdf). The daily quantity of food consumed should be calculated and compared with the calculated maintenance energy requirement (MER). However, it is important to note that a variation from this estimated requirement of up to ± 50% is not unusual in individual animals. Therefore, making comparisons with historical caloric intake that have maintained a stable body weight for that animal would allow for a more accurate comparison.

Whether the animal is fed raw food should also be ascertained, firstly, as this has been associated with nutritional hyperthyroidism and, therefore, could cause weight loss. Secondly, these diets may not be complete and balanced. Any pre-existing medical conditions should be assessed, and medication history, including deworming history, should be obtained. If the animal is receiving laxatives, levothyroxine supplementation, or medication for hyperthyroidism in cats, ensuring that any dose changes do not coincide with the onset of weight loss is important. Similarly, ensuring that weight loss did not start with the withdrawal of certain therapy, such as mirtazapine or pancreatic enzymes, is useful. Any changes that may have occurred in the environment, such as the introduction or death of an animal or family member or changes in housing, should also be ascertained.

### 2.4.5 Clinical evaluation

The degree of weight loss should be quantified as mild (less than 5% of body weight), moderate (5–10% of body weight), or severe (more than 10% of body weight); this will help to guide the extent of diagnostic investigations that should be pursued. Ascertaining whether the weight loss is associated with a decreased appetite, unchanged appetite, or increased appetite will help narrow down and prioritize the differential diagnosis list. The animal should also be assessed for additional signs such as dysphagia, regurgitation, diarrhea, vomiting, or extra-GI signs such as polyuria/polydipsia, as this will also help to guide diagnostic investigations.

### 2.4.6 Physical evaluation

A full physical examination assessing all body systems should be performed to try to ascertain the system primarily responsible for the weight loss. Hydration status should be assessed to ensure that acute changes in body weight are not the result of global fluid shifts. The oral cavity should be assessed for any dental disease that may result in anorexia and, therefore, weight loss. The oral mucosa should also be assessed for signs of anemia, icterus, or petechiae/ecchymosis. The swallowing reflex should be tested to rule out dysphagia as a cause for weight loss due to decreased caloric intake. The area of the thyroid gland should be palpated in both dogs and cats to assess for any goiter. Thorough auscultation of the heart

and lungs should be performed, together with the assessment of peripheral pulse quality, to rule out cardiopulmonary disease as the cause for weight loss. Abdominal palpation should be performed to assess for any pain, organomegaly, masses, free fluid, fluid-filled intestines, or constipation. A thorough dermatological examination should be performed to assess for any abnormalities. Rectal palpation will help to identify any changes associated with the stool, as well as allow assessment of the rectal wall and prostate. Fundic examination should be performed, and rectal temperature, peripheral lymph nodes, and joints should be assessed for any changes that might indicate systemic disease. A full neurological examination, as well as an orthopedic assessment, should be considered if the general physical examination does not yield any abnormal signs.

Body weight should be measured on a scale that is regularly calibrated, and the BCS should be assessed using a standardized scoring system. The WSAVA Global Nutrition Committee recommends the use of the 9-point scale for the assessment of BCS. Evaluating the muscle condition is important to identify cachexia. This can be performed subjectively using the 4-point scale recommended by the WSAVA Global Nutrition Committee. Muscle mass should be evaluated by visual assessment and palpation of the head, scapulae, epaxial muscles over the thoracic and lumbar vertebrae, and pelvic bones.

**NOTE**

It is important to ensure accuracy for both BCS and muscle condition. This should not just be assessed visually, but should also be assessed by palpation, especially in animals with medium or long-haired coats.

### 2.4.7 Differential diagnoses

Differential diagnoses for chronic weight loss are extremely broad, encompassing many categories of disease, such as neoplasia, gastrointestinal, pancreatic, hepatic, endocrine, infectious, cardiovascular, pulmonary, neurological, renal, dermatological, dental, musculoskeletal or medications, as well as non-disease related, such as physiological, dietary, and social (▶Tab. 2-4).

**Tab. 2-4** Causes of involuntary weight loss in dogs and cats, with specific examples

| **Non-disease related** | |
|---|---|
| **Category** | **Example(s)** |
| Physiological | Extreme exercise, decreased ambient temperature, pregnancy/lactation, growth |
| Dietary | Incomplete and unbalanced diet, inadequate amount of food offered due to inaccurate calculations, deliberate starvation due to neglect |
| Social | Increased competition from a new animal in the household |
| **Disease-related** | |
| **Category** | **Example(s)** |
| Neoplasia | Multicentric lymphoma |
| Gastrointestinal | Megaesophagus, chronic enteropathy, constipation |
| Hepatic | Cholangitis, copper-associated chronic hepatopathy |
| Pancreatic | Exocrine pancreatic insufficiency, pancreatitis |
| Endocrine | Hyperthyroidism, diabetes mellitus, hypoadrenocorticism |
| Infectious | Bacterial infection, fungal infection, endoparasites |
| Cardiovascular | Congestive heart failure |
| Pulmonary | Chronic bronchitis, pneumonia |
| Neurological | Acute polyradiculoneuritis, head trauma, cricopharyngeal achalasia or dyssynchrony |
| Renal/urinary | Chronic kidney disease, protein-losing nephropathy, ureteric obstruction in cats |
| Dental | Periodontal disease |
| Dermatological | Hepatocutaneous syndrome, exudative skin diseases |
| Musculoskeletal | Immune-mediated polyarthritis, mandibular fracture |
| Medications | Increased use of laxatives or levothyroxine, medications that can reduce appetite (e.g., omeprazole or doxycycline). |

### 2.4.8 Diagnostic investigations

Due to the extensive differential diagnosis list, an array of diagnostic tests may be needed to diagnose the underlying cause. However, this should be staged, starting with a complete blood count, biochemistry, total T4 concentration in cats ≥8 years of age, and urinalysis. If this does not reveal any abnormalities, then fecal flotation, diagnostic imaging with abdominal ultrasonography, serum cobalamin (vitamin $B_{12}$) and folate (vitamin $B_9$), baseline cortisol, and trypsin-like immunoreactivity concentrations, and a therapeutic dietary trial should be considered as the next diagnostic steps. For those cases with specific clinical signs, diagnostic investigations should be tailored depending on these signs. An algorithm for the diagnostic investigation of chronic weight loss is presented in ▶ Fig. 2-6.

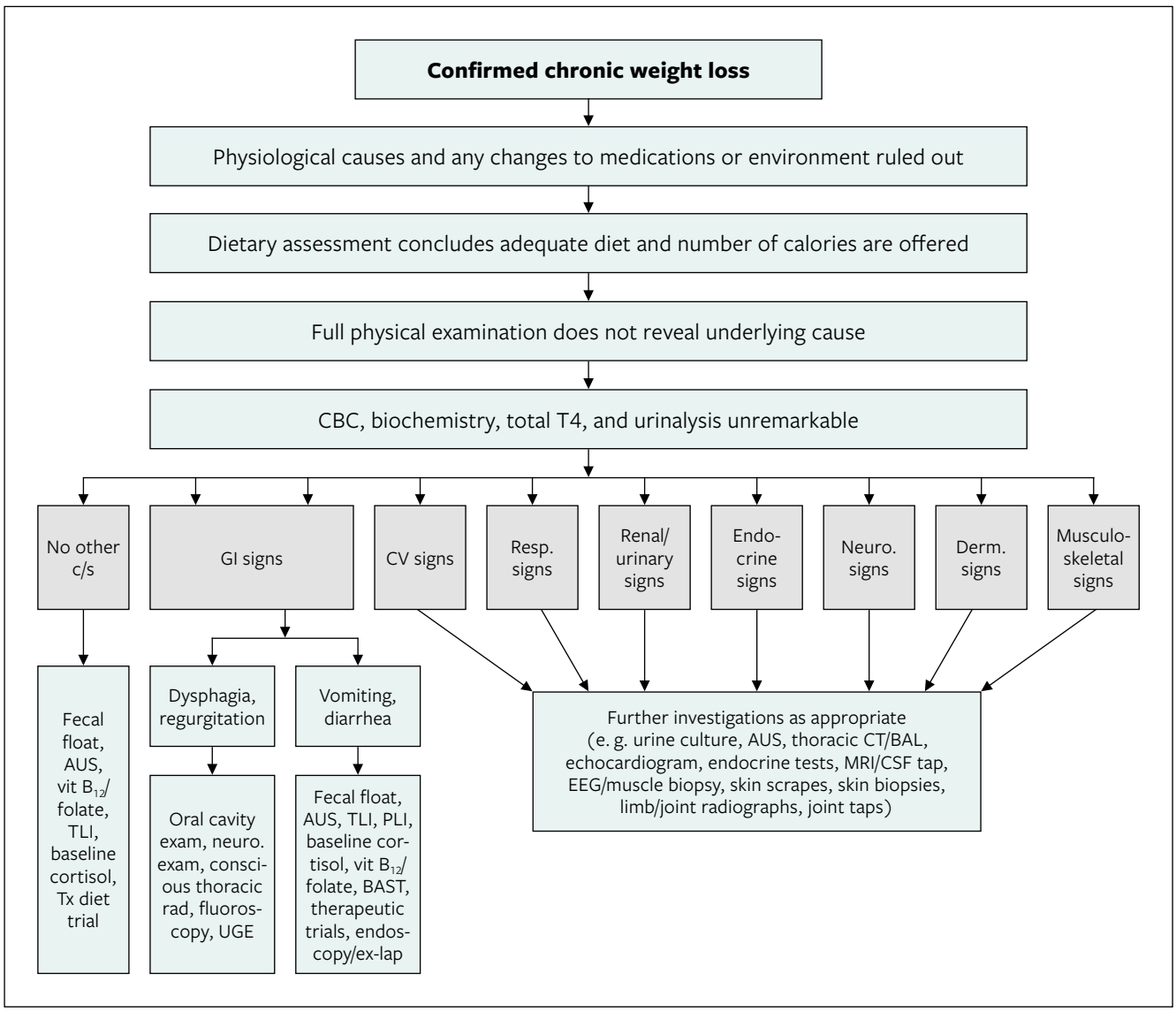



**Fig. 2-6** An algorithm for the diagnostic investigation of chronic weight loss in dogs and cats

**AUS** = abdominal ultrasound, **BAL** = bronchoalveolar lavage, **BAST** = bile acid stimulation test, **CBC** = complete blood count, **c/s** = clinical signs, **CSF** = cerebrospinal fluid, **CT** = computed tomography, **CV** = cardiovascular, **derm** = dermatological, **EEG** = electroencephalogram, **ex-lap** = exploratory laparotomy, **GI** = gastrointestinal, **MRI** = magnetic resonance imaging, **neuro** = neurological, **PLI** = pancreatic lipase immunoreactivity, **rad** = radiograph, **resp** = respiratory, **TLI** = trypsin-like immunoreactivity, **Tx** = therapeutic, **UGE** = upper (± lower) gastrointestinal endoscopy, **vit** = vitamin

### 2.4.9 Treatment

Treatment should be aimed at addressing the underlying cause of chronic weight loss. However, if treatment is likely to be prolonged or no definitive treatment is available (e.g., idiopathic megaesophagus), assisted feeding via an enteral feeding tube may be needed to ensure the animal meets its daily caloric intake to try to prevent further weight loss. Appetite stimulants such as mirtazapine may be considered prior to the placement of an enteral feeding tube, although this can have varied individual effects and may not increase voluntary intake to meet 100% of the resting energy requirement.

**KEY FACTS**

- Weight loss of less than 5% body weight is characterized as mild, between 5–10% as moderate, and above 10% as severe. Syndromes related to unintentional weight loss include cachexia and sarcopenia.
- Historical assessment should include the age of the animal, social factors, medical history, a comprehensive diet history, and an assessment of the quality and daily quantity of diet.
- A full physical examination assessing all body systems should be performed to try to ascertain the system primarily responsible for the weight loss.
- Body weight, BCS, and muscle condition should be measured with a standardized scoring system.
- Differential diagnoses for chronic weight loss are extremely broad, encompassing many categories of disease, such as neoplasia, gastrointestinal, pancreatic, hepatic, endocrine, infectious, cardiovascular, pulmonary, neurological, renal, dermatological, dental, musculoskeletal or medications, as well as non-disease related, such as physiological, dietary, and social.
- Treatment should be aimed at addressing the underlying cause of chronic weight loss. However, assisted feeding via an enteral feeding tube may be needed, and appetite stimulants may be considered.

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
svg.to/9842-02-04

## 2.5 Clinical evaluation of patients with constipation

Silke Salavati Schmitz

### 2.5.1 Definition

The normal frequency of defecation is not well defined in dogs and or cats. It is influenced by many internal (activity level, body condition, age, behavior, food intake) and external factors (stress, litter box competition), which cause inter-individual variation. However, most small animals will defecate at least once daily. **Constipation** is defined as infrequent, difficult, or painful evacuation of feces without permanent loss of function, while **obstipation** is defined as a complete inability to pass feces, often indicating permanent functional impairment. The most common clinical signs are therefore straining, tenesmus, and the production of small (often dry and hard) feces or no feces. Generalized dilation and hypomotility of the colon is termed **megacolon**.

**NOTE**

It is important to differentiate tenesmus associated with constipation from that due to colitis or lower urinary tract disease.

### 2.5.2 Pathophysiology and differential diagnoses

The main function of the **colon** (apart from immunological functions based on interactions with the microbiota) is the mixing/segmentation and propulsion of feces while retaining water and electrolytes (▶Chap. 8.2). The **rectum** serves as a short-term reservoir. Dilation of the rectal wall induces stronger tonic contraction of the inner rectal sphincter until a threshold is reached that will initiate defecation. This is consciously aided by relaxation of the outer rectal sphincter and tension of abdominal muscles.

The two main mechanisms of constipation are **decreased contractile pressure or increased resistance to the passage of feces**. Causes of increased resistance can be extramural (outside the colonic/rectal wall), mural (within the wall), or luminal, while decreased pressure is always of mural origin and can be of neuromuscular, endocrine, or metabolic origin, and can also be idiopathic (▶Tab. 2-5).

**Tab. 2-5** Causes of constipation

| Mechanism | Location/origin | Cause | Species difference |
|---|---|---|---|
| Increased resistance | Extramural | Pelvic misalignment (fracture) | Cat >> dog |
| | | Prostatic enlargement or paraprostatic cysts | Dog |
| | | Intrapelvic neoplasia | Dog > cat |
| | | Perineal hernia | Dog |
| | Mural | Benign solitary mass (e.g., polyp) | Dog >> cat |
| | | Malignant solitary mass (e.g., adenocarcinoma) | Dog = cat |
| | | Diffuse neoplasm (e.g., lymphoma) | Dog = cat |
| | | Stricture (trauma, inflammatory, neoplastic, idiopathic) | Dog > cat |
| | Luminal | Foreign body or material (e.g., bony meal) | Dog >> cat |
| Decreased pressure | Neuromuscular | Idiopathic megacolon<br>Hypo- or aganglionosis (Hirschsprung's disease) | Cat >> dog<br>Dog = cat |
| | | Lower motor neuron/spinal cord disease L4-S2:<br>• Cauda equina, intervertebral disc herniation<br>• Sacral spinal cord deformity<br>• Neoplasm | <br>• Dog >> cat<br>• Cat (Manx)<br>• Dog >> cat |
| | | Dysautonomia (Key-Gaskell syndrome) | Cat >> dog |
| | | Colic ganglioneuritis | Dog = cat |
| | Endocrine | • Hypothyroidism<br>• (post-treatment for hyperthyroidism) | • Dog<br>• Cat |
| | Metabolic | Electrolyte abnormalities (e.g., hypercalcemia, hypokalemia) | Dog = cat |

There are several **systemic or external causes** of constipation, like obesity, lack of physical activity (e.g., being hospitalized), a change in diet, or administration of drugs that reduce colonic motility (e.g., anticholinergics, opioids) or absorb fecal water (e.g., aluminum hydroxide, sucralfate, barium sulfate). Both general and local **pain** (e.g., bite wounds, anal gland inflammation, perineal hernia) can also cause a reduction in defecation frequency (avoidance behavior).

## 2.5.3 Diagnostic approach

### 2.5.3.1 Signalment, history, and physical examination

**Signalment** can help to pinpoint more likely differential diagnoses: In neonates, congenital abnormalities like hypo-/aganglionosis (Hirschsprung's disease) or *atresia ani* must be considered, while elderly animals are more likely to have neoplasia. In uncastrated male dogs, prostatic disease can lead to constipation. Breed-specific conditions include perianal fistulas in German shepherd dogs (▶Chap. 8.4.3), inflammatory colorectal polyps in miniature dachshunds,[1] intervertebral disc disease in chondrodystrophic dog breeds, and sacral malformations in Manx cats.

Specifics of the **patient history** should be aimed at establishing if a cause is likely local to the rectoanal or perineal area or if more extensive, neurological, or systemic illness is present. The duration of signs and any possible inciting causes (known traumatic events), any drug history, of changes in food or habitats (competition or limited access to litter trays) are important. Some animals can be erroneously presented to the veterinarian for diarrhea (▶Chap. 2.3) or fecal incontinence (▶Chap. 8.3) when only liquid fecal content can be evacuated.

The most important parts of the **physical examination** are abdominal palpation (to assess the severity of constipation/diameter of the colon), an inspection of the perineal region, and neurological and rectal examinations.

**CLINICAL PEARLS**

Physical examination is helpful in diagnosing **dysautonomia (Key-Gaskell syndrome)** (▶ Fig. 2-7). This condition is rare, but in endemic regions (Midwestern United States and the United Kingdom) patients (cats are more commonly affected than dogs) present with multiorgan involvement.

Findings include unresponsive mydriasis, ptosis, and third eyelid protrusion, dry rhinarium, reduced tear production (Schirmer tear test <5 mm/min), dry mucous membranes, bladder atony or overflow incontinence, and hypomotility of the gastrointestinal tract resulting in megaesophagus, small intestinal ileus, and megacolon (▶ Fig. 2-7).[2] 0.05% pilocarpine eye drops will induce miosis and retraction of third eyelids in an affected animal but have no effect in healthy animals. Prognosis is poor, and not many animals recover despite supportive treatment.

### 2.5.3.2 Laboratory testing and diagnostic imaging

The diagnostic approach to patients with constipation will vary depending on the findings from signalment, history and physical examination. Performing a **minimum database** (hematology, serum biochemistry, urinalysis) to detect systemic effects of illness (dehydration), comorbidities, and any metabolic causes (hypokalemia, hypercalcemia) is warranted.

**Diagnostic imaging** is nearly always indicated. Abdominal radiographs allow assessment of intraabdominal and intrapelvic structures, the severity of constipation, and colorectal content. Abdominal ultrasound allows further characterization of abnormalities (e.g., prostatic enlargement) and detection of intramural intestinal changes.

**Fine-needle aspiration (FNA)** of abnormal structures can be performed simultaneously. Advanced imaging procedures (CT, MRI) are appropriate to further characterize complex intrapelvic abnormalities or detect intervertebral or musculoskeletal disease.

**NOTE**

- Abdominal radiographs must be performed with two orthogonal views. Care should be taken to include the entire caudal abdomen and the pelvis.
- If initial radiographic findings are unclear and additional diagnostic imaging modalities are not available, repeat radiographs after instillation of negative or positive contrast per rectum can be informative.

### 2.5.3.3 Tissue biopsy

**Biopsy** of intra-abdominal or intrapelvic structures should be considered if the cytologic examination of FNAs is non-diagnostic. For mural changes (strictures, masses), **colonoscopy** is the method of choice as it allows assessment of the extent of disease, less invasive biopsy, and potentially treatment (dilation of stricture, removal or debulking of masses) simultaneously. Full-thickness colonic biopsies are not often performed due to the risk of postoperative complications, but to the author's knowledge, there are no studies investigating complication rates of large intestinal full-thickness biopsies only. Often, pathology in the intestinal muscle layers (e.g., due to feline idiopathic megacolon; FIM) or the enteric nervous system (e.g., hypo- or aganglionic megacolon, colic ganglioneuritis) is only diagnosed after colectomy or on postmortem examination.

**Feline idiopathic megacolon (FIM)** (▶ Chap. 8.3.6) is a diagnosis of exclusion. Radiographic abnormalities may begin in the descending colon and progress over time to involve also the ascending and transverse parts. The radiographic ratio of maximal diameter of the colon to L5 length can help in differentiating constipation from true megacolon: A ratio <1.28 is consistent with a normal colon, while a value of >1.48 is a good indicator of megacolon (sensitivity 77%, specificity 85%).[4]

## 2.5.4 Treatment and management

Treatment of constipation is guided by the underlying cause. Alleviating constipation or treating obstipation is warranted in addition in most cases. Specific therapeutic plans depend on the severity of constipation. Long-term management of idiopathic constipation or FIM with a combination of dietary

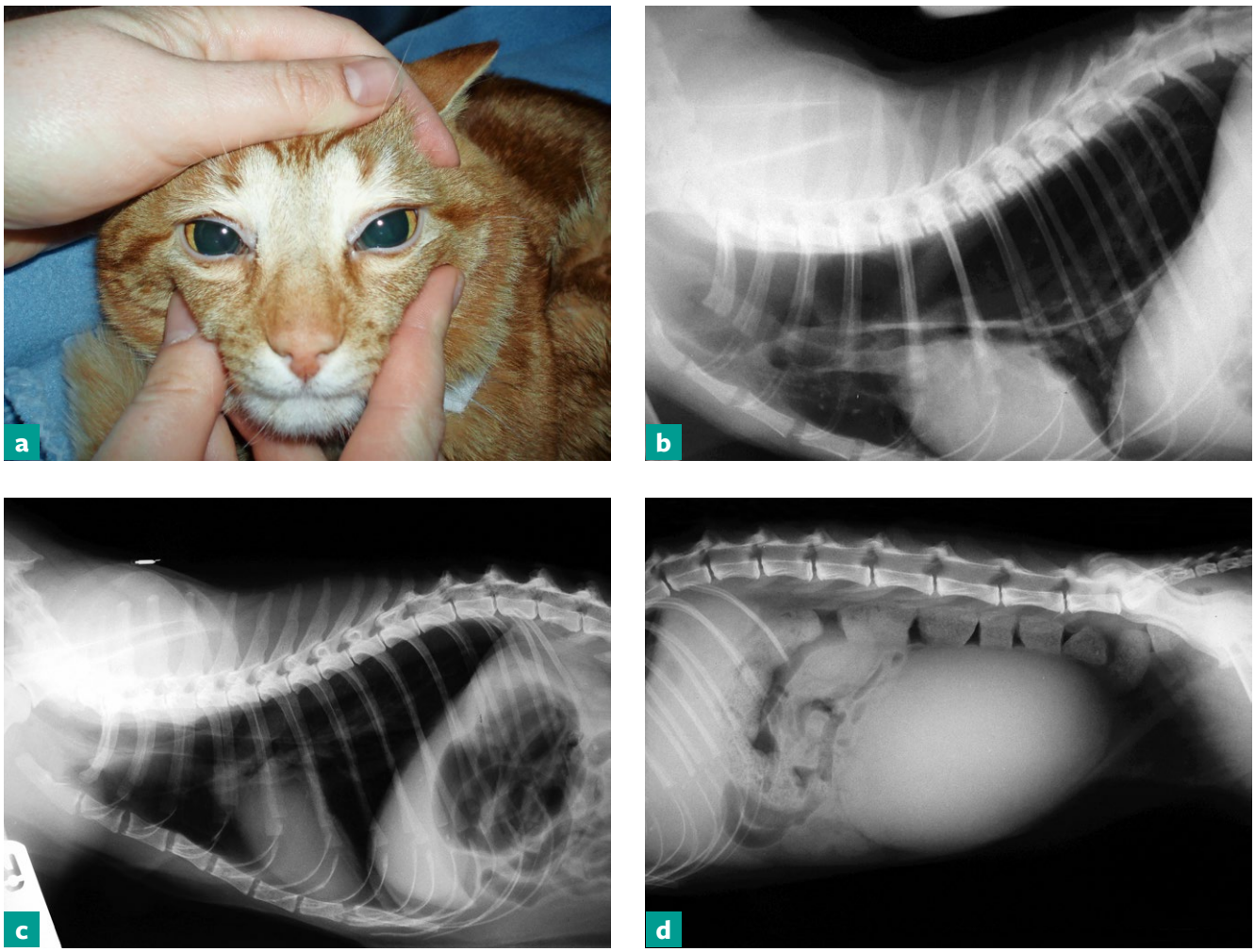



**Fig. 2-7** Features of feline dysautonomia (Key-Gaskell syndrome)
Mydriasis and dry eye (**a**), megaesophagus (**b**), dilatation of the stomach and small intestine (**c**), constipation and bladder atony (**d**)
(Courtesy of Prof. Danielle Gunn-Moore, University of Edinburgh, UK.)

modification, chronic use of laxatives, and prokinetics is appropriate.

### 2.5.4.1 Suppositories and enemas

**Single or first episodes** of constipation are often transient and may resolve without the need for any intervention. A single suppository or increasing the fiber content of the diet can be considered.

**Mild to moderate** recurrent constipation can mostly be managed on an outpatient basis. Treatment includes rehydration, suppositories, or enemas alone or in conjunction with oral laxatives. Enemas typically consist of warm tap water or isotonic saline (5–10 ml/kg) and can be mixed with lubricants (e.g., glycerin or mineral oil) as needed.

**Severe cases** usually require brief periods of hospitalization to correct fluid deficits, metabolic abnormalities, and treatment with suppositories, enemas, or oral laxatives. Before manual extraction of impacted feces is necessary, attempts with oral administration of larger volumes of laxatives (e.g., polyethylene glycol) should be made (▶Chap. 2.5.4.2), as they are less invasive and do not require general anesthesia.

Cases unresponsive to these measures may require manual softening and removal of impacted feces. Animals should be adequately hydrated. It may be advisable to reduce the fecal mass over a period of several days to reduce the risks of prolonged general anesthesia or damage to the colon.

- The use of **phosphate-containing** suppositories or enemas is **absolutely contraindicated** in cats. They induce potentially lethal hypernatremia, hyperphosphatemia, and hypocalcemia!
- Enemas in cats should always be performed under general anesthesia with an endotracheal tube in place, as due to their relatively short bowel, they are at a higher risk of aspiration of stomach contents (backflow from rectally administered liquids).
- Manual extraction of even severely impacted feces can be avoided in most cats by administering polyethylene glycol via nasogastric tube (6–10 ml/kg/h) over 6–18 hours. Most cats will defecate within 8–10 hours.

### 2.5.4.2 Laxatives

A plethora of laxatives with different mechanisms of action is available over the counter (▶Tab. 2-6). Unfortunately, not a lot of data relating to their efficacy or comparability in small animals is available, even though some toxicity studies exist. Products designed for people should be scrutinized for any toxic ingredients (e.g., xylitol).

Most **bulk-forming laxatives** are dietary fiber (DF) supplements, defined as carbohydrate polymers with >10 monomeric units that cannot be hydrolyzed by endogenous digestive enzymes.[5] However, there is no recommendation available about which DF (naturally occurring in food as consumed, or extracted from raw or synthetic materials) is most appropriate in constipation. General beneficial effects include increased fecal water content and stimulation of intestinal transit via their prebiotic effect.[6,7] Fiber-supplemented diets are available commercially. The most commonly used DF supplements are psyllium husk (1–4 teaspoon per meal), wheat bran (1–2 tablespoon per meal), or canned pumpkin (1–4 tablespoon per meal), but other sources are available (citrus/apple/carrot pomace, pea, peanut, soy, chicory fiber, beet pulp, kiwi extract). None of them can be particularly recommended over the other due to the lack of evidence. A commercially available psyllium-enriched dry diet was found to soften feces and significantly decrease the requirement for lactulose and cisapride in constipated cats.[8]

**Emollient laxatives** are anionic detergents that impair water absorption from the intestine. The clinical efficacy of these compounds has not been established in small animals. For example, dioctyl sodium sulfosuccinate inhibits water absorption in isolated colonic segments in vitro, but a dose of 30 mg/kg/day had no effect on fecal consistency in dogs.[9]

**Lubricant laxatives** like mineral oil or white petrolatum are generally only efficient in mild cases of constipation.

**Tab. 2-6** Types of laxatives and their mechanism of action

| Type | Action | Example agents | Comment |
|---|---|---|---|
| Bulk-forming (dietary fiber) | • Increased bulk when taken with water<br>• Modification of production of postbiotics | • Psyllium (husk)<br>• Methylcellulose | In people: not recommended for opioid-induced constipation |
| Stool softeners (emollient) | Increased fecal water content | • Dioctyol sodium sulfosuccinate (docusate sodium)<br>• Dioctyol calcium sulfosuccinate (docusate calcium) | • Should not be used in combination with another laxative.<br>• Efficacy questionable in small animals |
| Osmotic | Hypertonic increase in fecal water content | • Lactulose<br>• Polyethylene glycol, magnesium citrate, sulfate, or hydroxide (milk of magnesia) | – |
| Stimulating (prokinetic) | Increase peristalsis | • Bisacodyl<br>• Phenolphthalein<br>• Castor oil<br>• Cascara sagrada<br>• Senna | • In people: recommended for opioid-induced constipation<br>• Daily administration should be avoided |

They should be restricted to rectal administration/use in enemas because of the risk of aspiration pneumonia with oral administration, especially in unwell cats.

**Osmotic laxatives** consist of poorly absorbed polysaccharides, magnesium salts (not recommended), and polyethylene glycol. Lactulose can be very effective at producing soft feces (0.5 ml/kg q8–12 h PO). However, both decreases in dose due to excessive flatulence and/or diarrhea and increases due to subjective development of "tolerance" are occasionally required. Particularly in cats with chronic idiopathic constipation or FIM, long-term use of polyethylene glycol is safe[10] and can work better than lactulose. Polyethylene glycol products without sodium sulfate have better oral acceptance (due to a less bitter taste). The administration of polyethylene glycol as a constant rate infusion via a nasogastric tube has been reported to be an effective treatment for hospitalized severely constipated cats.

**Stimulating laxatives** are a diverse group of agents with mild prokinetic and pro-secretory actions. Bisacodyl, for example, can be effective at a dose of 5 mg/cat q24 h PO in small animals, but daily use should be avoided due to the potential for injuring myenteric neurons.[11]

#### 2.5.4.3 Probiotics

Based on a small pilot study in ten cats with poorly defined chronic constipation or FIM,[12] there is potential for management of constipation with probiotics. An improvement in clinical signs was noted, but no control group was included.

#### 2.5.4.4 Prokinetic drugs

Many drugs with a supposed prokinetic action on the colon have a limited clinical effect in small animals. **5-HT$_4$ serotonergic agonists** are most used, particularly cisapride (where available), as it stimulates feline colonic smooth muscle in vitro.[13] However, it has not been conclusively shown to improve colonic motility in vivo.

#### 2.5.4.5 Colectomy

Subtotal colectomy is the last resort in cats with FIM (▶Chap. 8.3.6.6) unresponsive to medical management, and several different techniques have been described in surgical texts. In the first few months after surgery, the patient often has soft stool or diarrhea. The fecal consistency usually gradually improves but may never be normal again.

### 2.5.5 Prognosis

The overall prognosis of constipation depends on the likelihood of successful treatment of any underlying condition. Idiopathic constipation or FIM is likely to progress over time. Early use of colonic prokinetics (in addition to one or more laxatives) may prevent the development of obstipation and delay colonic dilation. Cases of FIM requiring colectomy have had a generally favorable prognosis for recovery, although in some cases, mild to moderate diarrhea may persist for weeks to months postoperatively.

**KEY FACTS**

- Physical examination of a patient with constipation should always include rectal palpation and full neurological assessment, especially of the hind limbs.
- Check animals presented for constipation for systemic signs (mydriasis, ptosis, dry mucous membranes, bladder atony, general ileus) in case they suffer from dysautonomia.
- The two main mechanisms for constipation are decreased contractile pressure or increased resistance within the colonic/pelvic area.
- Abdominal radiographs ± rectally instilled contrast (negative contrast can be more helpful than positive contrast) are very useful initial diagnostic tools.
- In cats with (idiopathic) constipation, "trickle" administration of polyethylene glycol containing laxatives via a temporary nasogastric tube is nearly always successful in relieving constipation and frequently circumvents the need for manual fecal extraction.

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
svg.to/9842-02-05

## 2.6 Clinical evaluation of patients with jaundice/icterus

Micah A. Bishop

### 2.6.1 Introduction and definitions

The presence of jaundice or icterus indicates that a patient has either an excess production of bilirubin relative to excretion by the liver or there is red cell destruction causing excess bilirubin formation. The mechanisms and physiology of hemoglobin metabolism and bilirubin excretion are reviewed elsewhere and in (▶Chap. 9.2).[1–3] Clinically, the terms pre-hepatic, hepatic, and post-hepatic are further used to specify where the pathology is present in a patient with a high serum total bilirubin concentration. However, these individual processes are not mutually exclusive.[3]

**Potential causes of icterus in dogs and cats**

**Pre-hepatic**

- Immune-mediated hematolytic anemia (primary or secondary)
- Heinz body anemia due to toxins/drugs (e.g., acetaminophen, zinc, onions) or feline hepatic lipidosis
- Hypophosphatemia (cats)
- Infectious (e.g., *Babesia* spp, *Mycoplasma* spp, *Cytauxzoon felis*)

**Hepatic**

- Neoplasia (primary hepatic or metastatic)
- Toxins (e.g., *Amanita* spp., Cycads [Sago Palm], aflatoxin, *Cyanobacteria* spp.)
- Drugs (e.g., acetaminophen, azole drugs, trimethoprim sulfonamides, lomustine, phenobarbital, NSAIDs, azathioprine, methimazole)
- Infectious (e.g., feline infectious peritonitis, canine adenovirus-1, *Leptospira* spp, *Salmonella* spp., histoplasmosis, neutrophilic cholangitis)
- Inflammatory (e.g., canine copper-associated chronic hepatitis, canine idiopathic/immune-mediated chronic hepatitis, feline lymphocytic cholangitis)

**Post-hepatic**

- Pancreatitis
- Gall bladder mucocele (dogs)
- Neoplasia (hepatobiliary, pancreatic, or small intestinal)
- Duodenal foreign body
- Choleliths/choledocholiths
- Biliary rupture

**Pre-hepatic** causes of hyperbilirubinemia occur secondary to red cell destruction or hemolysis and thus overproduction of bilirubin. Common causes include immune-mediated hemolytic anemia (primary or secondary), infectious etiologies in some locales (e.g., *Babesia* spp., *Mycoplasma* spp., *Cytauxzoon felis*), red cell oxidative injury (e.g., due to zinc, acetaminophen), splenic masses (due to red blood cell fragmentation), and hypophosphatemia (e.g., due to insulin therapy), and incompatible blood product transfusions.[3]

**Hepatic** hyperbilirubinemia causes cholestasis and impaired bile flow, and as a result, both forms of bilirubin (unconjugated and conjugated) are released into the bloodstream. This is most commonly associated with disorders that cause hepatic necrosis or dysfunction.[3] Examples include canine copper-associated chronic hepatitis, canine idiopathic/immune-mediated hepatitis, feline hepatic lipidosis, cholangitis/cholangiohepatitis, hepatotoxins, and drug reaction/injury. A less common cause is a condition called the bystander phenomenon or cholestasis of sepsis.[4] In this situation, endotoxemia or inflammatory mediators are thought to alter bilirubin metabolism.[4] Another clinical scenario is the cat with weight loss that has a mildly elevated serum total bilirubin concentration but otherwise normal lab indices; it is not uncommon to find an intestinal mass present in these cats.

**Post-hepatic** hyperbilirubinemia is a bilirubin excretion problem where extrahepatic pathology obstructs (fully or partially) bile flow.[3] Common causes include an obstructive gallbladder mucocele, pancreatitis, duodenal mass, foreign body, choleliths/choledocholiths, flukes, and neoplasia (hepatobiliary, pancreatic, or small intestinal).

### 2.6.2 Historical assessment and signalment

A through history is essential for narrowing down potential differentials, especially when client financial resources are limited. Questions should be focused on determining if there is a history of prior hepatobiliary and pancreatic disease, as well as attempting to get a timeline regarding the presence and progression of systemic clinical signs. The signalment will also help narrow and focus further diagnostic evaluation. For example, older cats are more likely to have hepatic lymphoma, while younger cats are more prone to neutrophilic cholangitis, and obese cats are prone to hepatic lipidosis.[5] Some breeds of dogs are predisposed to disorders that can cause jaundice. For example, Shetland sheepdogs are especially prone to gallbladder mucoceles.[6] Labrador retrievers and other large breed dogs have a higher likelihood of having copper-associated hepatopathy than smaller breed dogs.[7]

Cocker spaniels are prone to immune-mediated hemolytic anemia, while American bull terriers are prone to *Babesia* spp. infections.[4]

**Key clinical features in dogs and cats with jaundice**

- Pattern, magnitude, and duration of previously documented liver enzyme activity increases
- Presence of weakness or collapse
- Behavioral changes
- Presence and duration of hyporexia or anorexia
- Exposure to hepatotoxins (acetaminophen, sago or other cycad palm, alliums, naphthalene, xylitol, *Amanita* mushrooms, algae)
- Comprehensive current medication list, particularly NSAIDs, phenobarbital, cannabidiol, doxycycline, insulin therapy, herbal remedies, and nutritional supplements
- History of pancreatic or gallbladder disease
- Infectious disease exposure (ticks, fleas)
- Changes in the consistency and color of feces

### 2.6.3 Physical assessment

Physical examination parameters that may be altered in cases of jaundice should be noted as these may help narrow the range of possible etiologies. The presence of yellowing of the gums, sclera, ears, and abdomen are the typical findings in a jaundiced animal.



**NOTE**

Jaundice may be subtle, especially in animals with yellow, brown, or orange fur.

However, the complete absence of obvious jaundice in a pet with a high total bilirubin concentration should warrant close scrutiny of the blood collection process as the presence of ex vivo hemolysis may falsely elevate the serum total bilirubin concentration (often secondary to multiple attempts at venipuncture). Artifacts should also be suspected if the other liver values are normal, in addition to the lack of clinical jaundice. Other pertinent abnormalities that may be discovered on physical examination could include a distended abdomen (due to ascites), hepatomegaly, enlarged peripheral lymph nodes, a new heart murmur, tachycardia, tachypnea, abdominal pain, altered mentation, or splenomegaly.

### 2.6.4 Diagnostic approach

Along with the patient history, signalment, and physical examination findings, a simple complete blood count and comprehensive serum biochemistry panel will not only confirm hyperbilirubinemia and, in most cases, narrow the differential list but may even provide a diagnosis.

The **complete blood count** will identify pre-hepatic hyperbilirubinemia cases by documenting the presence of a low hematocrit (<20% usually), RBC count, and packed cell volume. Evaluation of the reticulocyte count, saline agglutination test, and red cell morphology will alert the clinician to most cases of immune-mediated hemolytic anemia. Regenerative and hemolytic anemias without evidence of blood loss, autoagglutination, or spherocytes, would prompt the clinician to perform testing for hemotrophic organisms (*Babesia* spp., *Mycoplasma* spp.) appropriate for the species/breed. Blood smear evaluation is crucial in all cases of anemia to look for red cell abnormalities, evidence of oxidative damage, and infectious organisms. In general, most cases of hepatic or post-hepatic hyperbilirubinemia will have a normal hematocrit or low-grade non-regenerative anemia. Unexplained hemolysis may also prompt an abdominal radiograph series to look for causes of zinc toxicity (e.g., from ingestion of older United States pennies). The presence of visible hemolysis in a blood sample should also be noted in a patient with a normal hematocrit and a mild increase in serum total bilirubin concentration, as this could be an artifact.

The **chemistry panel** will confirm the presence of hyperbilirubinemia, which will generally correlate with the intensity of clinical jaundice, although different skin pigments/breeds can be difficult to evaluate. Most cases of increased total bilirubin also have elevations in the various liver enzymes. The pattern, magnitude, and duration (if known) of elevations may help narrow the list of differential diagnoses. Cats with hepatic lipidosis often have alkaline phosphatase (ALP) activity increases with a normal/mildly increased gamma-glutamyl transferase (GGT) activity, while cats with hepatic lymphoma or neutrophilic/lymphocytic cholangitis may have both increased alanine aminotransferase (ALT) and GGT activities. Most dogs with chronic inflammatory hepatopathies have increases in ALT and ALP (with ALT activities increases often being relatively greater), and dogs with gallbladder mucoceles often have a spike in ALT and total bilirubin just prior to gall bladder rupture.[4] The reader is recommended to review laboratory testing for liver and biliary disease in ▶Chap. 1.3.3.

In regard to the patient with increased total bilirubin, other chemistry values that are often helpful include the **functional liver markers** (albumin, cholesterol, and blood

urea nitrogen). Cholesterol is often increased in animals with extrahepatic bile duct obstruction, and in general, the total bilirubin concentrations will be much higher in these animals than in patients with hepatitis, copper-associated hepatopathy, or cirrhosis, although this is not always the case.[4] The presence of low albumin, cholesterol, and blood urea nitrogen concentrations is concerning for functional liver failure, particularly if the pet is exhibiting any signs of hepatic encephalopathy. Overall, the chemistry panel may help the clinician narrow down the list of differential diagnoses and will help to dictate further diagnostic steps. There is no benefit in measuring serum bile acids in the icteric patient unless there is some suspicion that the pet has both a hemolytic and primary hepatic disorder, as in this situation, their measurement seldom provides new information for the clinician.[4]

**NOTE**

**Bilirubin** is excreted in both the feces and the urine. Small amounts of bilirubin may be present in the urine of normal dogs, especially males. However, bilirubinuria is always abnormal in cats. Hemoglobinuria is observed in animals with intravascular hemolysis. In general, there is little value in the evaluation of urobilinogen in the urine or stercobilinogen in the feces, as many factors may cause false-positive results.[3,4]

Once pre-hepatic hyperbilirubinemia has been ruled out by the complete blood count, the next diagnostic step is usually an abdominal radiograph series or abdominal ultrasound, which has become increasingly more common. Radiographs may alert the clinician to the presence of hepato-splenomegaly or the presence of a mass in the liver and, probably, more importantly, to rule out concurrent conditions. However, other than finding the presence of a zinc source or mass, radiographs usually will not allow the distinction between hepatic and post-hepatic hyperbilirubinemia.

**Abdominal ultrasound** is an excellent, non-invasive method to further evaluate the patient with jaundice.[3] The appearance of the liver itself, gallbladder, bile ducts, pancreas, and the rest of the abdomen will help the clinician distinguish between hepatic and post-hepatic causes of hyperbilirubinemia and often allow a diagnosis to be made. The main value in these cases is finding the presence of post-hepatic lesions, such as an obstructive gallbladder mucocele, extrahepatic bile duct obstruction due to pancreatitis (common in dogs), or obstruction due to masses near the duodenal papilla (common in cats). This is important as it directs the clinician to recommend surgical intervention or direct therapy aimed towards relieving the obstruction (i.e., treating pancreatitis or administering ursodiol therapy). Choleliths/choledocholiths may also be seen, but it should be noted that many are non-obstructive, and the sonographer should look for evidence of obstruction (i.e., a dilated gall bladder or bile duct dilation proximal to a stone). Additionally, the detection of a large hepatic mass would also be invaluable as it allows the clinician to obtain a fine-needle aspirate for cytologic examination and possible diagnosis. It should be noted that hepatocellular carcinoma is difficult to diagnose cytologically as many are quite well-differentiated and appear similar to hepatic adenoma on cytology. An enlarged, hypoechoic, and nodular liver, splenomegaly, and/or enlarged lymph nodes on ultrasound would also guide the clinician to aspirate these organs for the evaluation of round cell neoplasia. In cats, visualization of the liver and gall bladder and ultrasound-guided fine-needle aspiration (of both) may help diagnose hepatic lipidosis, lymphoma, neutrophilic cholangitis (along with the cytological examination and bacterial culture of bile), or other conditions.

Ultimately, if the cause of hyperbilirubinemia appears to be primarily hepatic in origin (pre-hepatic causes ruled out and no evidence of post-hepatic disease), then **liver biopsy** will provide the gold standard for diagnosis. Laparoscopic or surgical biopsies are generally recommended over percutaneous needle or Tru-cut biopsies as the samples collected are more representative. Histopathologic evaluation is needed for the diagnosis of inflammatory diseases, such as copper-associated hepatopathy, idiopathic chronic hepatitis, cholangiohepatitis, cholangitis, lipidosis, and other conditions.[2,3]

**KEY FACTS**

- Patient history, signalment, and physical examination are valuable tools to narrow down the differential diagnoses list of patients with jaundice.
- A complete blood count and blood smear examination will identify the presence of pre-hepatic hyperbilirubinemia.
- Abdominal ultrasound is an essential diagnostic tool for differentiating hepatic from post-hepatic hyperbilirubinemia.
- Artifact due to ex vivo sample hemolysis is a common reason for an increased total bilirubin concentration.

## References

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# II Clinical nutrition

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# 3 Nutritional management of gastrointestinal diseases

## 3.1 Nutritional principles

Aarti Kathrani

This chapter focuses on the nutritional principles in the management of gastrointestinal diseases in dogs and cats and encompasses three main areas:

1. Assessment of the nutritional status of the patient, which is essential as these patients are at risk of malnutrition that can worsen the prognosis.
2. Assessment of the current diet, feeding management, and environment as these can act as triggers or exacerbate gastrointestinal signs.
3. Reassessment and monitoring to ensure compliance and evaluation of responses for the selected dietary strategy(s) of each gastrointestinal disease and to determine if any feeding plan adjustments are needed.

### 3.1.1 Assessment of nutritional status

#### 3.1.1.1 Malnutrition

The World Health Organization (WHO) refers to malnutrition as a deficiency, an excess or imbalance in a person's energy or nutrient intake. Factors such as severity and duration of disease, impaired digestion and absorption, and an incomplete or unbalanced diet are all risk factors for malnutrition in gastrointestinal disease in dogs and cats. In people, malnutrition has many detrimental effects and has been associated with the deterioration of muscle, respiratory and immune function, as well as delayed wound healing and recovery from illness. Further studies are needed to assess the impact of malnutrition in canine and feline gastrointestinal diseases and the impact of early nutritional support on clinical outcomes in these cases.

#### 3.1.1.2 Body weight

Body weight should be measured on a scale that is regularly calibrated. Assessing body weight, as well as trends, is not only important for nutritional assessment but may also provide prognostic information. Weight loss should be quantified as mild (<5% of body weight loss), moderate (5-10% of body weight loss), or severe (>10% body weight loss) in helping to determine the severity of undernutrition. One study showed 61 out of 71 dogs (88%) with protein-losing enteropathy (PLE; ▶Chap. 7.3.8) due to chronic enteropathy (CE) or lymphangiectasia had documented weight loss at the time of diagnosis, with 30 dogs (43%) having severe weight loss (≥10% of body weight).[1]

#### 3.1.1.3 Physical examination

Specific assessment of the animal's stature, body condition, musculature, hair coat, footpads, ocular, cardiovascular, neurologic and skeletal systems are important for assessing the overall nutritional health of the animal. In addition, dental examinations should be performed to assess for disease.

Assessment for poor wound healing is important, as this may indicate inadequate nutritional intake. Also, assessment for petechia, ecchymosis, bruising, or bleeding on physical examination, which may be evidence of a coagulopathy, is important, as this could be a contraindication to the placement of an enteral feeding tube. Additionally, ensuring adequate mentation and the presence of a gag reflex is essential if enteral assisted feeding is to be considered.

#### 3.1.1.4 Body condition score

Body condition score (BCS) is a measure of peripheral body fat and has good correlation with dual-energy X-ray absorptiometry. BCS assessments should be performed using a standardized scoring system. The World Small Animal Veterinary Association (WSAVA) Global Nutrition Committee recommends the use of the 9-point scale to assess BCS, which is based on the characterization of body silhouette and palpation of body fat. Using the 9-point BCS scale, each unit increase in BCS above an ideal of 4–5/9 for a dog and 5/9 for a cat is approximately equivalent to 10–15% over the ideal body weight. The owner should be taught how to assess BCS so this can be performed regularly at home.


Ideal BCS: 5/9

Body condition score is one of the measures used to assess nutritional status in dogs and cats. The prevalence of decreased BCS in canine PLE due to CE or lymphangiectasia was 47 out of 71 dogs (66%), with six out of 71 dogs (8%) being over-conditioned.[1] However, two studies documented that BCS at the time of diagnosis was not associated with treatment outcomes in dogs diagnosed with PLE.[1,2]


Ideal BCS: 4–5/9

However, BCS indicates peripheral fat status only and does not take into account intra-abdominal fat, muscle condition, or bone density, all of which could be affected by malnutrition and are likely important in the assessment of BCS.

#### 3.1.1.5 Muscle condition

Although the prevalence of reduced muscle condition has not been reported in dogs and cats with gastrointestinal disease specifically, one study showed that 75% of dogs with PLE due to CE or lymphangiectasia had serum creatinine concentrations below the reference range at diagnosis, which suggests that muscle atrophy is likely prevalent in this disease.[1] Low lean body mass is common in human patients with inflammatory bowel disease (IBD) and can predict osteopenia.[3] Also, the muscle condition around the third lumbar vertebra is prognostic for intestinal resection in human patients with Crohn's disease, a type of IBD.[4]

Unfortunately, no current information is available regarding the impact of muscle condition scoring on treatment, outcome, and prognosis in dogs and cats with gastrointestinal disease.

Unlike BCS assessments, there is currently no standardized scoring system for muscle mass in dogs and cats. Assessment of muscle condition can be performed subjectively by using the 4-point scale recommended by the WSAVA Global Nutrition Committee or by assessing the muscle mass as adequate or mild, moderate, or severe loss together with the location and symmetrical distribution of this loss. Muscle mass should be evaluated both by visual assessment and palpation of the head, scapulae, epaxial muscles over the thoracic and lumbar vertebrae and pelvic bones. It is important to note, that to ensure accuracy for both BCS and muscle condition, muscle mass should be assessed not just visually but also by palpation, especially in dogs and cats with medium or longhair coats.

#### 3.1.1.6 Clinicopathologic testing

Unfortunately, there are currently no laboratory tests available to definitively determine the nutritional status of dogs or cats. However, the presence of single micronutrient deficiencies, such as with cobalamin or folate, can help to define malnutrition.[5] Serum albumin was also found to be one of the most predictive parameters of malnutrition in human IBD patients with active disease.[6] However, these variables can also be influenced by other factors, such as loss or reduced uptake via the gastrointestinal tract or severity of gastrointestinal inflammation. Nevertheless, a minimum database consisting of a complete blood count, serum biochemistry, urinalysis, and serum cobalamin and folate in dogs and cats with chronic gastrointestinal signs will help to provide a gross overview of the nutritional status of the patient.

### 3.1.2 Assessment of diets, feeding plans, and environmental influences

#### 3.1.2.1 Diet history

A complete and thorough diet history will help to determine if the animal is consuming sufficient energy and nutrients, as well as the need for dietary interventions. The diet history should encompass all foods that the animal is eating, including all commercial pet foods, commercial treats, human foods, dietary supplements, foods used to administer medications and flavored medications, with specifications by the manufacturer, brand, dry or canned formula, and flavor where applicable. The ability to scavenge and hunt and have access to additional foods indoor or outdoor should also be included. A thorough assessment of the diet consumed just prior to or at the onset of gastrointestinal signs may help to determine if there could be a dietary trigger for the signs.

The Association of American Feed Control Officials (AAFCO) nutritional adequacy statement on the pet food label should be assessed to ensure the diet is complete and balanced. In addition, the diet should meet the recommendations outlined by the WSAVA Global Nutrition Committee (https://wsava.org/wp-content/uploads/2020/01/Selecting-the-Best-Food-for-your-Pet.pdf). This requires contacting the pet food manufacturer directly to ask a series of eight questions. The answers to these eight questions will help to determine the credentials of the person formulating the diet, whether the diet meets nutrient requirements via formulation

or animal feeding tests, where the foods are produced and manufactured, the quality control measures that are taken to assure quality and consistency of the ingredients and the final diet, whether they are able to provide full nutrient profiles for their diets and what research has been performed with regards to their diets and whether this has been published in peer-reviewed journals. One should select pet food manufacturers that employ individuals with a PhD or board certification in small animal nutrition, engage in good quality control and safety measures, provide full diet nutrient profiles, and publish research on their diets in peer-reviewed journals.

#### 3.1.2.2 Unconventional diets

It is important to determine if the dog or cat is consuming an unconventional diet, such as a home-prepared diet not formulated by a board-certified veterinary nutritionist, a diet consisting of raw meat; either home-prepared or commercially bought, a vegetarian or vegan diet, and a boutique, exotic, or grain-free diet.

Home-prepared diets not formulated by a board-certified veterinary nutritionist are often deficient in essential nutrients. Diets consisting of raw meat are not currently recommended, mainly due to concerns regarding bacterial contamination, which can pose a threat to both the animal and people in contact with them. It can also contaminate the enviroment and may not be complete and balanced. Therefore, at this time, these adverse effects outweight any potential health benefits of raw food and therefore these diets should be avoided.



Dogs are omnivores and can therefore be fed a vegetarian diet.

Although commercial vegetarian diets containing synthetic taurine are available for cats, one study demonstrated that most commercial vegetarian diets formulated for dogs and cats were not compliant with AAFCO labeling regulations, and there were concerns regarding the adequacy of amino acid content.[7]



Cats are obligate carnivores and require a dietary source of taurine, as well as other nutrients such as pre-formed vitamin A and arachidonic acid, which are devoid in plants to meet their daily requirements.

Therefore, commercial vegetarian diets for dogs and cats should be heavily scrutinized to ensure they are from a reputable manufacturer that meets the WSAVA Global Nutrition Committee recommendations. In addition, dogs and cats fed these diets should be closely and regularly monitored and assessed. Finally, boutique, exotic, and grain-free diets have been associated with dilated cardiomyopathy in dogs. Therefore, owners should be questioned about feeding these diets to their pets.[8]

#### 3.1.2.3 Estimating caloric intake

Estimating caloric intake is important to ensure that the animal is meeting their daily requirement. The estimated total number of daily calories consumed can be compared with the historical amount consumed, which had maintained weight stability for that individual animal. However, if this information is unavailable, then the number of daily calories consumed can be compared with daily maintenance energy requirement (MER) calculations to determine if the animal is consuming enough calories. However, it is important to note that the calculated MER provides a ballpark figure and may under or over estimate the actual energy requirement by up to 50% in individual animals. Therefore, comparisons with historical intake of calories that maintained weight stability for that individual animal should be used.

#### 3.1.2.4 Compiling an antigen exposure list

All ingredients in currently and historically fed diets should be included in an antigen exposure list, which can then be used to determine what would be novel for the animal. Also, determining if certain ingredients improved gastrointestinal signs can help to prioritize their use in a home-prepared diet or when selecting a commercial therapeutic diet.



Most commonly identified dietary antigens: beef, dairy products, and wheat.[9,10]



Most commonly identified dietary antigens: beef, dairy products, and fish.[9,10]

#### 3.1.2.5 Assessment of dietary fiber

Determining current and historical fiber intake and the effect of this intake on the gastrointestinal signs will help to determine if high fiber and low fiber (low-residue) strategies have been attempted and whether these strategies should be incorporated into the next dietary recommendation. However, the fiber content of the diet is not easily estimated from the pet food label. Crude fiber is listed on the label; it measures most but not all insoluble fiber and no soluble fiber. Total dietary fiber is a better measure of insoluble and soluble fiber, but this is often unavailable from the manufacturers of over-the-counter diets, although it is commonly found in the product guides of veterinary therapeutic diets.

#### 3.1.2.6 Assessment of dietary fat

The fat content of the diet should also be estimated to determine the impact on the gastrointestinal signs. The fat content should be compared on an energy basis to remove confounding factors of energy density between the diets. This can be done on a percentage or gram per 1,000 kcal metabolizable energy (ME) basis. Although there is currently no consensus on the definition of low-fat, diets <20% fat on a ME basis are considered to be suitably low in fat. The range of dietary fat that has been tried and the effects on the gastrointestinal signs will help to determine if a low-fat strategy should be prioritized.

#### 3.1.2.7 Assessment of digestibility

Digestibility refers to the extent to which the food or macronutrients present in the food are digested and absorbed by the intestinal tract and is usually expressed as a percentage. Unfortunately, the digestibility of a diet or its ingredients is not a constant value, as digestibility is influenced by many factors. This includes factors related to the ingredients and the processing of the diet, for example heat processing generally increases the digestibility of starch but decreases the digestibility of protein. Animal factors, such as breed, age, gastrointestinal health, physiologic status, and the amount of food fed also influence digestibility. The breed of the dog has an effect on digestion, with larger breed dogs typically displaying lower digestibility of food compared with smaller breed dogs.[11] Age also has an impact, with approximately 20% of cats older than 12 years of age having decreased protein digestibility.[12] Although there is currently no standard definition for a highly digestible diet, diets with a total digestibility of at least 80% and a macronutrient digestibility of at least 90% are considered to meet this definition. Commercial therapeutic gastrointestinal diets are generally classified as highly digestible.

#### 3.1.2.8 Feeding plan

Feeding small meals more frequently throughout the day is advantageous in gastrointestinal disease to prevent overloading of the gastrointestinal tract. If the animal has an ideal BCS, then the amount of daily calories that were previously fed can be continued. If the animal is underconditioned, then the daily amount of calories should be increased in 10% increments, to off-put any malassimilation from the gastrointestinal disease until an ideal condition is reached.

For those dogs and cats that are unable to meet their daily caloric requirements voluntarily, assisted feeding may be required. Assisted feeding includes enteral feeding via a feeding tube or parenteral feeding. Enteral feeding should be prioritized wherever possible to preserve intestinal barrier function and prevent intestinal atrophy, bacterial translocation, and sepsis. However, in certain scenarios, enteral nutrition is not possible, such as with intractable vomiting and diarrhea, dull mentation, absent gag reflex, or the inability to place an enteral feeding tube due to coagulopathy or contraindications to sedation or anesthesia. Therefore, in such cases, parenteral nutrition may be required for assisted feeding.

A slow transition to the therapeutic diet should be performed to help with acceptance of the diet and to allow for monitoring of any adverse effects. Dogs and cats on an exclusion diet trial should not have access to other sources of food, as this may adversely impact the efficacy of the diet in controlling the gastrointestinal signs.

#### 3.1.2.9 Environment

Diet may act as a significant environmental risk factor in susceptible animals with chronic enteropathy. Therefore, an assessment of the diet just prior to or at the onset of chronic gastrointestinal signs is important to identify any potential dietary triggers, which can then be avoided. With regards to cats, the role of the environment has been demonstrated in certain nutrient-sensitive disorders, such as feline lower urinary tract disease (FLUTD) and type 2 diabetes mellitus; however, further studies are needed to determine the impact of environmental stressors in cats with chronic gastrointestinal diseases.

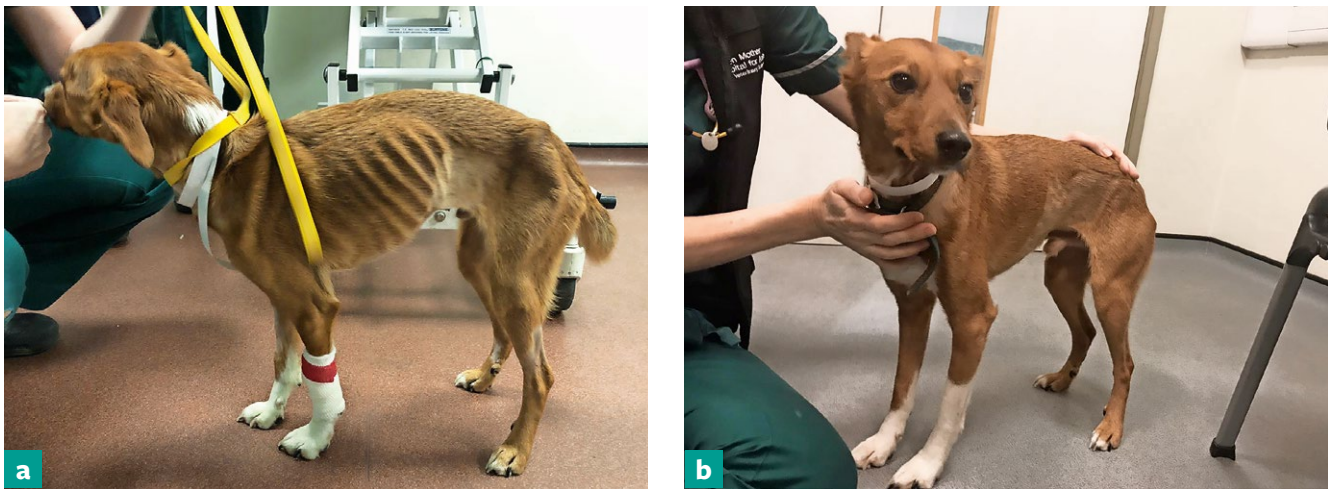


**Fig. 3-1** Body and muscle condition in a dog with PLE (protein-losing enteropathy)

**a** Marked decrease in body condition and muscle condition in a dog diagnosed with PLE (Courtesy of Sivert Nerhagen, Oslo, Norway.).

**b** Marked improvement in body condition, muscle condition, serum albumin concentration, and gastrointestinal signs in the same dog following a diet trial with Royal Canin Veterinary Diet Canine Hypoallergenic canned food, UK (Courtesy of Deirdre Mullowney, Alton, UK.).

### 3.1.3 Reassessment and monitoring

Reassessment and monitoring are important after the new diet has been introduced to ensure compliance and evaluate the effect of the dietary strategy(s), as well as to determine if any adjustments to the feeding plan are needed. The owner should regularly assess the animal's body weight and BCS to ensure an ideal body condition is maintained or achieved with the new diet (▶Fig. 3-1a). The owner should also monitor appetite and food intake, overall appearance and activity, as well as gastrointestinal signs. Return of normal activity, appetite, body weight, and BCS, with the absence of gastrointestinal signs, indicates successful dietary management (▶Fig. 3-1b).

Possible explanations for failure to respond to the new diet include the need for a different dietary strategy to control gastrointestinal signs, medication in addition to diet to control clinical signs, owner non-compliance with feeding, concurrent diseases or misdiagnoses of the gastrointestinal condition.

**KEY FACTS**

- Assessment of the nutritional status of dogs or cats with gastrointestinal disease is essential, as these patients are at risk of malnutrition, which may worsen their prognosis.
- Nutritional assessment includes assessment of the current diet, feeding management, and environment, as these may act as triggers or exacerbate gastrointestinal signs.
- Reassessment and monitoring are important after the new diet has been introduced to ensure compliance and evaluate the effect of the dietary strategy(s), as well as to determine if any adjustments to the feeding plan are needed.

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
svg.to/9842-03-01

## 3.2 Nutritional management of patients with gastrointestinal disease

### 3.2.1 Enteral feeding

Aarti Kathrani

#### 3.2.1.1 Introduction

Enteral feeding is beneficial for the gastrointestinal tract, as nutrients within the intestinal lumen stimulate intestinal mass and function and are an important stimulus for intestinal mucosal growth, repair, and integrity. Conversely, the absence of nutrients can result in atrophy of the small intestine within days, with suppressed crypt cell proliferation, a marked decrease in gastrointestinal-associated lymphoid tissue and function, decreased transport of glutamine and arginine, and increased intestinal permeability with the risk of bacterial translocation and sepsis.

Enteral feeding with as little as 10% of resting energy requirement (RER) to piglets resulted in significantly greater jejunal lactase and sucrase activities and taller villi and deeper crypts compared to animals fed nil per os.[1] Additionally, significantly higher survival was seen in cats and dogs receiving enteral nutrition with parenteral nutrition versus parenteral nutrition alone.[2] Therefore, enteral feeding should be prioritized whenever possible over fasting and parenteral nutrition, particularly in dogs and cats with gastrointestinal disease.

Enteral feeding in dogs and cats with gastrointestinal disease can be initiated with a commercial therapeutic diet or a home-prepared diet utilizing different dietary strategies. The different dietary strategies that may be beneficial in gastrointestinal disease include high digestibility, low-fat, hydrolyzed protein, novel limited-ingredient protein or high dietary fiber. This chapter will review the indications for these different dietary strategies for enteral feeding in dogs and cats with gastrointestinal disease.

#### 3.2.1.2 High digestibility

Digestibility refers to the extent to which the food or macronutrients present in the food are digested and absorbed by the intestinal tract and is usually expressed as a percentage. Unfortunately, the digestibility of a diet or its ingredients is not a constant value, as digestibility is influenced by many factors. This includes factors related to the ingredients, the processing of the diet; for example, heat processing generally increases the digestibility of starch but decreases the digestibility of protein, and animal factors, such as breed, age, gastrointestinal health and physiological status, and the amount of food consumed. The breed of the dog has an effect on digestion, with larger breed dogs typically displaying lower digestibility of food compared with smaller breed dogs.[3] Age also impacts digestibility, with approximately 20% of cats older than 12 years of age having decreased protein digestibility.[4] Although there is currently no standard definition for a highly digestible diet, diets with a total digestibility of at least 80% and a macronutrient digestibility of at least 90% are considered to meet this definition. Commercial therapeutic gastrointestinal diets are generally classified as highly digestible; formulas low in fat are also available within this category.

##### 3.2.1.2.1 Acute gastroenteritis

Commercial therapeutic gastrointestinal diets are frequently used for the nutritional management of acute gastroenteritis in dogs and cats due to their high digestibility. Acute gastroenteritis may compromise the digestion and absorption of nutrients, and therefore, diets with high digestibility can be advantageous in these cases. Additionally, diets with high digestibility produce fewer residues in the gastrointestinal tract, which can help to prevent overloading of the gut and alleviate osmotic diarrhea.

##### 3.2.1.2.2 Chronic enteropathy

Studies have documented the efficacy of commercial therapeutic gastrointestinal diets in cats with idiopathic chronic gastrointestinal signs.[5,6] Although the exact mechanism of how these diets improve clinical signs in cats with chronic gastrointestinal signs is unknown; likely explanations include the high digestibility resulting in less intact protein presented to the immune system, which may be dysregulated in cats with chronic enteropathy and less digestion required for these diets, which would be advantageous for the already compromised gastrointestinal tract.

However, for dogs with chronic enteropathy, diets with high digestibility alone may be unlikely to maintain remission, as one study showed that although a therapeutic gastrointestinal diet was able to induce remission, these dogs were less likely to remain asymptomatic at subsequent rechecks when compared to dogs managed with a hydrolyzed diet.[7]

However, further studies comparing therapeutic gastrointestinal diets with hydrolyzed diets are needed in both dogs and cats to define the subset of animals with chronic enteropathy that would likely benefit the most from these diets.

#### 3.2.1.2.3 Constipation

Commercial therapeutic gastrointestinal diets with high digestibility, and therefore, low residue and high caloric density should be fed to cats with obstipation, where the motility patterns of the large intestine are completely absent, as this will help to markedly reduce fecal content. In cats with obstipation, diets with increased fiber content and supplements containing fiber should be avoided, as they may worsen clinical signs, as all colonic motility has been abolished in these cats.

### 3.2.1.3 Low dietary fat

Low-fat diets may be beneficial in gastrointestinal disease, as high-fat diets have been shown to have many detrimental effects on the gut, including delayed gastric emptying and adverse effects on the microbiota, permeability, and the mucosal immune response in susceptible individuals.

#### 3.2.1.3.1 Acute gastroenteritis

Dogs and cats with acute gastroenteritis may benefit from a low-fat diet for two main reasons. Firstly, a reduction in dietary fat can help to hasten gastric transit and therefore may be advantageous for those animals with acute gastroenteritis resulting in nausea, regurgitation, or vomiting. Secondly, animals with acute gastroenteritis may experience reduced fat digestion and absorption resulting in excess dietary fat passing into the colon, which can potentially result in dysbiosis, as well as secretory diarrhea. Therefore, a low-fat diet should be considered in those animals with acute gastroenteritis with clinical signs that are likely to benefit from this strategy.

#### 3.2.1.3.2 Chronic enteropathy

In addition to delaying gastric emptying and the potential adverse effects on the colonic microbiota, high-fat diets may also adversely affect the mucosal immune response in susceptible individuals. For example, in an experimental model of inflammatory bowel disease, high-fat diets increased mRNA expression of the pattern recognition receptors (PRRs) nucleotide oligomerization domain (NOD) 2 and Toll-like receptor (TLR) 5.[8]

As the innate immune receptors, NOD2 and TLR5, have been implicated in the pathogenesis of canine chronic enteropathy,[9–13] there may be benefit of low-fat diets in dogs with dysregulated innate immune responses in the mucosa due to these receptors; although studies are needed to definitively assess this hypothesis.

Dietary fat did not seem to affect the outcome of cats with chronic diarrhea.[14] Therefore, dietary fat may be less of a nutrient of concern in cats compared to dogs with chronic enteropathy.

#### 3.2.1.3.3 Intestinal lymphangiectasia

There are two main reasons that low-fat diets are recommended to manage intestinal lymphangiectasia. First, low-fat diets may prevent lacteal dilation and lymph leakage by decreasing chylomicron production, thus decreasing lymphatic flow and pressure. Second, long-chain triglycerides have proinflammatory effects and can cause lipogranulomas. Therefore, a low-fat diet is prioritized in the management of intestinal lymphangiectasia. Glucocorticoids may also be used in intestinal lymphangiectasia to reduce intestinal inflammation. However, one small retrospective study in Yorkshire terriers with intestinal lymphangiectasia showed that some dogs responded satisfactorily to a low-fat diet alone in the short-term.[15] Another study documented that dietary fat restriction could be used as an effective treatment in dogs with intestinal lymphangiectasia that were unresponsive to prednisolone or had experienced a relapse with dose reduction.[16]

Supplementation with medium-chain triglycerides (MCTs) are used in people with intestinal lymphangiectasia as they are directly absorbed into the portal vein. However, in dogs, MCTs are absorbed into the lymphatic system, and therefore, may not help reduce lymph flow.[17] MCTs have also been shown to modulate intestinal inflammation and cause less damage than long-chain triglycerides in an animal model of ileitis.[18] Therefore, the use of MCTs may help to reduce inflammation in canine intestinal lymphangiectasia.

### 3.2.1.4 Hydrolyzed protein

Commercial therapeutic hydrolyzed diets contain proteins that are considered small enough to theoretically avoid a type 1 IgE-mediated hypersensitivity immune response. They avoid this immune response by preventing cross-linking of two IgE-antibody receptors on a mast cell. Therefore, this strategy is beneficial for those cases suspected of having a gastrointestinal food allergy or hypersensitivity driven by a type 1 IgE-mediated response. However, these diets employ additional strategies that may also be beneficial in gastrointestinal diseases, such as high digestibility and inclusion of immunomodulatory ingredients, including soy and omega-3 fatty acids. Some formulas are also lower in fat or are gluten-free or vegetarian formulations.

#### 3.2.1.4.1 Chronic enteropathy

Hydrolyzed diets have been used successfully in the management of chronic enteropathy in dogs and cats.[7,19–23] These diets may be effective as they employ a number of different dietary strategies that may be beneficial. Firstly, the hydrolyzed strategy may help to impact the immune system, which is known to be dysregulated in this disease. Two studies assessing the whole blood ex vivo cytokine response to commercial hydrolyzed diets showed that these diets elicited no to minimal response in both dogs and cats.[24,25] The hydrolyzed approach also helps to increase digestibility, which may be beneficial for gastrointestinal disease. Some hydrolyzed formulas have a lower fat content, which may also be beneficial for some cases. Some hydrolyzed diets contain soy and/or omega-3 fatty acids, which are immunomodulatory and therefore may be beneficial for some animals with chronic enteropathy. Some hydrolyzed formulas are vegetarian; a study in humans showed that a semi-vegetarian diet was highly effective for maintaining remission in IBD patients.[26] Gluten-free diets have also been shown to improve clinical symptoms in people with IBD.[27] Therefore, as some hydrolyzed formulas are gluten-free, this strategy may explain the improvement in clinical signs associated with these diets in some dogs and cats with chronic enteropathy.

#### 3.2.1.4.2 Adverse reaction to food

Adverse gastrointestinal reactions to food can be subclassified into toxic and non-toxic causes. Non-toxic causes are further classified into immune-mediated and non-immune-mediated causes. Immune-mediated causes are termed food allergy or food hypersensitivity (▶Chap. 11.1) and encompass those cases involving either the innate immune system or the adaptive immune system. Food allergy involving the adaptive immune system can be categorized into IgE-mediated, non-IgE-mediated, or mixed IgE- and non-IgE-mediated. Although the proportion of dogs and cats with a gastrointestinal food allergy attributed to a type 1 IgE-mediated hypersensitivity is unknown, hydrolyzed diets are used to diagnose and treat this condition. However, one study showed that a significant proportion (21%) of dogs sensitized to the intact protein still reacted adversely to a hydrolyzed diet.[28] Therefore, persistent signs may be anticipated with the use of hydrolyzed diets, particularly in dogs and cats with a non-IgE-mediated etiology for their gastrointestinal food allergy.

### 3.2.1.5 Limited-ingredient novel protein

Commercial therapeutic limited-ingredient novel protein diets contain ingredients from a limited number of sources, which are not considered to be used frequently in over-the-counter dog and cat diets, and are therefore more likely to be novel for the animal.

#### 3.2.1.5.1 Chronic enteropathy

Studies have shown that nearly 50% of cats and 60% of dogs with chronic gastrointestinal signs responded to a novel protein diet[29,30] with one study documenting no difference in response rate between hydrolyzed and limited ingredient novel protein diets for dogs with chronic enteropathy.[22] Deciding which specific novel protein formula to use will depend on currently and historically fed diets to identify which ingredients the animal has not been exposed to. As one study showed the presence of other common food antigens in over-the-counter novel protein diets, these diets should be avoided for the management of chronic enteropathy.[31]

#### 3.2.1.5.2 Adverse reaction to food

Novel protein diets may be beneficial for cases of gastrointestinal food allergy because the animal has not been sensitized to the novel proteins as they have not been previously fed. Therefore, these diets should theoretically not elicit an immune-mediated response within the gastrointestinal tract of these animals. Although, the animal may become hypersensitized to these novel antigens over time.

### 3.2.1.6 High dietary fiber

Dietary fibers are plant-based carbohydrates that cannot be digested by mammalian enzymes. Dietary fiber can have many beneficial effects on the gastrointestinal tract, including modification of gastric emptying, normalization of intestinal motility, optimizing intestinal barrier function, anti-inflammatory effects via generation of short-chain fatty acids, buffering of toxins, binding of excess water, supporting the growth of beneficial bacteria, and altering the viscosity of the ingesta.

#### 3.2.1.6.1 Acute gastroenteritis

Diets high in fiber may be beneficial for those cases of acute gastroenteritis with predominantly large intestinal signs. However, not all animals with large intestinal signs will

respond to a high fiber dietary strategy. Therefore, trial and error with this approach is needed and should be prioritized for those cases with large intestinal signs that do not respond to a highly digestible diet and especially before the use of antimicrobials.

#### 3.2.1.6.2 Chronic enteropathy – large bowel signs

Unfortunately, there have been a minimal number of studies published assessing dietary fiber in canine and feline chronic enteropathy. One retrospective study showed that treatment with a commercial therapeutic highly digestible diet supplemented with soluble fiber resulted in a very good to excellent response in most dogs with chronic idiopathic large bowel diarrhea (▶Chap. 8.3.5).[32] In another study, 19 dogs with chronic colitis that had failed a low-fat diet responded to a fiber-supplemented diet, and maintenance could be achieved without the concurrent need for other medications.[33] One study assessing the effects of chondroitin sulfate and several prebiotics, including resistant starch, beta-glucan, and mannan oligosaccharides, in 27 dogs with IBD showed that the histologic score of dogs that received the supplement together with a hydrolyzed diet decreased 1.53 fold.[34] Finally, one study documented that the combination of a high fiber diet and a probiotic mixture in 30 dogs with chronic colitis that were unresponsive to various dietary and pharmacological interventions was able to induce remission of clinical signs in a mean of 8.5 days.[35] For cats with colitis, one published study demonstrated response to diets high in fiber or supplemented with fiber.[36]

#### 3.2.1.6.3 Constipation

For cats presenting with constipation that still have some level of colonic motility remaining, insoluble or a mix of insoluble and soluble fiber may help to improve clinical signs. Insoluble fibers provide fecal bulk, which helps to improve colonic motility by causing distension of the colon. Soluble fibers are generally fermentable in the large intestine resulting in the production of short-chain fatty acids, which have numerous advantageous effects on the colonocytes and colonic motility, as well as increasing the water content of the feces.

Psyllium is a soluble fiber with low fermentability that can form a gel when mixed with water. One uncontrolled trial in cats with constipation showed that a commercial psyllium-enriched dry diet was able to improve stool quality and clinical outcomes in over 80% of cats within a week of starting the diet.[37]

### 3.2.1.7 Home-prepared diets

There are many advantages of feeding a home-prepared diet to dogs and cats with gastrointestinal disease. First, a home-prepared diet allows the avoidance of antigens that may develop or become unmasked during the processing of commercial diets to which the animal may be allergic, and therefore, may be the cause of the adverse gastrointestinal reaction to food. Second, home-prepared diets avoid the use of certain emulsifiers and preservatives shown to have negative effects on the gastrointestinal tract in animal models. Third, the use of a home-prepared diet allows the macronutrient content to be precisely set, for example the fat content, and may allow for an amount lower than is currently available commercially. Fourth, home-prepared diets allow the use of exotic ingredient sources that may not be available in a commercial therapeutic diet and are particularly valuable for those cases with an extensive antigen exposure list. Lastly, home-prepared diets may be more palatable for the animal and are therefore advantageous in those cases that have reduced appetite. Guidance from a board-certified veterinary nutritionist is required for home-prepared diets to ensure that these diets are complete and balanced.

### 3.2.1.8 Feeding plan and monitoring

#### 3.2.1.8.1 Acute gastroenteritis

Animals with acute gastroenteritis likely benefit from small frequent meals throughout the day to prevent overloading of the gastrointestinal tract. Once gastrointestinal signs have fully resolved, the regular diet can be slowly reintroduced over the next few days. If the animal has an ideal body condition, then the number of daily calories that were previously fed can be continued.

The prognosis for full recovery in most cases of acute gastroenteritis is very good. Monitoring of body weight, hydration status, and gastrointestinal signs should be performed at least daily during hospitalization. Further diagnostic investigations are required if the gastrointestinal signs persist or become chronic.

#### 3.2.1.8.2 Chronic enteropathy

A slow transition to the new diet should be performed over 7–10 days, and although this diet should be fed exclusively, a recent study suggested that dogs with food-responsive enteropathy did not need to receive these diets exclusively for effectiveness at controlling clinical signs.[22] Feeding multiple

small meals throughout the day will help prevent overloading of the gastrointestinal tract. If the animal has an ideal BCS, then the number of daily calories that were previously fed can be continued. If the BCS is decreased, then the calories fed should be increased at 10% increments to offset any malassimilation from the chronic enteropathy until an ideal BCS is reached.

Most dogs and cats with chronic enteropathy can be transitioned back to their original diet without showing signs of relapse. In one study, 21% of dogs and in another study, 29% of cats with gastrointestinal signs relapsed following challenge;[22,38] these cases may have been food allergic. Unfortunately, at this time, it is not possible to distinguish food allergy, intolerance (non-toxic, non-immune mediated causes of gastrointestinal adverse reaction to food), or chronic enteropathy that are responsive to diet alone.

Regular monitoring of appetite, activity, body weight, BCS, and gastrointestinal signs will help to determine the effectiveness of the diet. Serial measurement of the chronic enteropathy clinical activity index will help to provide a more objective measure of treatment response. Fortunately, studies have shown a clinical response to diet in dogs and cats with chronic enteropathy within or at 2 weeks of feeding.[21,38–40]

#### 3.2.1.8.3 Intestinal lymphangiectasia

A slow transition to the low-fat diet should be performed in dogs with intestinal lymphangiectasia. If a commercial therapeutic low-fat diet does not help to improve gastrointestinal signs or biochemical parameters, then a home-prepared diet formulated by a board-certified veterinary nutritionist to further reduce dietary fat should be considered. Studies have shown the efficacy of commercial low-fat therapeutic diets and low-fat home-prepared diets for canine intestinal lymphangiectasia.[15,16] Appetite, body weight, body condition, muscle condition, gastrointestinal signs, and serum albumin, globulin, and cholesterol concentrations should be regularly assessed.

#### 3.2.1.8.4 Adverse reaction to food

For those cases of suspected gastrointestinal food allergy, a strict exclusion diet trial should be performed for at least 6–8 weeks. After this time, a provocation challenge with the original diet or single ingredients would be needed to confirm the diagnosis of food allergy. Unfortunately, this is not frequently performed; and therefore, the diagnosis remains tentative in these cases.

#### 3.2.1.8.5 Constipation

Appetite, body weight, and fecal frequency and consistency should be monitored at least daily during hospitalization. Cats with constipation should be well rehydrated before a diet with high fiber is introduced. For obstipated cats, cleansing enemas with or without mechanical removal of impacted feces should be performed before dietary changes are introduced. Feeding multiple small meals throughout the day may help to improve colonic motility and reduce the amount of ingesta entering the colon at one time. A weight reduction program should be considered for overweight cats. Ensuring adequate hydration following discharge from the hospital via access to different types of water sources is important.

**KEY FACTS**

- Nutrition has many direct beneficial effects on the gastrointestinal tract and is therefore important in the management of various canine and feline gastrointestinal diseases.
- Enteral feeding in dogs and cats with gastrointestinal disease can be initiated with a commercial therapeutic diet or a complete and balanced home-prepared diet formulated by a board-certified veterinary nutritionist, utilizing different dietary strategies.
- The different dietary strategies that may be beneficial for gastrointestinal disease in dogs and cats include high digestibility, and the use of low-fat ingredients, hydrolyzed protein and limited-ingredient novel proteins, and high dietary fiber.

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
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## 3.2.2 Placement and management of feeding tubes

Natalie Hughes, James Howard, Valerie J. Parker

Feeding tubes should be considered in any hemodynamically stable patient who is at risk for malnutrition. Afflictions that increase the risk for malnutrition include trauma, sepsis, peritonitis, or nearly any acute or chronic inflammatory condition (e.g., acute necrotizing pancreatitis, acute kidney injury). Assisted enteral nutritional support should be provided to animals that have been anorexic or hyporexic for at least 3–5 days. The most commonly used feeding tubes in small animal clinical practice include: nasoesophageal/nasogastric (**NE/NG**), esophageal (**E**), and percutaneous endoscopic gastrostomy (**PEG**) or surgical gastrostomy tubes (**G**). Jejunostomy (J) and gastrostomy-jejunostomy (G-J) tubes are rarely indicated. Further details on their use can be found elsewhere.[1–4]

### 3.2.2.1 Types of feeding tubes

#### 3.2.2.1.1 Nasoesophageal/nasogastric tubes

Nasoesophageal and nasogastric tubes (**NE tube** and **NG tube**, respectively) are an excellent option for dogs and cats that require short-term nutritional support (i.e., <7 days). They are the optimal choice for patients that cannot tolerate general anesthesia, sometimes bridging the time until a longer-term feeding tube can be placed. A NE tube ends in the distal third of the esophagus, whereas an NG tube passes through the lower esophageal sphincter (LES) and terminates in the stomach. One benefit of having an NG tube is the ability to remove residual gastric volume if ileus is present. Some clinicians worry about the increased risk of gastroesophageal reflux or vomiting with an NG tube, but no difference in complication rates between NE tube and NG tube was observed in one retrospective study.[5]

Placement of an NE/NG tube can cause mild epistaxis, and these tubes should be avoided in patients with severe thrombocytopenias or thrombocytopathias. They should be avoided in patients with nasal disease to prevent further respiratory compromise. Other potential contraindications to NE/NG tube placement include lack of a gag reflex (due to increased risk of aspiration) and facial trauma (which may affect nasal anatomy; alternatively, the tube may increase pain). Typically an NE tube should not be placed in an animal with esophageal dysmotility due to increased risk of aspiration, but an NG tube could be considered. While generally well-tolerated, these tubes may cause discomfort, and animals may sneeze and try to remove them. Elizabethan collars are often required to prevent inadvertent dislodgement.

Cats and small dogs typically require a 5 Fr (French) tube, whereas medium and large dogs can tolerate 8 Fr and 10 Fr tubes, respectively. For kittens and small puppies, pediatric 3.5 Fr tubes are available. Additionally, for large dogs with especially thick gastric contents that warrant aspiration, 12 Fr tubes may be placed to evacuate the stomach. There are several options for tube types, including red rubber, polyurethane, silicone, or polyvinyl chloride (PVC). Some tubes contain stylets to better facilitate placement by providing a rigid core allowing the tube to be manipulated through collapsed esophageal tissue or penetrate a constricted LES; weighted tubes are also sometimes advantageous when attempting to traverse the LES.

The following supplies are needed for NE/NG tube placement: Topical anesthetic for nostril, tube, marker or tape, sterile lubricant, 3–6 mL syringe, non-absorbable suture, and instruments to secure the tube (e.g., needle drivers or hemostats; alternatively a 22-gauge hypodermic needle).

While general anesthesia is not required, mild sedation may make the placement of these tubes more tolerable. The steps for placement of an NE/NG tube are as follows:

1. Measure the approximate length needed to reach from the external nares to the stomach (NG tube; approximately last rib) vs. distal esophagus (NE tube; approximately seventh to ninth intercostal space). Mark the tube either with a marker or a piece of tape.
2. Instill 3–5 drops of 0.5% proparacaine hydrochloride ophthalmic solution in one or both nostrils.
   **Tip:** Sometimes, if placement is difficult in one nostril, the other nostril may be easier.
3. Apply sterile lube to the distal tube tip.
4. Insert the tube in the nostril and direct it ventromedially through the ventral nasal meatus. Advance the tube until the marker or tape is reached.
   **Tips:**
   - Some animals will react to seeing a tube near their faces, and it can be helpful to cover the animal's eyes while holding the face still.
   - Utilizing a "pig nose" technique (i.e., pushing the tip of the nose dorsally) may help better guide the tube ventrally.
   - Stop and redirect the tube if resistance is encountered or if the animal begins coughing.

5. Once the tube has been placed, remove the stylet (if used). A syringe can be applied to the tube and aspirated. Getting negative pressure (or gastric contents) is typically a sign of proper placement, but proper placement should always be confirmed either with fluoroscopy or cervical and thoracic radiographs.
6. Secure the tube to the lateral aspect of the nares either with a finger trap suture pattern or with tape and suture.
   **Tips:**
   - Some clinicians prefer to pass the suture through a needle on the side of the alar fold, thus eliminating the need for needle drivers or hemostats. Additionally, tucking the tube behind the alar fold in the most abaxial portion of the alar fold crease and then suturing the alar fold around the tube provides additional security.
   - The tube can also be secured either to the forehead or the cheek with tape and suture (▶ Fig. 3-2).
7. Once placement is confirmed, flush the tube with sterile saline or tap water.
8. An Elizabethan collar should be placed on the animal to avoid inadvertent removal.

Small bore tubes require liquid diets, which can be fed either via intermittent bolus feeding or continuous rate infusion (CRI). There are several liquid enteral options currently available for dogs and cats with varying nutritional requirements (▶ Tab. 3-1) or dogs that require both protein and fat restriction. Some human products may be considered; however, they do not provide complete and balanced nutrition and should only be used short-term. Tubes should be flushed well to avoid clogging. If an animal requires assisted enteral nutrition for more than one week, an E or G tube should be placed.



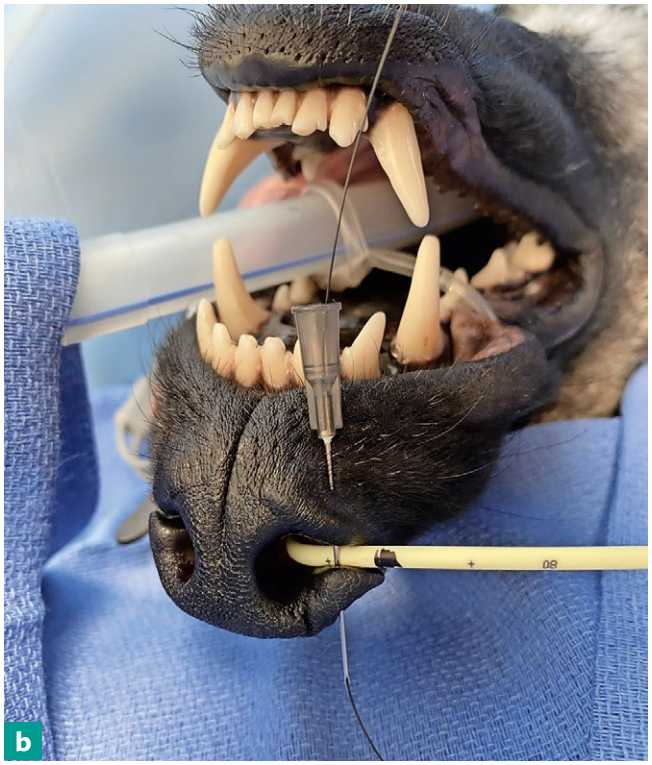

**Fig. 3-2** Nasogastric tube security

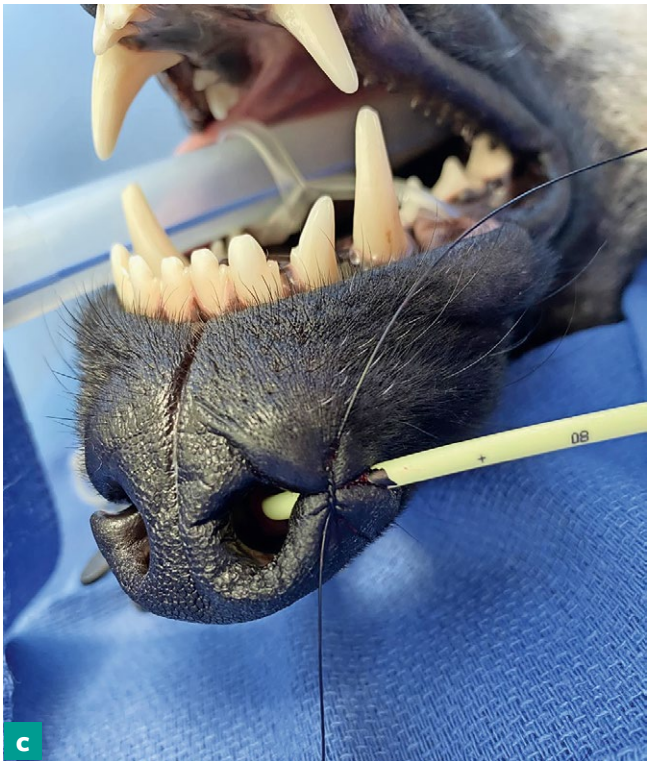
**a** Note the tube tucked into the "alar fold crease" in the most lateral aspect of the alar fold. A needle is placed through the ventral aspect of the nose and into the alar fold.

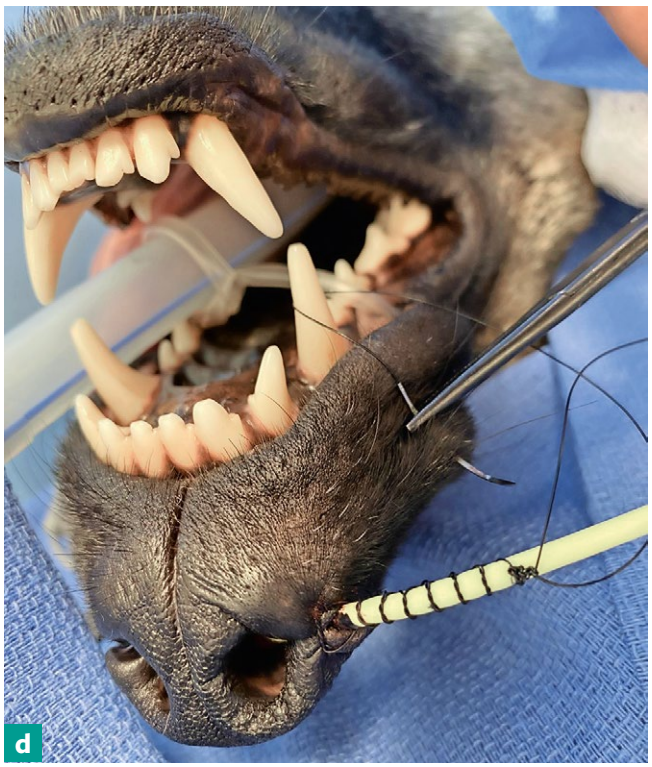
**b** A suture is inserted into the needle cannula through the encircling nasal tissue.

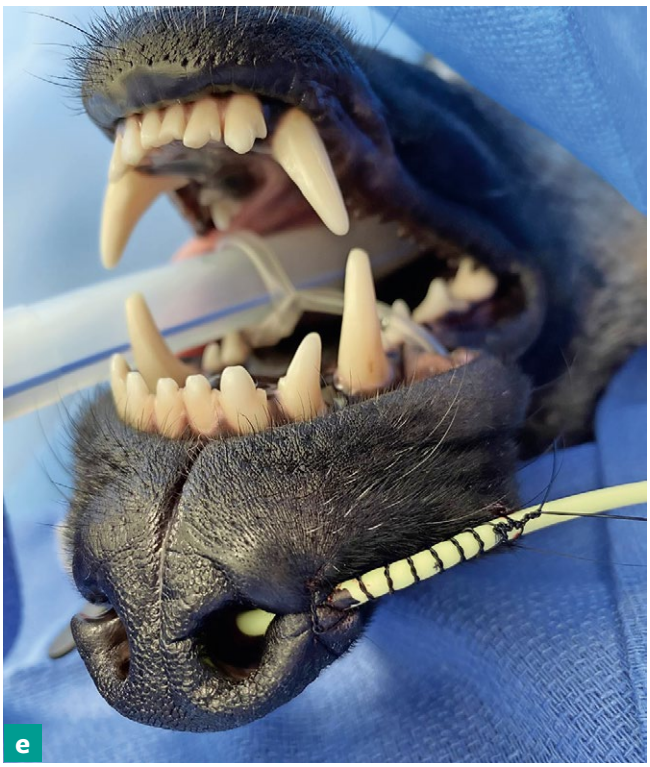
**c** The suture is tied with a surgeon's throw to secure the tube within the pocket created between the alar fold and nasal planum tissue.

**d**, **e** A finger trap is used to secure the tube in place, and the swaged-on needle is used to tack the secured tube to the lateral side of the animal's face.


b


c


d


e

**Tab. 3-1** Comparison of selected nutrients from a few veterinary therapeutic "critical-care" diets and liquid enteral diet options currently available for dogs and cats. Two human enteral products are listed for comparison. Nutrients listed per 100 kcal.

| Diet | Calories (per can or bottle) | Calories (kcal/mL) | Protein (g) | Fat (g) | Phospho-rus (mg) | Potassium (mg) | Sodium (mg) |
|---|---|---|---|---|---|---|---|
| **Veterinary canned diets** | | | | | | | |
| Purina Pro Plan Veterinary Diets CN (5.5 oz can) | 206 | 1.4* | 8.2 | 7.4 | 260 | 250 | 90 |
| Hill's Prescription Diet a/d (5.5 oz can) | 183 | 1.0* | 9.0 | 6.7 | 237 | 242 | 182 |
| Royal Canin Recovery ultra-soft mousse in sauce (5.1 oz can) | 149 | 0.9* | 10.1 | 6.2 | 250 | 210 | 290 |
| **Veterinary liquid enteral products** | | | | | | | |
| Royal Canin Recovery Liquid (237 mL bottle) | 213 | 0.9 | 8.6 | 5.4 | 170 | 210 | 100 |
| Royal Canin Gastrointestinal Low Fat Liquid (237 mL bottle; canine only) | 213 | 0.9 | 9.2 | 2.0 | 180 | 220 | 100 |
| Royal Canin Renal Support Liquid Feline (237 mL bottle; canine) | 308 | 1.3 | 3.7 | 3.7 | 90 | 160 | 100 |
| Royal Canin Renal Support Liquid Canine (237 mL bottle; feline) | 213 | 0.9 | 7.5 | 5.9 | 80 | 180 | 90 |
| **Human liquid enteral products** | | | | | | | |
| Ensure Original Vanilla Nutrition Shake (237 mL bottle) | 220 | 0.9 | 4.1 | 2.7 | 137 | 168 | 91 |
| Perative (237 mL carton) | 308 | 1.3 | 5.1 | 2.9 | 68 | 133 | 80 |
| **For reference:** | | | | | | | |
| AAFCO minimum (canine adult maintenance) | – | – | 4.5 | 1.4 | 100 | 150 | 20 |
| AAFCO minimum (feline adult maintenance) | – | – | 6.5 | 2.3 | 125 | 150 | 50 |

* Estimated kcal per mL of slurry from 1 can diet + 25 mL water.
These nutrient profiles are from product guides as of January 2021.
**AAFCO** = Association of American Food Control Officials

#### 3.2.2.1.2 Esophagostomy tubes

Esophagostomy tubes (**E tubes**) are appropriate for long-term nutritional support and can be left in place for months, even years, for patients with chronic disease resulting in hyporexia. These tubes are contraindicated in patients with esophageal disease (e.g., esophageal stricture, megaesophagus, or dysmotility) due to increased risk of aspiration.

E tubes should be placed with animals under general anesthesia. Smaller cats and dogs typically tolerate 12–14 Fr tubes, while medium to large dogs can accommodate 14–18 Fr tubes. It has been reported that up to 30 Fr tubes may be placed; however, one study reported using larger tubes resulted in more complications (e.g., infection or swelling at the stoma).[6] There are several options for tube types, including red rubber, polyurethane, silicone, or polyvinyl chloride (PVC). Generally, polyurethane or silicone tubes are softer and more comfortable for long-term use.

The following supplies are needed for E tube placement: anesthetic agent, E tube, clippers, surgical scrub and alcohol, marker, sterile gloves, curved hemostats of appropriate size, scalpel blade (number 11 or 15), antibiotic ointment, cloth collar or bandaging material.

1. The animal should be placed under general anesthesia, with an endotracheal tube in place and positioned in right lateral recumbency.
2. Clip and aseptically prepare the left lateral neck from the caudal aspect of the ear to the thoracic inlet. Note where the jugular furrow is so as to avoid placing the tube in that area.
   - Alternatively, an E tube can also be placed in the right cervical region, with the patient in left lateral recumbency. The primary indication for this would be if a previously placed left-sided E tube necessitated removal due to infection.
   - Left-sided placement is advantageous due to the regional anatomy of the esophagus in that area.
3. Hover the tube over the animal, keeping it sterile. Place the distal tube tip at approximately the seventh to ninth intercostal space, and mark the tube where it will exit the lateral neck, at about the middle of the shaved area. Replace the tube in the sterile field.
4. Insert the curved hemostats (either Kelly or Carmalt) into the esophagus. Apply pressure upwards so that the tip can be clearly seen externally.
   **Tip:** For E tube placement in large dogs, it can be helpful to have one person use two hands to apply pressure upward with the hemostats and another to focus on making the incision.
5. Use the scalpel to incise directly over the hemostats. The incision should be only big enough to advance the tips of the hemostats through it.
6. Once the hemostats are exteriorized, open them and slide the E tube over one tip. Clamp down and pull the tube retrograde through the mouth.
7. Then, turn the tube around and advance the tip back down the esophagus. Occasional traction on the tube outside of the animal's neck may help relieve any kinks in the tube. Align the marked place on the tube with the lateral neck skin.
8. Secure the tube either with a purse-string suture and finger trap or alternatively two lateral stay sutures and finger traps.
9. Confirm proper placement of the E tube either with fluoroscopy or radiographs. The distal tip of the tube should terminate in the distal third of the esophagus (approximately seventh to ninth intercostal space).
10. Some E tubes may require excess tubing to be removed at the oral end.
11. Apply antibiotic ointment and soft padding or a cloth collar (e.g., Kitty Kollar®, CathCollar™).

Nearly any canned diet can be blended and fed via an E tube. Some veterinary therapeutic "critical care" diets are designed to be administered easily via feeding tubes. When mixed with a small amount of water (25 mL per 5.5–5.8 oz can), these diets provide approximately 1.0 kilocalories (kcal) per mL. For patients with specific morbidities, other canned diet options may be more appropriate.

#### 3.2.2.1.3 Gastrostomy tubes

Gastrostomy tubes (**G tubes**) can be placed either percutaneously with endoscopic guidance (**PEG tubes**) or surgically. G tubes have similar indications to E tubes, with the added indication of esophageal disease (e.g., esophageal stricture, severe esophagitis, megaesophagus, ▶Fig. 3-3). One additional, albeit rare, indication for G tubes is for cases of chronic bloat refractory to conservative dietary and medical management. These tubes are placed under general anesthesia and should ideally remain in place for at least 2 weeks to ensure a stoma has formed between the stomach and the body wall. Anything that would impair stoma healing could be considered a contraindication to G tube placement (e.g., significant gastric mucosal disease, hypoalbuminemia, immunosuppressive medications).

Some veterinarians do not place PEG tubes in large, deep-chested dogs for risk of excessive motion and potential dis-

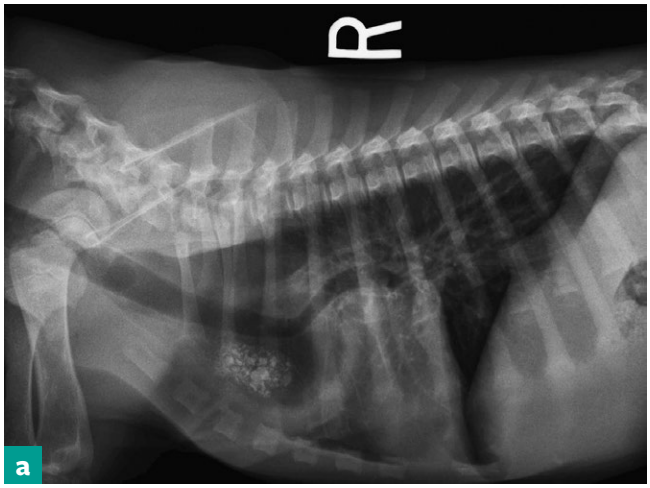












**Fig. 3-3** PEG tube in dog with megaesophagus

Right lateral (**a**) and ventrodorsal (**b**) thoracic radiographs in a 3-month-old female German shepherd dog showing segmental megaesophagus secondary to persistent right aortic arch with esophageal foreign material. After ligamentum arteriosum ligation, a PEG tube was placed and maintained for approximately 6 weeks at which time it was removed because the dog was able to successfully eat by mouth and was gaining weight.

The puppy at the time of PEG tube placement (**c**) and 6 weeks later at the time of tube removal (**d**).










**Fig. 3-4** PEG tube in dog with esophagitis

An 8-year-old castrated male German shepherd dog had a PEG tube placed (**a**) to provide nutritional and medical support while his severe esophagitis (**b**) was managed. The tube was successfully managed for 6 weeks at which time it was removed because the dog was able to eat by mouth and maintain body weight. This dog was a working police dog who remained active with his PEG tube in place (**c**).

lodgement; however, the authors routinely successfully place and use PEG tubes in large, deep-chested dogs (▶Fig. 3-3).

Most patients can accommodate 16–24 Fr G tubes of either latex, silicone, or polyurethane material. Historically, most people have used mushroom-tipped G tubes. More recently, commercially available PEG tube kits have become available, and this has shifted many clinicians toward using bumper-tipped G tubes. Low-profile balloon-tipped PEG tubes may be preferred for extended use.

Variable placement techniques have been described (e.g., endoscopically, surgically, or via blind technique).[7,8] This choice is generally dictated by available equipment (e.g., endoscope) and clinician comfort. The technique for standard PEG tube placement is described here. The following equipment is needed: general anesthesia, clippers, surgical scrub and alcohol, sterile gloves, flexible endoscope with biopsy lumen and snare, scalpel blade (number 11 or 15), PEG tube kit (or equivalent), cloth netting or bandage material.

1. The animal is placed in right lateral recumbency under general anesthesia.
2. Clip and aseptically prepare the left lateral abdomen, from approximately the last rib to the hip.
3. The endoscope is passed through the mouth to the stomach, and insufflation is applied until the stomach is full and flush with the body wall. The light from the endoscope should be visible externally, reducing the risk of splenic entrapment.
4. With sterile gloves, one person should gently but firmly depress a finger at a 45° angle cranioventrally on the skin over the stomach in the area where the tube would be placed. This is typically 2–4 cm from the last rib, about halfway from the dorsum to the ventrum. This allows the endoscopist to visualize the depression created by the external finger and to ensure location appropriateness internally.
5. A scalpel blade is used to make a stab incision through the skin. This is visualized by the endoscopist ensuring an appropriate location and penetration depth.

6. An over-the-needle introducer catheter is then positioned through the stab skin incision and inserted into the gastric lumen. The stylet is removed, ensuring the catheter remains in the gastric lumen. The insufflation of the stomach helps to keep the stomach and abdominal wall in contact throughout the procedure.
7. If using a pre-made PEG tube kit, pass the wire through the catheter and retrieve it with grasping forceps via endoscope.
8. Remove the endoscope and wire through the patient's mouth, leaving the other end of the wire outside the animal's lateral side through the previously made incision. At this time, the catheter can be removed from the stomach and body wall; the wire will traverse from outside the animal's mouth, through the esophagus and stomach, to outside the animal's lateral body wall.
9. Attach the PEG tube to the wire with a square knot. Lubricate the tube and wire. From the animal's lateral side, gently apply traction to the wire pulling the tube into the animal's mouth, down the esophagus, and into the stomach.
   Depending on the size of the animal and the PEG tube, the tapered tip of the tube may reach the stomach wall while the bumper tip is still in the animal's mouth.
10. Continue applying gentle traction to the tube until the bumper reaches the stomach. The skin incision may need to be slightly extended to facilitate the tube exiting the skin.
11. The endoscopist should visualize the tube in the stomach to ensure it is secure against the gastric mucosa without excessive pressure.
12. Use a marker to denote where the tube exits the skin.
13. Affix a bumper/phalange externally, leaving at least 5 mm space between the bumper and skin to avoid inducing a pressure sore.
    There will be some movement once the stomach is deflated.
14. A T-shirt or other cloth wrap (e.g., ThunderShirt, Thunderworks, NC) should be applied to keep the tube close to the body wall. Some animals may require an Elizabethan collar to prevent inadvertent disruption of the PEG tube.

Animals with PEG tubes should be fed similarly to those with E tubes. Some clinicians prefer to wait approximately 24 hours after tube placement to allow for some stoma healing; however, there is no evidence to specifically encourage this practice.

### 3.2.2.2 Feeding instructions

Small-bore NE/NG tube (i.e., 5-10 Fr) require liquid enteral diets. In most cases, a veterinary-specific diet should be utilized to ensure that complete and balanced nutrition is provided. In some cases, liquid enteral formulations designed for human use may be administered short-term to dogs; however, these are not adequate for long-term nutritional support, and they should not be administered to cats. Larger bore tubes (i.e., >12 Fr) can accommodate canned blended diets. Nearly any canned food can be prepared as a blended slurry; however, the amount of water required to achieve an adequate consistency for administration varies greatly, as does the resultant caloric density (i.e., kcal per mL).

**Equation to determine the caloric density of the blended canned diet**

$$\frac{(\text{kcal per can} \pm \text{kcal liquid added})}{(\text{mL of can} + \text{mL liquid})} = \frac{\text{kcal}}{\text{mL}}$$

Example: Blend 1 can = 13.4 oz (380 g) of Purina Pro Plan Veterinary Diets EN (432 kcal per can). Since 1 gram = 1 mL, assume that 1 can = 380 mL. Through some trial and error, by adding small increments of water at a time, if you determine that it takes 150 mL water to achieve a smooth consistency to be fed via a 14-Fr esophagostomy feeding tube, that means the following:

$$\frac{432 \text{ kcal (1 can EN)} + 0 \text{ (water)}}{380 \text{ mL (1 can EN)} + 150 \text{ mL (water)}} = \frac{432 \text{ kcal}}{530 \text{ mL}}$$

= 0.65 kcal per mL

**Note:** Theoretically, if a higher caloric density were required, a liquid enteral diet could be substituted for water. For example, if Royal Canin Gastrointestinal Low Fat Liquid (0.9 kcal per mL) were used to blend the canned Purina EN diet, it would add an additional 135 kcal, increasing the resultant kcal/mL to 1.07 kcal/mL. When only a small volume of water is required to prepare a canned diet for provision via a feeding tube, this difference is fairly insignificant, and the cost-to-benefit ratio is low.

The caloric density and consistency of diets change frequently, and the veterinarian should confirm that a recommendations for a canned slurry "recipe" is appropriate for client preparation.

Depending on how long the patient has been hyporexic or anorexic, it is typically recommended to initiate feedings at approximately 25–33% of RER on day 1. This can be administered either in 3–4 bolus feedings or as a CRI. Initial volumes of food to be administered via a feeding tube should not exceed 5–10 ml/kg per feeding. For patients that have been chronically hyporexic, aiming for a smaller volume will decrease the risk of nausea, regurgitation, or vomiting after feeding. Volumes of feedings can gradually be increased over the next several days to weeks. Although maximal stomach capacity may be up to 60–80 ml/kg,[9,10] most animals will not tolerate more than 30–40 ml/kg, and each patient needs to be individually evaluated for tolerance of volume per feeding.

### 3.2.2.3 Maintenance of feeding tubes

Monitoring and management of the site and tube are crucial steps in order to keep the tube patent and minimize the risk of future complications. The tube site should be checked daily, kept clean and dry, and bandages surrounding the tube should be changed at least daily or when needed. This will help prevent the development of moist dermatitis, cellulitis, and infection. Antibiotic ointment may be placed around the stoma as well.

The tube should be monitored for migration and loosening of sutures. To do this, a permanent marker line should be made on the tube at the level of the skin to record the position of the tube. It is important to note any erythema or discharge at the stoma site; this may indicate signs of an infection, reported in up to 17% of patients with long-term feeding tubes.[6,11] Sutures can be replaced as needed over time. Lastly, body weight, body condition score, and muscle condition score should be monitored over time to determine if adequate energy requirements for the patient are being met. Adjustments to caloric intake should be made to achieve and maintain an ideal body composition.

### 3.2.2.4 Potential complications of feeding tubes

Complications have been reported to occur in up to 46% of patients with feeding tubes, with no significant difference in incidence between dogs and cats.[6] The most common complication reported for a variety of feeding tubes is tube stoma discharge, often presumptively or definitively diagnosed as a superficial bacterial pyoderma. Necrotic skin around the stoma site has a prevalence of 4.8% and is six times more likely to occur in cats than dogs.[6] This highlights the importance of proper tube management, even after animals begin eating on their own (▶Fig. 3-5). Additional complications can be categorized as mechanical, gastrointestinal, and metabolic.

#### 3.2.2.4.1 Mechanical complications

Mechanical complications include tube migration, premature tube removal, and tube obstruction. Tube migration can be monitored by marking the location of insertion on the tube and visually inspecting the position daily. Premature tube removal can occur for a variety of reasons, especially patient noncompliance and suture failure. This can result in minimal to severe complications. NE/NG tubes and E tubes can be prematurely removed with minimal consequences. However, a tube that is coughed or vomited up through the mouth and chewed off can then be swallowed or aspirated by the patient, which may require surgical removal. Early removal or migration of G tubes can result in septic peritonitis.

Tube obstruction is a commonly reported complication. Causes of tube occlusion include inadequate tube flushing, improperly administered medications, and accumulation of diet within the feeding tube lumen. It is important to ensure that the consistency of the diet to be administered via the tube is appropriate. Adequate flushing is crucial to maintain patency of the feeding tube lumen. For most tubes, flushing with 3–5 mL of water is sufficient. When more tube is exposed, the amount of flush will need to be adjusted accordingly. Tubes should always be flushed after the administration of food, medications, etc. After use, the tube should be capped to maintain the water line in the tube and prevent reflux of gastric contents.

If medications are given through the tube, first determine if they are appropriate for tube feeding and if they can be reconstituted into a solution or suspension. If so, they should be finely crushed or dissolved in water. Some medications not appropriate for administration via feeding tubes include capsules containing enterically-coated beads, extended-release medications, or highly viscous suspensions.

If a tube obstruction does occur, gentle suction can be attempted to clear the tube, or a warm water flush can be applied. In one study, the best solution for diet clot dissolution was a mixture of 0.25 teaspoon Viokase® (pancreatic lipase enzyme), 325 mg of sodium bicarbonate, and 5 mL of warm water.[12] In the same study, carbonated beverages were no more effective at clot dissolution than tap water alone.[12]

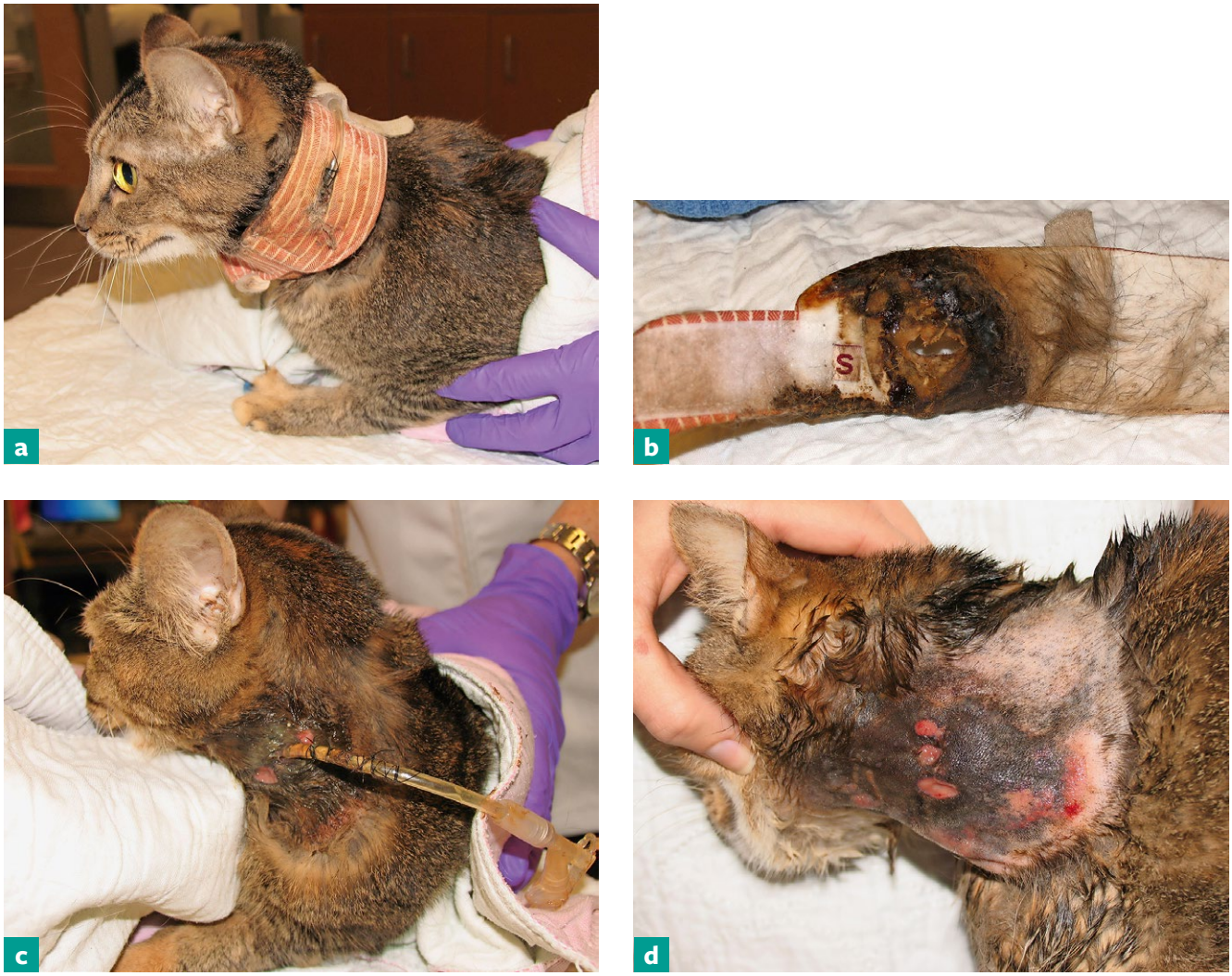



**Fig. 3-5** A 5-year-old spayed female domestic shorthair cat (DSH) had an E tube placed to provide nutritional support while recovering from hepatic lipidosis. The cat began eating voluntarily by mouth, and the tube site was subsequently neglected by the owner.

The cat was presented for evaluation of lethargy and a foul odor (**a**). Upon removal of the cloth collar (**b**), a marked amount of malodorous brown discharge was noted, the skin was thickened, and hyperpigmentation was noted (**c**). The tube was removed, and the site was cleaned (**d**).

#### 3.2.2.4.2 Metabolic complications

Potential metabolic complications include overhydration, electrolyte disturbances, and refeeding syndrome. To prevent overhydration, all dietary water sources should be accounted for, including water used for flushing the tube, water used to mix diets and medications, and the water content of the diet itself. If there is still a water deficit, or if the patient is still dehydrated, after adding up all sources of water intake, additional water may be provided through the tube. If there is an underlying disease that causes a water deficit or predisposes the animal to further dehydration (e.g., chronic kidney disease, diabetes mellitus), then additional water may be supplemented. In these cases, it is imperative to avoid contributing to free water intoxication.[13] Serum electrolytes should be monitored regularly. If hyponatremia develops, it may be necessary to administer a balanced electrolyte solution via the tube.

Refeeding syndrome may occur in cases where prolonged nutrient depletion has occurred. It is typically observed once nutritional support has been reintroduced if the body cannot adapt from a chronically catabolic state to an anabolic one. This syndrome is characterized by hypophosphatemia, hypokalemia, and hypomagnesemia. Altered glucose homeostasis (both hyperglycemia and hypoglycemia) and vitamin deficiencies may also be observed. Anecdotally, it seems as though cats are at greater risk of developing refeeding syndrome than dogs.[14–17]

If there is any concern for a patient developing refeeding syndrome (e.g., prolonged starvation), enteral feedings should be instituted gradually (e.g., 10–15% RER on day 1), and electrolytes should be closely monitored. Electrolyte derangements typically occur within the first week of initiating enteral support. Enteral feeding can be slowly increased to 100% RER over the next 5–10 days, depending on the degree of tolerance and presence (or absence) of electrolyte derangements. Electrolyte supplementation should be administered as needed. In most cases, parenteral replenishment will be provided; however, in some animals that are otherwise stable, enteral supplementation may be attempted.

#### 3.2.2.4.3 Gastrointestinal complications

With any enteral feeding, complications can occur; the most common include nausea, vomiting, abdominal discomfort, or diarrhea. If nausea or vomiting is noted during or shortly after a feeding, decreasing the volume administered and/or increasing the frequency of feedings may alleviate clinical signs. Anti-nausea medications may also be useful. There may be some instances where the fat concentration of the diet is too high for an individual patient, and a lower fat diet may improve gastric emptying time and/or be indicated in cases of pancreatitis.

Some animals will develop diarrhea transiently after initiation of assisted enteral nutritional support. This may be due to a few factors, including osmolality of the diet, as well as fat and fiber concentrations. The osmolality of an enteral diet is most affected by amino acids, small peptides, electrolytes, and simple carbohydrates; thus, calorically dense diets with hydrolyzed nutrients tend to be most hyperosmolar. If soft stool persists beyond the initial 24–48 hour transition period, clinicians should consider supplementing the diet with additional fiber (e.g., psyllium). It is not advisable to put psyllium into a feeding tube due to the risk of clogging it, so it is preferable if the animal will tolerate fiber by mouth. Alternatively, consider switching to a different diet that may be better tolerated.

### 3.2.2.5 Removing the tube

In the hospital, NE/NG tubes can be removed either when the animal begins to eat on its own or when the animal gets transitioned to a longer-term feeding tube (E or G tube). After cutting the suture securing the tube to the face, kink the tube to prevent deposition of gastroesophageal contents in the nasopharynx, and gently pull the tube out of the nose.

For animals with chronic illnesses characterized by hyporexia (e.g., chronic kidney disease), E and G tubes may be properly maintained at home for months to years. For patients that do not require their E or G tubes indefinitely (e.g., feline hepatic lipidosis), it is recommended that the animal be eating its full energy requirement on its own for at least one week and maintaining body weight before removing the tube. During this period of tube inactivity, the tube should be flushed with water q6–12h. When removing an E tube, cut the suture(s), kink the tube to prevent deposition of residual food or fluid from the lumen of the tube into the subcutaneous tissues, and apply gentle traction. The tube site should heal by second intention within a few days, and bandaging is not typically required.

It is typically recommended that G tubes be in place for at least 7–10 days to allow for adequate adhesion formation between the stomach and body wall. Adhesions may form more quickly in healthy dogs and may take longer to form in debilitated animals or those receiving immunosuppressive medications.[18] Specific instructions for removal of a PEG tube will vary slightly depending on the type of tube in place. Either the mushroom tip or the bumper requires some com-

pression or deflation, and firm traction is required to remove the tube. In some instances, the mushroom tip may be either purposefully or inadvertently left in the stomach, and it can be allowed to pass through the intestinal tract (this carries an increased risk for intestinal obstruction in smaller patients), or it can be retrieved endoscopically. The tube site should heal by second intention within a few days, and bandaging is not typically required.



### 3.2.2.6 Conclusions

Provision of adequate calories and nutrients is imperative to provide optimal care to both hospitalized and outpatient dogs and cats. The type of feeding tube chosen and the diet fed should be determined based on each individual animal's nutritional assessment, underlying disease, clinician comfort, and owner preference.

**KEY FACTS**

- Assisted enteral nutritional support should be provided in animals that remain anorectic for >3-5 days despite supportive care.
- Nasoesophageal/nasogastric tubes are optimal tubes for short-term (<1 week) assisted enteral nutritional support.
- An esophagostomy tube is typically the easiest, most cost-effective tube to provide long-term (weeks to months) nutritional support.

**References**

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# 4 Oral cavity

## 4.1 Anatomy and physiology

Ana C. Castejon-Gonzalez,
Alexander M. Reiter

The oral cavity is part of the digestive system. It extends from the lips and cheeks (rostral and lateral) to the hard and soft palate (dorsal), tongue and sublingual tissues (ventral), and palatoglossal folds (caudal).[1,2] Its surface is covered by oral mucosa. The alveolar, vestibular, and oral mucosa of the soft palate is very elastic, with non-keratinized or parakeratinized stratified squamous epithelium. The oral mucosa of the gingiva and hard palate are firmly attached to the periosteum and consist of keratinized squamous epithelium. The transition from the gingiva to loose alveolar mucosa is called mucogingival junction. Draining tracts of dental or periodontal origin frequently open at the mucogingival junction.[1,2]

The teeth are used for prehension, mastication, grooming, and socialization. The shape of the teeth defines their specific function. Incisors cut, canines prehend, premolars prehend and tear, and molar teeth grind. Chewing decreases the size of food particles while increasing their surface exposure to saliva, which initiates deglutition.[1]



Dental formula (adult dog):
I3/3, C1/1, P4/4, M2/3

Enamel, dentin, and cementum are dental hard tissues. Enamel covers the crown of the tooth and is the body's hardest tissue (96% mineralized). It is avascular and, once formed, cannot be repaired. Dentin (70% mineralized) forms the bulk of the tooth. Its production and deposition continue throughout the tooth's life by odontoblasts in the periphery of the pulp.[3] Dentin contains small dentinal tubules (40.000–70.000/mm$^2$) that extend from the periphery of the pulp to the enamel or cementum. The tubules contain odontoblastic processes and scant dentinal fluid, and occasionally nerves. Fluid movement inside the tubules causes pain when dentin is exposed. Wear and fracture without exposing the pulp induce tertiary dentin production to protect the underlying pulp. Tertiary dentin is more irregular than the secondary dentin, has fewer dentinal tubules, and tends to easily absorb pigments, causing a yellow-brown discoloration. Cementum (45% mineralized) is avascular, similar in composition to the bone, and covers the root(s) of the tooth.[1]

The pulp is localized within the tooth's pulp cavity, which contains blood and lymph vessels, nerve fibers, odontoblasts, fibroblasts, and stem cells. The pulp communicates with the periodontal ligament and periapical bone through the apical delta, an accumulation of many small foramina that penetrate the root's apex.[1,2]

Periodontal tissues support and anchor the tooth to the alveolus. The four components of the periodontium are the gingiva, cementum, alveolar bone, and periodontal ligament. The gingiva is attached to the alveolar bone and tooth. The free gingiva of a tooth with healthy periodontium reaches from the tooth's cementoenamel junction to the gingival margin, forming the gingival sulcus (0.5 mm deep in cats, up to 3 mm deep in dogs).[1,3] Integrity of this area is essential for maintaining periodontal health. The periodontal ligament attaches the tooth to the alveolus through horizontally or obliquely arranged fibers that span from the cementum of the tooth to the alveolar bone.[1]



- Dental formula (adult cat): I3/3, C1/1, P3/2, M1/1.
- The lingual molar salivary gland is present only in cats

Saliva lubricates the oral cavity, protects the oral mucosa and teeth, and has immunologic, antimicrobial, and cleansing functions. Saliva is also involved in taste sensation and digestion. The high mineral content and pH of the saliva (pH approx. 7.5–8.5) protects dogs and cats against caries but predisposes their teeth to an increased accumulation of calculus.[2]

The saliva is excreted into the oral cavity through the papilla of salivary ducts (major salivary glands) or small excretory openings in the oral mucosa (minor salivary glands). The major salivary glands are the parotid (its duct opens in the alveolar mucosa dorsal to the maxillary fourth premolar tooth), the zygomatic salivary gland (duct opening in the alveolar mucosa adjacent to the maxillary first molar tooth), and sublingual and mandibular salivary glands (their ducts open in the sublingual caruncle in the most rostral portion of the lingual frenulum). Saliva of the parotid gland is very fluid (serous), whereas that of the mandibular gland is mucoid and more viscous. The sublingual and lingual molar glands (the latter is only present in cats, lingual to the mandibular first molar tooth) produce mixed saliva. The zygomatic salivary gland produces saliva with the highest viscosity.[4]

The tongue is a muscular organ involved in prehension, nursing, and the swallowing of food and liquids. The dorsal mucosa of the tongue consists of cornified stratified squamous epithelium that contains filiform (protection and grooming), fungiform (taste buds), vallate (taste buds), or foliate (taste buds) papillae.[1,2] Impaired mobility or loss of the tongue can have serious consequences for the patient's quality of life, especially in cats.

**KEY FACTS**

- The oral cavity is important for prehension, deglutition, grooming, and socialization.
- The high mineral content and pH of the saliva in dogs and cats protect against caries but predisposes the teeth to increased calculus accumulation.

**References**

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## 4.2 Diseases of the oral cavity

### 4.2.1 Gingivostomatitis

Lara Boland

Feline chronic gingivostomatitis (FCGS) is characterized by chronic oral inflammation, which may be severe and of unclear etiology. Previously used terms include chronic stomatitis, plasma cell stomatitis, and faucitis, among others. The prevalence of FCGS ranges from 0.7–12% of cats.[1,2,3] There is no sex predisposition, and the median age of affected cats is approximately 5–8 years, and most reports involve domestic breed cats.[2,4–8]

#### 4.2.1.1 Etiopathogenesis

The etiology of FCGS may be multifactorial, with inappropriate immune responses to oral antigenic stimulation considered the most likely cause. The response of some cats to immunomodulatory treatments supports the role of an aberrant immune response.[9] Infectious, genetic, and environmental factors may be involved in disease development.[9–12] Multi-cat households appear to be a risk factor for FCGS, possibly due to increased infectious disease risks.[12,13]

Higher levels of $CD8^+$ T-cells compared to $CD4^+$ T-cells, both within oral lesions and in the circulation of cats with FCGS, suggests a cytotoxic cell-mediated immune response, supporting a potential viral etiology.[11,14–16] Low circulating CD4/CD8 ratios indicate an aberrant immune response contributes to the development of FCGS.[14–16]

Several infectious diseases have been investigated as possible causes of FCGS, including oral bacteria, feline calicivirus (FCV), feline herpesvirus 1 (FHV-1), feline immunodeficiency virus (FIV), feline leukemia virus (FeLV), and *Bartonella* species.[17–28] The strongest evidence exists for FCV to be associated with FCGS; however, some reports are that contradictory, presumably due to the use of RT-PCR primers targeting poorly conserved sites in the FCV genome.[9] A recent study of 23 FCGS cats using unbiased metatranscriptomic next-generation RNA sequencing identified FCV as the only microbe strongly associated with FCGS.[9]

#### 4.2.1.2 Clinical presentation

FCGS is distinct from periodontal disease as inflammation extends beyond the mucogingival junction. FCGS causes mild to severe proliferative and/or ulcerated inflammatory lesions involving the mucogingival junction, alveolar and

buccal mucosa, and mucosa of the caudal oral cavity (tissue lateral to the palatoglossal folds, ▶ Fig. 4-1). Lesions can also involve the palate, pharynx, dorsal tongue, and sublingual tissue.[7,10,12] The severity of inflammation is often disproportionate to any concurrent dental disease. Associated clinical signs may include mandibular lymphadenomegaly, halitosis, pain on opening the mouth, ptyalism, inappetence/anorexia, weight loss, pawing at the mouth, and oral bleeding.[6–8,10,12] Duration of clinical signs is often over months to years, with significant impacts on quality of life.[12]

#### 4.2.1.3 Diagnosis and differential diagnoses

Diagnosis is based on the patient history, clinical signs, oral cavity biopsy, and associated laboratory findings. Hematology and biochemistry may show neutrophilia and hyperglobulinemia.[12,14] Histopathology reveals marked epithelial and subepithelial infiltrates of lymphocytes, plasma cells, and variable numbers of neutrophils, Mott cells, and mast cells.[7,10,14] Immunohistochemistry reveals $CD3^+$ T lymphocytes within the epithelium and $CD3^+$ and $CD20^+$ cells within the subepithelial stroma.[14]

Differential diagnoses include other proliferative and/or ulcerative diseases of the oral cavity, such as squamous cell carcinoma, eosinophilic granuloma complex, uremic stomatitis, and acute FCV infection. The suspicion for FCGS may be increased given the chronic disease course and typically symmetrical involvement of the caudal oral cavity.

#### 4.2.1.4 Treatment and prognosis

Spontaneous resolution of FCGS has not been documented. Treatment aims to achieve a cure or reduction in disease severity. Treatment options include the removal of teeth to reduce immune stimulation by removing plaque and medications with anti-inflammatory, immunomodulatory, antiviral, or antibacterial effects.[29] Levels of evidence and the scoring systems used to document responses to treatment vary between studies, making comparisons of different treatments difficult.[29] The variable response rates, particularly the lack of a 100% effective treatment, likely reflect the multifactorial nature of FCGS.[29]

Initial medical management involves routine dental prophylaxis, analgesia, anti-inflammatories (e.g., prednisolone or nonsteroidal anti-inflammatories), and antimicrobials (e.g., clindamycin). These treatments may effect a cure or reduce inflammation and clinical signs in some cases.



**Fig. 4-1** Moderate to marked gingivostomatitis in a cat that persisted despite full-mouth teeth extractions

(Courtesy of Dr. Jane Yu, University of Sydney, Australia.)

##### 4.2.1.4.1 Tooth extraction

In cats that are refractory to routine medical management, the next recommended treatment is tooth extraction with confirmation of root removal. It remains to be studied if early intervention prevents severe progression of the disease.[12] Surgical extractions lead to approximately 67–80% of cats achieving either resolution or significant improvement of lesions, with complete remission in 28–60% and no response in 6–30%.[4,5,10,12] Responses may not differ between cats that have individual premolars and/or molars (partial-mouth extraction) versus all teeth removed (full-mouth extraction).[12,20] Most cats require ongoing supportive care (e.g., anti-inflammatories) for weeks to months following extractions before a complete response to treatment is achieved.[12]

#### 4.2.1.4.2 Cyclosporine

Two studies assessing the use of cyclosporine for FCGS found that 77–100% of cats show significant improvement and/or clinical remission.[6,30] No significant difference in response to cyclosporine was seen between cats with or without dental extractions or those with partial- or full-mouth extractions.[6] Recommended doses vary from 2.5–5 mg/kg q24h PO, and treatment response occurs gradually over 6–12 weeks.[6,30] Cats that enter remission may have treatment discontinued, while those with disease reduction may continue with reduced maintenance doses.



#### 4.2.1.4.3 Interferon

Recombinant feline interferon omega (rFeIFN-ω) has antiviral effects against FCV and other viruses.[31] There are several reports of using rFeIFN-ω in FCGS cats refractory to dental extractions and routine medical management. Most are small case series, and two larger studies compared rFeIFN-ω to corticosteroid treatment.[31–35] Reported are varying doses, treatment lengths, and routes of administration, including oromucosal, subcutaneous, and intralesional rFeIFN-ω. With also varying levels of evidence, most studies report 50% or more of cats showing improvement or cure.[31–35]

A randomized, multicenter, controlled, double-blind study in 39 cats compared topical oromucosal administration of 0.1 MU rFeIFN-ω/day for 90 days to oral anti-inflammatory doses of prednisolone for 3 weeks.[31] During the study, 45% of cats in the rFeIFN-ω group vs. 23% of prednisolone-treated cats were markedly improved or cured, with no significant difference between groups.[31] A prospective study comparing 13 FCV-positive FCGS cats treated with 1 MU/kg rFeIFN-ω SC on days 1, 2, 3, 7, 8, 9, 14, and 21 to four cats treated with 1 mg/kg prednisolone SC on the same days identified the reduced viral load (determined by real-time quantitative PCR) in cats treated with rFeIFN-ω to correlate with improved total stomatitis scores.[33]

#### 4.2.1.4.4 Stem cell therapy

Mesenchymal stem cell (MSC) therapy is a promising immunomodulatory treatment option for refractory FCGS. Stem cell therapies are not yet widely available, and local drug registration regulations may prohibit their use outside research settings.[36] Three pilot studies examined a total of 32 cats with refractory FCGS following full-mouth extractions.[14,15,37] The cats were treated with 2 IV infusions of $20\times10^6$ adipose-derived MSCs at a one-month interval using either autologous or allogeneic MSCs, and either significant improvement or cure was seen in approximately 70% of cats.[6,37] Low $CD8^{lo}$ T-cell levels in the blood prior to treatment were predictive of a positive response.[37] No response to MSCs was seen in 5 cats with FCGS prior to tooth extractions.[38] Good responses occurred in 8 FCGS cats with partial- or full-mouth extractions to a single infusion of cryopreserved allogeneic neonatal MSCs.[39] Uncommon short-term adverse events included increased respiratory rate, vomiting, diarrhea, lethargy, and injection-site leg edema.[14,37,39] One cat developed skin necrosis.[37]

#### 4.2.1.4.5 Laser therapy

Two different dual-wavelength near-infrared laser therapy protocols were used for ten FCGS cats to reduce oral inflammation and found clinical improvements in both groups.[40] Surgical resection and ablation of proliferative inflammatory oral tissue in a cat was performed with a $CO_2$ laser, combined with prednisolone treatment, which cured the disease within 18 months following multiple sessions.[41]

#### 4.2.1.4.6 Other therapies

Other therapies with variable levels of reported evidence include thalidomide and lactoferrin,[42] bovine lactoferrin and piroxicam,[43] dietary ω-6/ω-3 polyunsaturated fatty acids,[4] a *Lactobacillus plantarum* probiotic,[44] Zincreo germicidal astringent obtundent,[45] and local paramunization with PIND-ORF (parapoxvirus ovis).[46]

**KEY FACTS**

- Feline chronic gingivostomatitis causes mild to severe proliferative and/or ulcerated inflammatory lesions with significant impacts on quality of life.
- Treatment options include removing teeth and medications with anti-inflammatory, immunomodulatory, antiviral, and/or antibacterial effects.

**References**

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## 4.2.2 Eosinophilic granuloma complex

Lara Boland

Eosinophilic granuloma complex (EGC) describes a cutaneous, mucocutaneous junction, or mucosal reaction pattern commonly observed in cats and rarely in dogs.[1,2] Hence, this chapter focuses on EGC in cats.

EGC is divided into three distinct clinical subtypes with similar histopathological lesions: indolent (eosinophilic) ulcers, eosinophilic granulomas, and eosinophilic plaques.[3] Histopathological lesions may occur alone or in combination.

### 4.2.2.1 Etiopathogenesis

Most cases of EGC are believed to be due to hypersensitivity reactions, including fleas, food, or feline atopic skin syndrome (FASS).[3–7] Primary bacterial or immune-mediated causes of EGC are unlikely.[8] In a retrospective study of feline dermatologic diseases, only 2.9% of cats were diagnosed with idiopathic EGC.[9] The same study identified approximately one-third of cats with skin disease to have hypersensitivities, including flea, food, mosquito, and FASS. In two other retrospective studies, EGC accounted for 10–11% of feline oral cavity lesions.[10,11]

### 4.2.2.2 Physical examination

Physical examination of cats with indolent ulcers typically reveals unilateral or bilateral upper lip lesions involving the mucocutaneous junction at the level of the upper canines and philtrum. Lesions are well demarcated and vary from small and superficial to extensive deep ulcerations. Lesion margins may be raised, and the ulcerated surface can be erythematous or purulent. Lesions are usually not painful or pruritic.

Eosinophilic granulomas may occur in the oral cavity or elsewhere (chin, caudal thigh). Oral locations include the hard palate, tongue, and lower lip. Lesions are usually well-demarcated and vary from small to extensive, raised to nodular and/or ulcerated erythematous lesions, which may be exudative (▶Fig. 4-2). Hard palate ulcerations can cause acute or chronic hemorrhage requiring blood transfusion and surgical intervention.[12]

Eosinophilic plaques typically involve the ventral abdominal skin and appear as well-demarcated, raised erythematous lesions that may be ulcerated and pruritic.



**Fig. 4-2** Eosinophilic granuloma of the tongue and palate of a cat
Note the extensive raised, erythematous and exudative lesions. (Courtesy of Dr. Nicolle Kirkwood, University of Sydney, Australia.)

### 4.2.2.3 Differential diagnoses

Depending on the appearance, location, and geographic region, differential diagnoses include neoplasia (particularly squamous cell carcinoma), feline herpesviral 1 (FHV-1) dermatitis, cowpox, dermatophytosis, mycobacterial infections, and trauma.[3,11,13,14]

### 4.2.2.4 Diagnosis

Cytology of oral cavity lesions usually identifies eosinophilic inflammation, but mixed inflammation and/or secondary bacterial infection may be observed. Histopathology is required to diagnose EGC. However, identification of the underlying cause requires the collection of a detailed dermatological history. Flea control and dietary elimination trials support the diagnosis. Histopathology may not be warranted in cats with classic upper lip indolent ulcers. However, other oral cavity presentations cannot be differentiated from neoplasia grossly. EGC lesions are rarely reported in dogs, and biopsy is required for diagnosis.

Differential diagnoses can be excluded (dependent on the clinical subtype observed) by the following:

- Malassezia dermatitis: sticky tape preparations
- Mite infestations: skin scrapes
- Dermatophytosis: Wood's lamp examination, trichography, fungal culture
- FHV-1 infection: histopathology, immunohistopathology, PCR
- Neoplasia: cytology, histopathology

Intradermal allergen testing and allergen-specific IgE serology may support a diagnosis of flea allergy or atopy when combined with other findings and treatment responses.[4,15]

#### 4.2.2.5 Treatment

Treatment focuses on identifying and managing the underlying cause, when possible, for example, through strict parasite control and elimination diet trials. The use of $H_1$-receptor antihistamines and/or allergen-specific immunotherapy for FASS has moderate to good efficacy based on limited evidence.[6,15] Cats that do not respond may require immunomodulatory or immunosuppressant drugs.

EGC lesions usually respond rapidly to systemic glucocorticosteroids (1–2 mg/kg PO q24h).[6] Titration to the lowest effective dose for chronic use should be aimed to reduce glucocorticosteroid side effects. Alternative treatments should be considered if this is not possible. Synthetic progestins and depot corticosteroid preparations, although effective, should be avoided if possible due to their diabetogenic and other glucocorticosteroid side effects, which can be prolonged.

EGC lesions usually respond well to treatment with cyclosporine (7 mg/kg PO q24h until clinical signs resolve, then dose q48h to twice a week).[6,16,17] Side effects of cyclosporine include gastrointestinal signs, secondary infections, malignant neoplasia, and gingival hyperplasia.[18–20]

Off-label use of oclacitinib, a Janus-kinase inhibitor, is described in cats with FASS to have good efficacy, although not superior to glucocorticosteroids.[21–23] However, there is limited evidence about the response to treatment, medication side effects, and recommended dose.[6]

Eosinophilic plaques can reduce in size or resolve with amoxicillin-clavulanate, where indolent ulcers show less of a response, likely by treating secondary bacterial infection.[24] The author does not recommend antimicrobials as first-line or sole treatment for EGC, given the suspected allergic etiology and concerns of antimicrobial resistance development.

#### 4.2.2.6 Prognosis

EGC lesions can spontaneously resolve or be recurrent or persistent without appropriate treatment.[25] Treatment can be curative and may be required intermittently or persistently.

**KEY FACTS**

- Eosinophilic granuloma complex describes a cutaneous, mucocutaneous junction, or mucosal reaction pattern, mostly due to a hypersensitivity reaction.
- Treatment focuses on identifying and managing the underlying cause, and immunomodulatory or immunosuppressant drugs may be required.

**References**

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### 4.2.3 Salivary disorders

Ana C. Castejon-Gonzalez,
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#### 4.2.3.1 Introduction

Salivary gland disease is rare in small animals (0.3%), but it should be included in the differential diagnosis list for patients with pain and swelling of the head and neck.

Salivary gland neoplasia is more frequent in cats than in dogs.

Sialocele, sialadenitis, sialolithiasis, sialadenosis, necrotizing sialometaplasia, and neoplasia usually involve the major salivary glands (mandibular, sublingual, zygomatic, and parotid glands). However, the minor salivary glands (distributed within the oral mucosa) can sometimes be affected.[1]

#### 4.2.3.2 Salivary gland diseases

**Sialocele** is an accumulation of saliva in the subcutaneous or submucosal tissue caused by leakage from a salivary gland or corresponding ducts. The leakage results in an inflammatory

reaction in the surrounding tissues. Trauma, foreign bodies, and sialoliths have been identified as causes, although the cause remains unknown in most instances. A possible immune-mediated etiology has also been reported. Young dogs and poodles are predisposed,[2,3] and the monostomatic portion of the sublingual salivary gland is most often affected. Sialoceles can be classified as cervical, pharyngeal, sublingual, or retrobulbar, depending on the location of the swelling. The soft, fluid-filled swelling is often not painful (particularly in chronic stages). However, because sialoceles can be present with sialadenitis, sialadenosis, necrotizing sialometaplasia, and tumors, pain can be present in some cases. Patients with pharyngeal sialocele may show signs of upper airway obstruction, and those with zygomatic sialocele show retrobulbar swelling extending periorbitally.[4,5]

**Sialadenitis** is inflammation of a salivary gland secondary to infection, trauma, or foreign bodies. Pain may be elicited on palpation of the affected region, opening the mouth, or during deglutition. Thick and purulent discharge from the corresponding ducts, sialoliths, and sialoceles might be seen or be developing.[1,2]

**Sialoliths** (composed of calcium carbonate, calcium phosphate, and/or calcium oxalate) and **foreign bodies** can obstruct the salivary duct causing dilation and/or rupture of the duct and sialadenitis.[1,6]

**Sialadenosis** is an idiopathic, painless, non-inflammatory, non-neoplastic enlargement of the salivary glands.[1,7] It tends to be bilateral. The mandibular glands are most frequently affected, but it is not unusual to see an enlargement of multiple glands. The cause is unknown, although autonomous nervous system dysfunction and an unusual form of epilepsy are suggested as possible etiologies.[8,9] Dogs may present with clinical signs of lethargy, anorexia or hyporexia, dysphagia, and weight loss. Retching, gulping, snorting, lip-smacking, hypersalivation, and regurgitation are also reported. A firm cervical swelling (affected mandibular and/or parotid glands) can be palpated on physical examination. When the zygomatic salivary gland is involved, exophthalmos, decreased retropulsion of the eye, and a palpable swelling within the soft palate can be identified.[1]

**Necrotizing sialometaplasia**, also known as salivary gland infarction or necrosis, is characterized by squamous metaplasia of the mandibular gland parenchyma and ducts. Unlike sialadenosis, patients with necrotizing sialometaplasia tend to show pain (on palpation and when opening the mouth) and more severe clinical signs of systemic disease (weight loss, lethargy, and anorexia), respiratory and gastrointestinal disease (retching, gulping, gagging, regurgitation, vomiting, coughing, tachypnea, and increased respiratory effort).[1,2,10] The cause is unknown, but parasympathetic stimulation is believed to contribute to the pathogenesis.

Salivary gland **neoplasia** is uncommon. The disease primarily affects older dogs and cats. The mandibular and parotid glands are most frequently affected, but other glands (including the minor salivary glands of the oral mucosa) can also be affected. Malignant tumors such as simple or mixed adenocarcinomas are most common. Clinical signs and physical examination findings include dysphagia, halitosis, and the presence of a firm mass in the affected region. Adenocarcinoma of salivary glands in the oral mucosa is frequently ulcerative.[11,12]



Young adult dogs are predisposed to sialocele, middle-age dogs to sialadenosis and necrotizing sialometaplasia, and older dogs to sialadenitis and neoplasia.

#### 4.2.3.2.1 Diagnosis

Fine-needle aspiration of sialocele fluid typically reveals a low-cellularity, stringy, clear to blood-tinged to brownish fluid. Because sialoceles can be present with other diseases of the salivary glands, a diagnosis of sialocele does not exclude any of these, and a final diagnosis should be based on the combination of clinical presentation, diagnostic imaging, and other diagnostic test results. Fine-needle aspiration and incisional biopsy of salivary gland tissue can support a presumptive diagnosis. Bacterial culture and sensitivity testing aim to target the antibiotic treatment in cases of infectious sialadenitis.[1,13,14]

Radiography and ultrasonography can identify sialoliths. Sialography can localize the gland and/or duct of origin of a sialocele. Sialoceles are easily diagnosed by ultrasonography. However, CT and MRI can provide more detailed information and show the full extent of salivary disorders. CT and MRI can identify tumors, sialoceles, lesions consistent with sialadenitis (heterogeneous contrast enhancement), and sialadenosis (enlargement with no other abnormality). Differentiating between inflammation and neoplasia is not always possible, and the definitive diagnosis requires a biopsy in these cases.[14,15] Tumor staging (size, lymph node involvement, and distant metastasis) is a prognostic factor in dogs with salivary gland neoplasia.

Determining the salivary gland involved in cervical sialoceles (parotid vs. mandibular or sublingual gland) can be

challenging. Positioning the patient in exact dorsal recumbency may shift the sialocele to the side where it arises. Sialography can also be performed to detect the affected gland and determine the extent of the sialocele. The parotid and zygomatic ducts are easier to cannulate than the mandibular and sublingual ducts.[1] Sialoceles of minor salivary glands have been described in brachycephalic dogs.[16]

The diagnosis of sialadenosis is based on detecting an enlarged gland without abnormal findings on cytology and histology. Diagnostic imaging (CT or MRI) shows gland enlargement with otherwise normal findings.

The diagnosis of necrotizing sialometaplasia is based on clinical signs, fine-needle aspiration and/or biopsy findings, and the exclusion of other gastrointestinal diseases. Diagnostic imaging findings include focal lesions consistent with necrosis or abscess formation. In the presence of esophageal or gastrointestinal signs, the diagnostic evaluation should include testing to rule out causes of vomiting, nausea, and regurgitation.



#### 4.2.3.2.2 Treatment

Recommended treatment for **sialoceles** is sialadenectomy of the affected salivary gland and removing the free saliva by suction. When the mandibular or sublingual glands are involved, both should be removed, as they share the capsule and, in about 30% of cases, also the duct. A ventral or a lateral approach with or without tunneling generally has a good outcome. Recurrence is possible if salivary tissue of the affected gland is not or insufficiently removed. Compared to the lateral approach, the ventral approach increases the exposure of the polystomatic portion of the sublingual gland and the ducts rostral to it.[1,17,18] An intraoral approach can localize the remaining portion of the polystomatic sublingual gland up to the ligature of the ducts from the lateral approach. Parotidectomy is even more challenging because of the gland's scattered appearance and intimate contact of its capsule with the surrounding tissue. Major complications are reported in 35% of the patients.[19] Radiation therapy can be beneficial for incomplete parotid gland resection or recurrent sialocele.[20]

Treatment of **sialadenitis** should be directed against the underlying cause. Fine-needle aspiration, microbial culture, and antimicrobial sensitivity testing of saliva (purulent discharge from the ducts or aspirates) should be performed. Affected patients usually respond to antibiotic treatment, pain management, and anti-inflammatory drugs. Sialadenectomy is recommended in patients with a concurrent sialocele.[1]

Surgical treatment for **sialadenosis** and **necrotizing sialometaplasia** is contraindicated, as it leads to minimal or no clinical improvement. Medical management should include anti-inflammatory and analgesic drugs. Oral administration of phenobarbital (1–2 mg/kg q12h) is reported to result in a rapid improvement (within 72 hours), particularly in sialadenosis-affected dogs.[1,14]

Treatment of **salivary gland neoplasia** aims to achieve locoregional control of the disease by surgically removing the affected salivary gland and regional lymph nodes with or without adjuvant radiation therapy. Complete surgical excision might be difficult if tissues adjacent to the gland are infiltrated and important neurovascular structures are located in the field of surgery. Radiation therapy is indicated if there is residual disease after surgery, histological margins are narrow, or the patient is not a candidate for surgery.[1,12,21]

**KEY FACTS**

- Salivary gland disease arising from the mandibular/sublingual glands is most common, followed by disease of the zygomatic and parotid glands.
- Salivary gland disease, lymphadenopathy, neoplasia, foreign body, and abscess should always be considered as differential diagnoses in dogs and cats with pain and/or swelling in the neck area and/or exophthalmos.
- Advanced diagnostic imaging is recommended before treating salivary gland disease.

**References**

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## 4.2.4 Neoplastic conditions of the oral cavity

Heather Wilson-Robles

### 4.2.4.1 Introduction

Oral tumors are common in dogs and cats, representing 5–7% of all canine cancers and up to 10% of all feline cancers.[1,2] In dogs, the most commonly diagnosed oral tumor is malignant melanoma (MM), followed by squamous cell carcinoma (SCC) and fibrosarcoma (FSA).[3,4] Breeds at increased risk for developing these tumors include cocker spaniels, German shepherd dogs, German Shorthair pointers, Weimaraners, golden retrievers, miniature poodles, chow chows, and boxers.[3–5] Benign oral tumors in dogs arise from the periodontal ligament and represent 5–10% of oral tumors diagnosed. Peripheral odontogenic fibromas are proliferative lesions with an affinity for the maxilla and third premolar teeth that often have intact epithelium.[6,7] Acanthomatous ameloblastoma (AA) is a more aggressive odontogenic tumor that frequently invades the underlying maxilla or mandibular bone.[7,8]



- The most common oral tumor in the dog is malignant melanoma, followed by fibrosarcoma and squamous cell carcinoma.
- Dogs also are commonly affected by benign oral tumors such as a peripheral odontogenic fibroma or acanthomatous ameloblastoma.

Up to 70% of the oral tumors diagnosed in cats are SCC, followed by FSA, representing 13% of oral tumors in cats.[1,9] Domestic shorthair cats are the most commonly affected. However, Maine coon cats, Persians, and British shorthairs may also be at increased risk.[9]



- 70% of oral tumors in cats are squamous cell carcinomas.
- In general, the prognosis for this disease is poor; however, aggressive multimodal therapy can improve survival.

The clinical presentation of oral tumors is similar for both dogs and cats. In many cases, the pet owner will notice a mass or swelling in the mouth or on the face. Other common clinical signs include halitosis, increased salivation, difficulty eating, blood-tinged saliva, and oral pain.[1,2,7,9,10] MM in the dog and oral tumors in cats typically occur in older pets with an average age at diagnosis of 10–12 years, while FSA, epulides, SCC, and osteosarcomas (OSA) tend to occur in slightly younger animals ranging from 7–9 years of age.[1–3,7,9–11]

### 4.2.4.2 Diagnosis and staging

A thorough physical examination is the cornerstone for the diagnosis of many neoplastic conditions, and oral tumors are no exception. It is important to evaluate the patient's face for asymmetry, the regional lymph nodes for asymmetry or firmness, the eyes for retropulsion, and an oral cavity evaluation. In many cases, a sedated oral examination is necessary to thoroughly evaluate the oral cavity, the pharynx, the base of the tongue, and the tonsils. Samples for cytology or histopathology may also be collected at this time. Histopathology is the preferred diagnostic tool for many oral tumors as MM in the dog and SCC in both the dog and cat are often associated with significant inflammation and necrosis.

Undifferentiated and non-pigmented MM may be particularly difficult to differentiate from other oral sarcomas and require immunohistochemical stains. Melan-A, PNL2, and tyrosinase-related proteins 1 and 2 have demonstrated high sensitivity and specificity for the diagnosis of canine oral MM and may be used to differentiate this disease from other oral tumors.[17]

Imaging plays a major role in the work-up for oral tumors regardless of species or tumor histology. Radiographs of the skull and dental radiographs may help determine bone involvement. However, they are difficult to interpret and limited as radiographic evidence of bone lysis is not evident until 40% or more of the cortex has been destroyed.[18] Computed tomography (CT) imaging is a far more sensitive tool for determining the extent of disease, regional lymph node size, and surgical planning and is recommended in most cases with oral tumors.[18] Additionally, the ability to map sentinel lymph nodes using CT can be an invaluable tool for staging oral tumors in dogs and cats (▶ Fig. 4-3).[12]

Diagnostic imaging of the lungs should be performed in all cases diagnosed with a malignant tumor. This may include 3-view thoracic radiographs or thoracic CT.

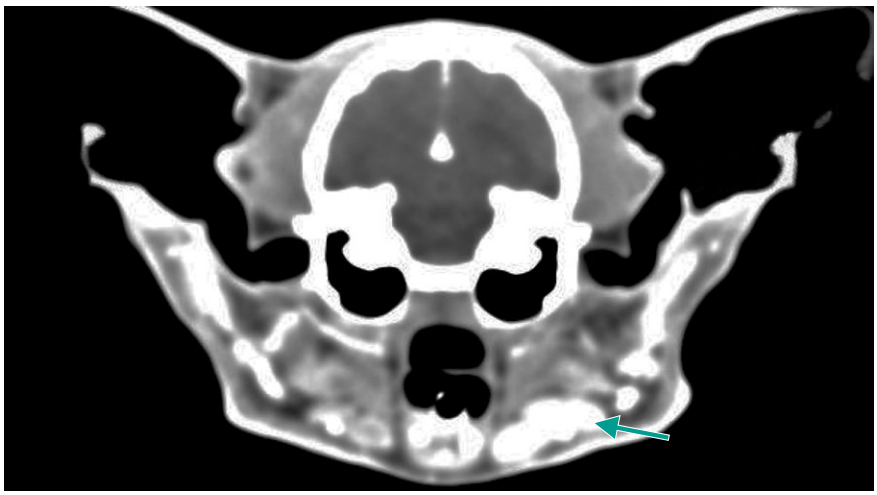


**Fig. 4-3** Computed tomography (CT) image of a cat with a buccal carcinoma after lymph node mapping

A contrast medium was injected around the primary tumor, and serial CT images were obtained to demonstrate the lymphatic drainage of the tumor to the submandibular lymph node (**arrow**).



**Tab. 4-1** Biologic behavior of common oral tumors in dogs and cats.[1–3,5,11,16,21,23,26,29,33,34]

| Species | Tumor type | Bone invasion | Regional metastasis | Distant metastasis | Prognosis |
|---|---|---|---|---|---|
| Canine | **MM** | Common (>50%) | Common (>60%) | Common (>60%) | Guarded to fair |
| | **SCC** | Very common (>75%) | Rare, except for tonsillar SCC (>75%) | Rare, except for tonsillar SCC (>30%) | Good, except for tonsillar SCC |
| | **FSA** | Common (>60%) | Rare (<30%) | Rare (<20%) | Guarded to fair |
| | **Epulides** | Rare, except for AA (>80%) | None | None | Excellent |
| Feline | **SCC** | Common | Moderate (~ 35%) | Rare | Poor to guarded |
| | **FSA** | Common | Rare | Rare | Poor to guarded |

**MM** = malignant melanoma, **SCC** = squamous cell carcinoma, **FSA** = fibrosarcoma, **AA** = acanthomatous ameloblastoma

Regional lymph node aspirates should be performed in all cases where a malignant tumor has been diagnosed regardless of size (▶Tab. 4-1). Up to 50% of metastatic oral melanoma lymph nodes will be normal in size.[10] Typically, retropharyngeal lymph nodes are only aspirated if they are enlarged due to their location and relative inaccessibility. However, diagnostic imaging remains a poor way to detect metastasis in this particular lymph node center.[19–21]

#### 4.2.4.3 Treatment

Surgery is the mainstay of therapy for most oral tumors, though complete margins may be difficult to achieve, given the size of the animal and the size and location of the tumor. The underlying bone must be removed for all tumors associated with the maxilla or mandible, with the exception of peripheral odontogenic fibromas, where the tooth and associated dental ligament should be removed. In general, dogs tolerate oral surgery very well; however, feline patients experience increased morbidity and mortality associated with large oral surgeries.[22] Recently, the dogma associated with poor outcomes in cats after radical mandibulectomy has been challenged. Survival times >700 days have been reported in cats with SCC undergoing radical mandibulectomy.[23] All cats require a feeding tube postoperatively, but >80% will regain the ability to eat on their own with time.[22,23]

Radiation therapy is another mainstay of local therapy for oral tumors in cats and dogs. Radiation therapy can be used as adjuvant therapy after incomplete excision of a primary tumor, in the neoadjuvant setting to improve surgical outcomes, or as the primary therapy with either definitive or palliative intent. In dogs, MM, SCC, and epulides are known to be responsive to radiation therapy.[10,24–27] Radiation therapy alone appears to be less effective for feline oral tumors, though it may be used in an adjuvant setting or for palliation.[27–31]

Chemotherapy is often used in the adjuvant setting for malignant oral tumors in dogs and cats. Carboplatin has been used to treat MM, SCC, and OSA in dogs and SCC in cats.[10,29,30,32,33] Toceranib phosphate has demonstrated a modest benefit in cats with oral SCC, especially when used in conjunction with nonsteroidal anti-inflammatory agents (NSAID).[34]

#### 4.2.4.4 Prognosis

The prognosis for most malignant oral tumors in dogs and cats is poor to guarded (▶Tab. 4-1). However, implementing multimodal therapy or aggressive surgery can improve outcomes in those patients with locally aggressive tumors.[23,25,31] The prognosis for benign tumors of the oral cavity remains excellent with local therapy.[7,8,11]

**KEY FACTS**

- Oral tumors are common in dogs and cats.
- A sedated oral examination and advanced diagnostic imaging are often necessary for complete staging.
- In many cases, the underlying bone must be removed with the primary tumor for complete margins.

**References**

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# 5 Esophagus

## 5.1 Anatomy

Joao Felipe de Brito Galvao

The esophagus begins at the upper esophageal sphincter (UES; pharyngoesophageal sphincter), comprised of the cricopharyngeus and thyropharyngeus muscles. The cervical portion of the esophagus lies dorsally and to the left of the trachea. The thoracic portion of the esophagus extends from the thoracic inlet to the diaphragmatic hiatus. The esophagus is positioned dorsal to the trachea at the carina, where it then crosses the midline and is positioned to the right of the aortic arch. From here, it is located very close to the median plane as it passes between the caudal lung lobes. The short abdominal portion of the esophagus lies in the abdominal cavity between the diaphragm and stomach.

The esophageal wall is thickest in the cervical (~4 mm) and abdominal portions (~6 mm). The thoracic esophagus is approximately 2.5 mm thick. The esophagus consists of four layers: adventitia, muscularis, submucosa, and mucosa.

The canine muscular layer is comprised of two oblique layers of striated muscle throughout its entire length. These continuous oblique bundles spiral around the esophagus and cross at right angles, thus making up the two main muscular layers. Approximately 5–10 cm from the cardia, the muscle fibers of the inner layer become more transversely oriented while those of the outer layer become more longitudinal.

The gastroesophageal sphincter comprises an outer layer of longitudinal striated muscle and an inner circular smooth muscle layer. These longitudinal striated fibers continue and partially blend with some of the gastric smooth muscle fibers.

The only smooth muscle in the canine esophagus is the muscularis mucosae, which contributes little, if anything, to peristalsis.

The submucosal layer loosely attaches the mucosal and muscular layers and contains mucus glands. In the dog, this loose connection allows the relatively inelastic mucosal layer to be thrown into longitudinal folds. There are approximately ten primary longitudinal folds, which confers great distensibility to the esophagus. The least distensible areas occur at the beginning, as it passes through the thoracic inlet, and at the end.

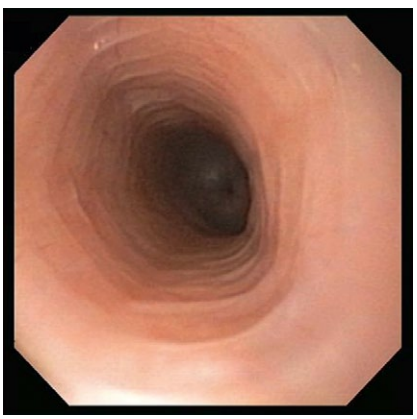


**Fig. 5-1** Endoscopic view of the distal esophagus in a cat

Note the characteristic "herringbone" appearance of the mucosa. (Courtesy of Prof. Dr. Romy Heilmann, University of Leipzig, Germany.)

In the cat, the tunica muscularis is comprised of striated muscle cranial to the base of the heart, whereas caudal to the heart, it is comprised of smooth muscle. The feline gastroesophageal sphincter consists solely of smooth muscle.

The mucosal layer contains longitudinal and transverse folds from the level of the heart base distally. This combination of longitudinal and transverse folds gives the mucosal layer of the esophagus of the cat its characteristic "herringbone" pattern (▶Fig. 5-1).

The mucosal layer comprises cornified, stratified squamous epithelium, which contains openings of the ducts belonging to the submucosal glands.

Branches of the cranial and caudal thyroid arteries serve as blood supply to the cervical portion of the esophagus. The esophageal portion of the bronchoesophageal artery supplies the cranial two-thirds of the thoracic portion of the esophagus, the remaining third being supplied by branches of the dorsal intercostal arteries. The terminal portion of the esophagus receives its blood supply by a branch of the left gastric artery. Venous drainage occurs via satellites of the arteries that supply it. These veins mostly empty into the azygos vein. Lymphatic vessels from the esophagus drain into various lymph nodes, including the retropharyngeal, mediastinal, bronchial, and portal nodes. Lymphatics and lymphatic vessels of the esophagus lie in the submucosal layer.

Branches of the vagus nerve innervate the striated muscle of the UES and esophageal body. The dorsal branches of both right and left vagal nerves run dorsocaudally across the side of the thoracic esophagus and unite with each other on the dorsum of the esophagus, 2–4 cm cranial to the dorsal part of the esophageal hiatus. The right and left ventral branches of the vagi unite immediately caudal to the root of the lungs to form the ventral vagal trunk. This trunk at first lies in contact with the esophagus and then arches ventral in the caudal mediastinum before it passes through the esophageal hiatus with the esophagus. The vagus nerve also contains autonomic nerves to the smooth muscle and visceral afferents from sensory receptors. Sensory innervation distributes to the spinal segments C1–L2, with the cervical portion reaching segments C2–C6 and T2–T4, the thoracic portion reaching segments T2–T4 and T8–T12, and the lower esophageal sphincter (LES) reaching segment T1–L3.

Sympathetic nerves also innervate the esophagus.[1-3]



The distribution of the feline sensory innervation includes C1–T8 for striated muscle, C5–L2 for smooth muscle, and T1–L3 for the lower esophageal sphincter.

## References

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## 5.2 Physiology

Joao Felipe de Brito Galvao

Swallowing consists of sequential well-coordinated events that carry ingested material from the mouth to the stomach. This process has been divided into three major phases: oropharyngeal, esophageal, and gastroesophageal.

The **oropharyngeal phase** is further subdivided into oral, pharyngeal, and cricopharyngeal stages. The oral stage of the oropharyngeal phase begins with the prehension of food and the formation of a bolus in the oropharynx, which is then passed to the base of the tongue. This bolus stimulates a series of pharyngeal contractions that move the bolus into the laryngopharynx, which is the pharyngeal stage. At this time, all other pharyngeal openings are closed (the oral cavity, the nasopharynx, and the opening of the trachea) by the actions of various muscle groups and movement of the tongue. These reflex events are initiated by stimulation of various sensory receptors in the laryngopharynx, for which the nerve fibers are located in branches of the trigeminal, glossopharyngeal, and laryngeal nerves. Once the bolus of ingested material is in the oropharynx, the cricopharyngeal and thyropharyngeal muscles relax to allow passage of the bolus into the cranial esophagus. This sphincter closes promptly after passage of the bolus and remains closed at all other times. Once the bolus has passed into the esophagus, the **second, or esophageal, phase** of swallowing begins. The peristaltic wave that started in the pharynx continues and is propagated throughout the esophagus carrying the bolus aborally to the stomach. This peristaltic wave is termed primary peristalsis. A secondary peristaltic wave can be generated via local esophageal distention to carry out the passage of the bolus into the stomach if the primary peristaltic wave is inadequate. The third and **final phase** of swallowing is the relaxation of the gastroesophageal sphincter (GES), which allows passage of the bolus into the stomach. The GES then contracts again to prevent reflux of material back into the esophagus.

Swallowing is mediated by a long and complex neural arc. Sensory receptors in the esophagus trigger the reflex response via visceral afferent fibers in the trigeminal, vagus, and glossopharyngeal nerves. These impulses are integrated in the nuclei solitarius and ambiguous, and the swallowing center in the lateral reticular formation. The efferent neurons from the dorsal vagal motor nucleus pass to the pharyngeal and esophageal musculature via the trigeminal, facial, glossopharyngeal, vagus, and hypoglossal nerves.[1-4]

**References**
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## 5.3 Diseases of the esophagus

### 5.3.1 Cricopharyngeus muscle dysfunction

Romy M. Heilmann, Stanley L. Marks

Cricopharyngeus muscle dysfunction (CPMD) is an umbrella term that reflects poor compliance through the pharyngoesophageal segment. CPMD occurs secondary to abnormal function of the cricopharyngeus muscle that constitutes a major portion of the upper esophageal sphincter. The disorder is associated with **cricopharyngeus muscle achalasia** (**CPA**) caused by **impairment of maximal opening diameter of the upper esophageal sphincter** (**UES**) or **cricopharyngeus muscle dyssynchrony** (**CPD**) caused by incoordination of the UES opening with bolus presentation. The latter can be caused by a reduction in pharyngeal driving pressure or impairment of hyolaryngeal complex elevation. The common denominator with CPA and CPD is delayed or reduced bolus transit through the pharyngoesophageal segment.

Cricopharyngeus muscle dysfunction occurs in dogs with a predisposition for miniature dachshunds, Maltese, toy poodles, springer spaniels, and cocker spaniels. A hereditary cause of cricopharyngeus muscle dyssynchrony has been identified in golden retrievers, and segregation analysis suggests that a single recessive allele of large effect contributed to the expression of this disease in the breed.[1]

#### 5.3.1.1 Clinical presentation

CPMD is a congenital or acquired neuromuscular disorder of the UES. CPA and CPD are typically recognized in puppies prior to weaning; however, CPD can also present in middle-aged to older dogs subsequent to developing pharyngeal weakness. Pharyngeal weakness can cause delayed propulsion of the bolus through the UES, with subsequent asynchrony between pharyngeal contraction and relaxation of the UES.

Affected animals demonstrate progressive swallowing impairment that is typically worse when drinking water.[2–4] Clinical signs are characterized by repeated swallowing attempts, gagging, retching, and nasal regurgitation. Additional clinical signs include food falling from the mouth while the animal attempts to swallow, hypersalivation, and coughing due to aspiration. Affected puppies can be normal in size or small for their breed and age.

**NOTE**
The clinical signs of dogs with cricopharyngeus muscle achalasia are indistinguishable from those of cricopharyngeus muscle dyssynchrony.

#### 5.3.1.2 Diagnosis

A thorough patient history is vital. Suspected patients should be carefully observed while eating (both kibble and canned food) and drinking, which should confirm the presence of oropharyngeal dysphagia, given the inherent differences in clinical signs compared to animals with esophageal dysphagia. Of most importance, swallowing impairment in dogs with CPMD occurs within seconds of deglutition, unlike most dogs with esophageal dysphagia, in which dysphagia is more delayed. The physical examination is usually unremarkable. A complete neurological examination with careful evaluation of the cranial nerves is important to rule out an underlying generalized neuromuscular disorder (e.g., myasthenia gravis, muscular dystrophy, inflammatory myopathy, or polyneuropathy).

Routine clinicopathologic results are usually unremarkable. However, a neutrophilic leukocytosis with or without a left shift can be observed in animals with aspiration pneumonia. A thyroid panel (i.e., serum total and free T4, endogenous thyroid stimulating hormone [TSH], and anti-thyroglobulin antibody concentrations) should be performed to rule out hypothyroidism.[5] Serology for acetylcholinesterase receptor antibodies helps exclude acquired myasthenia gravis. Measurement of serum creatine kinase (CK) concentration should routinely be performed to interrogate for a polymyopathy. Exploring the oropharynx under sedation or anesthesia is essential to detect a foreign body, cleft palate, oropharyngeal neoplasia, and laryngeal paralysis.

Diagnostic imaging (i.e., survey radiographs of the thorax and neck, computed tomography [CT], and/or magnetic resonance imaging [MRI]) is important to evaluate the dog for other causes of dysphagia (e.g., foreign bodies, myositis, neoplasia), concurrent conditions (e.g., esophageal hypomotility, megaesophagus ▶Chap. 5.3.8), or complications (e.g., aspiration pneumonia). Electrodiagnostic testing,

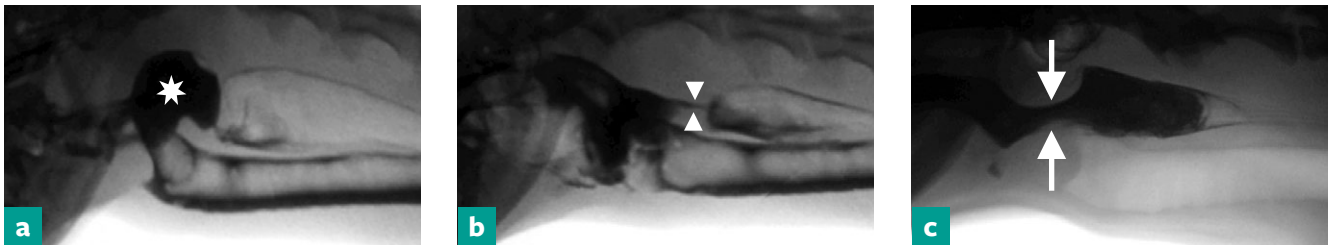



**Fig. 5-2** Videofluoroscopic examination of the pharynx and proximal esophagus (single frame images) in a dog with cricopharyngeus muscle achalasia

**a, b** Oral administration of liquid barium is followed by pooling of the liquid bolus in the oropharynx (**asterisk**) and delayed passage of a small amount of the bolus through the noncompliant cricopharyngeal muscle (**arrowheads**) into the esophagus. Notice the aspiration of barium into the trachea.

**c** A healthy dog can pass a complete liquid bolus through the relaxed cricopharyngeus muscle (**arrows**) into the proximal esophagus.

(Modified from: Heilmann RM, Marks SL; 2019[13] with permission from Wiley).



including electromyography (EMG) and nerve conduction velocity (NCV) measurement, should be considered based on neurological examination and laboratory results.

A videofluoroscopic swallow study with standardized concentrations of liquid barium (▶Fig. 5-2) and both canned food and kibble mixed with barium in the non-sedated, standing, or seated patient is required to confirm the diagnosis of CPMD (i.e., restricted transsphincteric passage, distorted shape and distension of the pharynx, repeated pharyngeal contractions with small streams of contrast entering the esophagus, pharyngeal weakness, and prolonged time to proximal esophageal sphincter opening) and differentiate CPA from CPD.[6–8] Many affected dogs with CPA have a prominent cricopharyngeal "bar" visible on videofluoroscopy, a radiologic descriptor of a posterior impression at the pharyngoesophageal segment (▶Fig. 5-3).

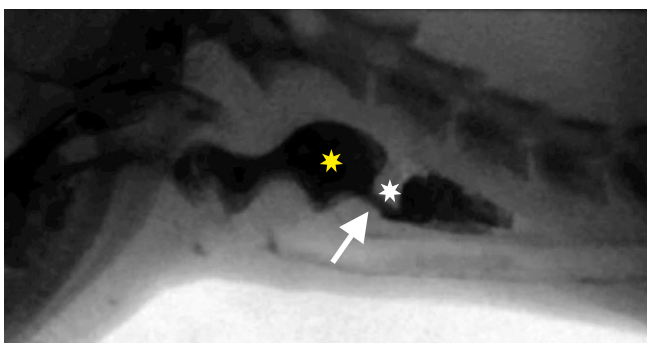


**Fig. 5-3** Videofluoroscopic swallow study in a 7-month-old female miniature dachshund with severe dysphagia secondary to cricopharyngeus muscle achalasia

The pharynx (**yellow asterisk**) is filled with liquid barium with a prominent posterior impression at the pharyngoesophageal segment due to a cricopharyngeal "bar" (**white asterisk**) obstructing the movement of the bolus from the pharynx into the proximal esophagus. Notice the attenuated column of barium being squeezed through the narrow opening of the upper esophageal sphincter (**arrow**).

### 5.3.1.3 Treatment and prognosis

It is pivotal that dogs are carefully screened for systemic disease prior to surgical intervention, and that hydration status and aspiration pneumonia are adequately managed. Definitive treatment for CPMD involves **surgical transcervical cricopharyngeal myectomy or myotomy** with or without a partial or complete thyropharyngeal myotomy.[3,9] A bilateral approach is recommended, given the higher incidence of recrudescence following a unilateral procedure.[4] A closed endoscopic $CO_2$ laser cricopharyngeal myotomy is being increasingly utilized, with reduced anesthesia time and morbidity compared with the more traditional transcervical approach.[10] However, the transcervical (open) approach affords a more complete dissection and collection of muscle for histopathologic assessment. Reported success rates are highly variable, ranging from 40–100%, and dogs with CPA tend to have a good response.[3,4,9]

The removal of virtually the entire UES will increase aerophagia markedly with subsequent gastric distention, belching, and flatulence for up to 12 months post-myectomy. The placement of a gastrostomy tube (▶Chap. 3.2.2.1.3) during anesthesia will facilitate the removal of air during the recovery period and prevent contamination of the surgical site with food and water during the first week post-operatively. Removal of the gastrostomy tube should be predicated on decreased volumes of air being aspirated from the stomach, and owners should be advised of the potential for prolonged placement of the gastrostomy tube. It is not recommended to place an esophagostomy feeding tube (▶Chap. 3.2.2.1.2)

in lieu of a gastrostomy tube due to the higher likelihood of esophageal reflux of food and subsequent contamination of the surgical site.

Dilation of the UES and cricopharyngeus muscle with a balloon over a guidewire affords precise dilation under direct vision with an endoscope placed in the pharynx. In patients with severe obstruction, a series of three dilations separated by 2–3 weeks can be performed. In light of the kidney-shaped UES, **balloon dilation** is better facilitated using two 15–16–18 balloons adjacent to one another, which provides more successful outcomes than single dilation using a 20 mm balloon.

Botulinum toxin injection into the cricopharyngeus muscle can provide temporary relief (2–4 months) following injection under direct laryngoscopic visualization or via fluoroscopic and/or electromyographic guidance (45 IU, split into injections at three different regions of the cricopharyngeus muscle). The authors have moved away from the routine use of botulinum toxin injection for CPMD in dogs for several reasons, including the temporary benefit of the drug, the potential for dispersal of the toxin into the hypopharynx or cervical esophagus, exacerbating the dysphagia, and the fact that a lack of improvement following botulinum toxin administration does not preclude success following surgical myotomy. The authors do not advocate the administration of the phosphodiesterase inhibitor sildenafil for the management of CPMD because the drug will only affect the smooth muscle of the lower esophageal sphincter (LES). Sildenafil has limited application for the management of esophageal achalasia in people and dogs in which the LES fails to relax.[11,12]

Malnutrition must be avoided. An altered feeding position (Bailey chair) is usually not effective, but kibble diets are often better tolerated than canned food or water. The authors recommend maintaining hydration status by feeding beef or chicken-flavored ice cubes or adding flavored thickeners containing modified cornstarch and maltodextrin to water. Gastrostomy tube feeding is a viable option to manage dogs with CPMD in lieu of surgical intervention or for dogs with a concurrent esophageal stricture (▶Chap. 5.3.5), megaesophagus, or after failed surgical correction. CPMD associated with hypothyroidism will likely respond to L-thyroxine supplementation.[5]

CPMD has a moderate prognosis for cure with successful surgery. However, recrudescence of clinical signs of swallowing impairment has been recognized in some dogs 3–4 months following apparent successful surgical intervention. The prognosis is guarded to poor in dogs with severe pharyngeal weakness and in dogs with failed surgical correction.

**KEY FACTS**

- Cricopharyngeus muscle dysfunction (CPMD) is an umbrella term that reflects poor compliance through the pharyngoesophageal segment. For diagnosis, a thorough patient history is vital, as well as a thyroid panel to rule out hypothyroidism.
- A videofluoroscopic swallow study with liquid barium is required to confirm the diagnosis of CPMD and differentiate cricopharyngeus muscle achalasia from cricopharyngeus muscle dyssynchrony.
- Definitive treatment for CPMD involves surgical transcervical cricopharyngeal myectomy or myotomy.

**References**

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## 5.3.2 Esophagitis

Joao Felipe de Brito Galvao

Esophagitis is an acute or chronic inflammatory disorder of the esophageal mucosa. The disease process may occasionally extend into the submucosal and muscular layers when severe. Esophagitis can result from persistent vomiting, foreign body obstruction, pill-induced in cats (e.g., doxycycline, clindamycin), ingestion of corrosive or caustic substances, thermal burns, infectious agents, gastric hyperacidity (e.g., Zollinger-Ellison syndrome), hiatal hernia (▶Chap. 5.3.9), eosinophilic inflammation, esophageal neoplasia (▶Chap. 5.3.12), and, most commonly, gastroesophageal reflux (GER ▶Chap. 5.3.3; e.g., during general anesthesia).[1–7] The esophageal mucosa has a barrier function to prevent damage by various substances, including gastric acid. This barrier function is provided by the stratified squamous epithelium, tight junctions between the epithelial cells, the mucus layer, prostaglandin production, surface bicarbonate ions, and peristaltic clearance of material from the esophagus.[8]

### 5.3.2.1 Clinical presentation

The clinical signs are often related to the severity and depth of inflammation. Characteristic signs include dysphagia, ptyalism, regurgitation, gagging, varying degrees of inappetence, repeated swallowing motions with extension of the head and

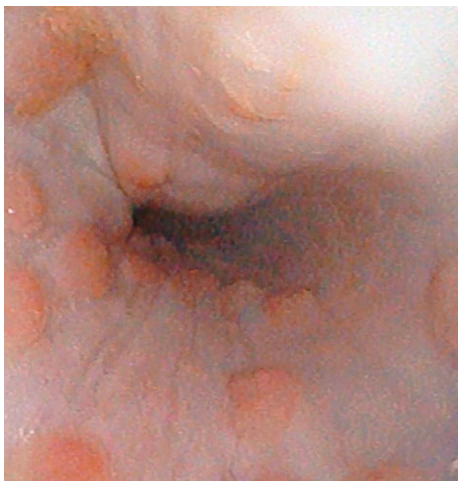


**Fig. 5-4** Esophagitis: Endoscopic image of the esophagus of a 6-year-old spayed female Pekinese with chronic intermittent vomiting

Note the hyperemic, nodular to plaque-like lesions, indicating esophagitis.

(Courtesy of Prof. Romy Heilmann, University of Leipzig, Germany.)

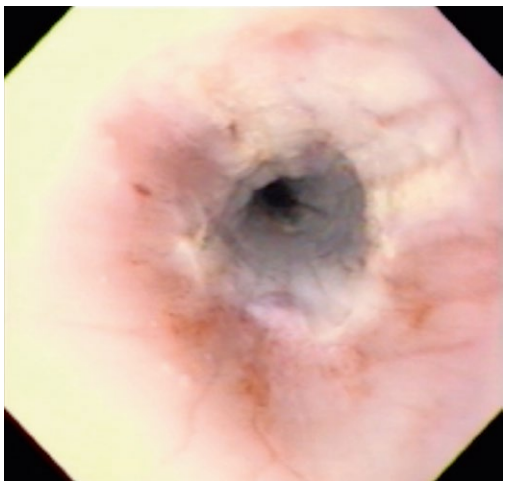


**Fig. 5-5** Esophagitis: Endoscopic view of the proximal esophagus of a 17-year-old spayed female domestic shorthair cat with protracted vomiting of 4 days' duration

Note the longitudinal lines of acid reflux, thickening, lack of distensibility, and hyperemia indicating esophagitis.



neck, odynophagia, lethargy, and weight loss.[2–4] A barium esophagram (▶Chap. 1.4.3) performed under fluoroscopy may show GER, segmental dilation of the esophagus, an irregular esophageal mucosa, and/or decreased esophageal motility.[2,3] A definitive diagnosis is made via endoscopy and histopathology. During endoscopy, the mucosa may appear hyperemic and irregular, and polypoid masses, nodules (▶Fig. 5-4), and/or ulcerations with spontaneous bleeding may be seen (▶Fig. 5-5).[2–4,9] Loss of distensibility of the esophagus is characteristic of chronic esophagitis. The esophagus can be difficult to biopsy with standard instruments due to its rigid stratified squamous epithelium. However, abnormal, eroded, ulcerated, or proliferative esophageal lesions can generally be biopsied easily.[2,9] Histopathology may show an eroded, ulcerated, hyperplastic, or dysplastic epithelium, and/or lymphocytic, plasmacytic, or neutrophilic infiltrates of the submucosa.[2,3]

### 5.3.2.2 Treatment and prognosis

Various medical therapies are recommended. **Gastric acid suppression** is the most important therapy and is best accomplished using a proton pump inhibitor (e.g., omeprazole 1.5–2 mg/kg PO q12h).[10] Prokinetic agents are also recommended to increase lower esophageal sphincter tone and promote gastric emptying, thus decreasing the amount of GER.[2,3,5] Metoclopramide (0.2–0.5 mg/kg PO q8–12h) and cisapride (0.2–0.5 mg/kg PO q8–12h) have been used for this purpose. Several compounding pharmacies offer cisapride as it is no longer available in human medicine. Ranitidine and nizatidine stimulate gastrointestinal motility by inhibiting acetylcholinesterase activity and M3-muscarinic agonist activity and may be useful for promoting gastric emptying in patients with esophagitis.[11] Oral sucralfate suspension (0.25–1.0g/cat or dog PO q6–8h) is also recommended.[12] Sucralfate has cytoprotective properties when bound to an eroded or ulcerated site.[13,14] However, sucralfate theoretically requires an acid pH to adhere to the ulcerated area, and there are no clinical studies showing that sucralfate is effective in patients with esophagitis.

Eosinophilic esophagitis is a rare form of esophagitis in companion animals.[15] The treatment of choice for eosinophilic esophagitis, described in one dog and a cat, is systemic glucocorticoid and elimination diet therapy.[6,16]

The prognosis of esophagitis varies with the severity and the underlying cause. The development of an esophageal stricture is a potential sequela (▶Chap. 5.3.5).

## References

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### 5.3.3 Gastroesophageal reflux

Joao Felipe de Brito Galvao

Gastroesophageal reflux disease (GERD) is one of the most commonly diagnosed gastrointestinal disorders in humans. In contrast, GERD has been considered an uncommon disorder in dogs and cats but is likely more common than previously assumed.[1–4] One study showed that 17% of dogs undergoing general anesthesia had acid (pH <4) gastroesophageal reflux (GER).[5] Another study showed 55% of dogs undergoing ovariohysterectomy had GER.[6] GER is caused by relaxation of the lower esophageal sphincter (LES) leading to reflux of gastric material into the esophagus. Varying degrees of esophagitis (▶Chap. 5.3.2) may result. Refluxed material may contain acid, pepsin, or even trypsin and bile acids, which can damage the esophageal mucosa. The frequency and content of the reflux determine the severity of the condition.[7] Gastric acid alone often causes mild esophagitis, whereas acid combined with pepsin, trypsin, and/or bile acids can lead to severe esophagitis, and the more frequent the contacts, the more likely esophagitis is to develop.[2,4] The **most common cause** of GER is **general anesthesia**, especially in those animals undergoing intra-abdominal procedures.[1,2,4,8,9] Other disorders such as chronic vomiting, hiatal hernia, laryngeal paralysis, brachycephalic upper airway obstruction, and esophageal foreign body may also predispose an animal to GER, but GER may also be idiopathic.[1,3,4,10]

#### 5.3.3.1 Clinial presentation

Clinical signs of GER may mimic those of esophagitis. Animals with mild GER may regurgitate small amounts of material and may be seen to eructate, followed by swallowing movements, or may even be completely asymptomatic. Regurgitation, odynophagia, multiple attempts at swallowing with extension of the head and neck, and ptyalism may all be seen with moderate to severe disease.[2,3] The pet owner should be carefully asked whether the animal has recently undergone general anesthesia. Physical examination is often unremarkable, and results of the minimum database, including thoracic radiographs, are often within normal limits. Laryngeal dysfunction has also been described as a potential consequence of GERD.[11]

#### 5.3.3.2 Diagnosis

A definitive diagnosis is made with a combination of contrast videofluoroscopy and endoscopy. Contrast videofluoroscopy can demonstrate reflux of gastric contents into the distal esophagus, decreased esophageal motility, and potentially reveal evidence for an underlying condition, such as a hiatal hernia (▶Chap. 5.3.9).[2,3] A radiotelemetric pH capsule (e.g., Bravo pH system) can be placed in the distal esophagus for continuous pH recording.[12] A sliding hiatal hernia may become apparent by applying gentle pressure to the abdomen. Radiograph-assisted esophagram should not be used to rule out GER. Endoscopy may be normal, but if esophagitis is present, varying degrees of mucosal hyperemia, irregularity, and/or erosion or ulceration may be seen.[2,3] Various agents used to pre-medicate and induce animals for general anesthesia can decrease LES tone, which must be considered when an open LES is seen during endoscopy.[9,13] Certain drugs like morphine prior to anesthesia can also significantly increase the incidence of GER during the subsequent anesthetic episode.[14] Feeding 3 hours prior to anesthesia also significantly increases the odds of a GER event.[15]

#### 5.3.3.3 Treatment

Treatment for GER is similar to that for esophagitis. Addressing the esophageal damage is important, as is reducing gastric acidity and promoting an increase in LES tone and gastric emptying.

Therefore, a proton pump inhibitor along with a prokinetic agent should be administered.[2,3,16–18] The incidence of strongly acidic reflux in dogs decreased from 55% to 7% with the administration of omeprazole at 1 mg/kg PO in the evening and 3 hours before anesthesia.[6] One dose of omeprazole did not significantly improve GER and esophageal acid pH compared to the control group.[6] Cats also benefited from two doses of omeprazole (1.45–2.2 mg/kg PO q12h) prior to anesthesia, which improved the pH and frequency of GER.[19] Esomeprazole given at 1 mg/kg IV 12–18 hours and 1–1.5 hours prior to anesthesia did not decrease the frequency of GER events but significantly increased the GER pH.[20] The combination of 1 mg/kg cisapride (also given in two doses) and esomeprazole IV decreased the number of reflux events and improved GER pH.[20] The mean percentage of procedure time that the esophageal pH was <4.0 for the esomeprazole group was 2.0 ± 6.6%. This was significantly lower than the mean percentage of procedure time that the esophageal pH was <4.0 for the placebo group (15.5 ± 32.8%) and similar to the mean percentage of procedural time that the esophageal pH was <4.0 for the combination of esomeprazole and cisapride (0 ± 0%).[20] Metoclopramide given at 1 mg/kg IV followed by 1 mg/kg/h CRI was associated with a 54% reduction in relative risk of developing GER.[21] Maropitant prevents vomiting, but not GER, in anesthetized dogs premedicated with acepromazine-hydromorphone.[22]

Oral sucralfate suspension is used if esophageal erosions or ulcerations are detected, or the clinician aims to prevent such changes.[23] Additionally, a low-fat diet has been recommended as dietary fat may delay gastric emptying and LES tone.[24] Any underlying conditions that can be identified causing GER should also be corrected. However, surgical intervention to correct primary GER has not been recommended in veterinary patients to date, as has been the case in some human patients.[25]

**KEY FACTS**

- Gastroesophageal reflux (GER) may be much more common than typically documented.
- Empirical treatment for GER is recommended in patients with vague clinical signs, especially after general anesthesia, severe vomiting, and even coughing.



**References**

The complete list of references for this chapter can be downloaded from vetline.de:
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## 5.3.4 Esophageal foreign bodies

Joao Felipe de Brito Galvao

Esophageal foreign bodies occur more commonly in the dog than in the cat.

The most commonly encountered esophageal foreign bodies in dogs are bones (30–81%[1–5]), fishhooks, food, and dental or compressed chew treats.[6–11]

Small breed dogs (e.g., West Highland white terriers, Yorkshire terriers, Maltese, and shih tzus) appear to be predisposed to esophageal foreign bodies.[2,13]

In cats, fishhooks, needles, and trichobezoars are most common.[8,12]

Foreign bodies generally lodge in those areas of the esophagus that are less distensible, particularly the thoracic inlet, heart base, and cardia (the most common location where 45–50% of esophageal foreign bodies are detected).[1,2,7–9,14] The severity of damage caused by the foreign body depends on the duration of the obstruction as well as the size and angularity of the foreign body.[15] Pressure necrosis of the esophageal wall can occur and tends to be more severe with larger foreign bodies and those that have been present for a longer period of time. Full-thickness damage may occur, resulting in esophageal perforation, mediastinitis, pleuritis, and occasionally fatal hemorrhage.[6]

### 5.3.4.1 Clinical presentation and diagnosis

Clinical signs are those of esophageal obstruction. Most commonly, retching, gagging, regurgitation, ptyalism, food avoidance, dysphagia, halitosis, and odynophagia are seen.[7,8,10] In some cases, the owner may have seen the animal eat or swallow the offending object. Physical examination may be normal but typically will reveal signs of esophageal pain, including multiple attempts to swallow with extension of the head and neck, ptyalism, and possibly a hunched appearance.

Diagnosis is often made by historical information and survey thoracic radiographs (▶Fig. 5-6a, ▶Fig. 5-6b). Occasionally, a contrast study may be needed to detect radiolucent objects (▶Fig. 5-6c, ▶Fig. 5-6d). Evidence of esophageal perforation may be present and includes pneumomediastinum, pneumothorax, and mediastinal or pleural effusion, but these findings may be unreliable.[16]

### 5.3.4.2 Treatment and prognosis

Removal of the foreign body should be attempted as soon as possible. Dogs with foreign bodies present in the esophagus for >24 hours are significantly more likely to have severe esophagitis increasing the risk of stricture formation and esophageal perforation (▶Chap. 5.3.5).[1] Endoscopy is the preferred method of removal if the esophagus has not been perforated (▶Fig. 5-7).[7,8,10,12,17] The foreign object may be removed via the mouth or gently pushed into the stomach and removed via gastrotomy or allowed to be digested (e.g., bones or food). Extreme care must be exercised when attempting to remove an esophageal foreign body via endoscopy to avoid perforation. It is not uncommon for graspers to fail to remove the foreign object. In the author's experience, esophageal balloon-assisted foreign body removal is often faster and more effective than the use of graspers, especially for large and/or irregular foreign bodies. Occasionally, both graspers and balloon-assisted removal are employed.

Balloon-assisted foreign body removal is done by passing an esophageal balloon catheter aborally to the proximal aspect of the foreign body, inflating the balloon with distilled water,




**Fig. 5-6** Esophageal foreign body

Lateral projection (**a**) and ventrodorsal (**b**) radiographs of a 14-year-old female Dachshund with acute retching and vomiting after eating broccoli. The foreign body is not easily visible on plain radiographs. Esophagram (**c**) delineates the foreign body. Picture showing pieces of broccoli that were filling the entire length of the esophagus (**d**).

and then pulling orally while monitoring with the endoscope. Iohexol may also be added to the balloon allowing to monitor the foreign body retrieval via fluoroscopy and endoscopy concurrently (▶Fig. 5-8). The balloon size is chosen based on the patient's esophageal diameter. The balloon used does not need to be very large but should not be too small and pass between the esophageal wall and foreign body while inflated. Most of these procedures can be done in <5 minutes. The procedure is also faster than attempting to push the foreign body into the stomach. Additionally, pushing the foreign object into the stomach can be dangerous, especially when manipulating sharp foreign bodies. Once the foreign body has been removed, the esophageal mucosa should be fully evaluated for any potential damage (▶Fig. 5-7b). An erythematous mucosa and mild erosions are common. Thoracic radiography should be repeated after the endoscopic removal of a foreign body to assess the possibility of perforation.

Surgical removal may be needed in cases where endoscopic removal is unsuccessful or when perforation has occurred.[7,10,16,17] While surgical intervention is usually recommended, 4 of 5 dogs (80%) with esophageal perforation were successfully medically managed.[18] One dog in that study was euthanized after developing aspiration pneumonia.

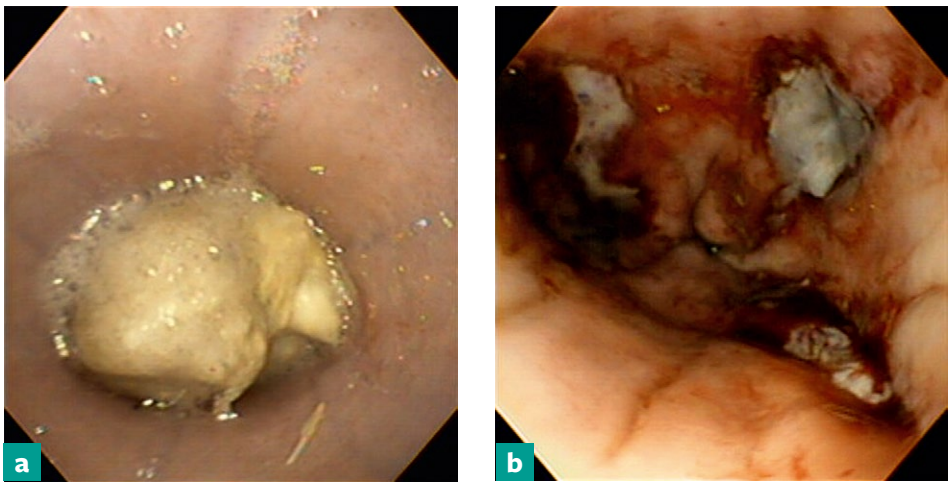



**Fig. 5-7** Esophageal foreign body
Endoscopic view of a rawhide esophageal foreign body before (**a**) and after (**b**) endoscopic removal in a 7-year-old male West Highland white terrier with a 2- to 3-day history of vomiting, anorexia, and lethargy.



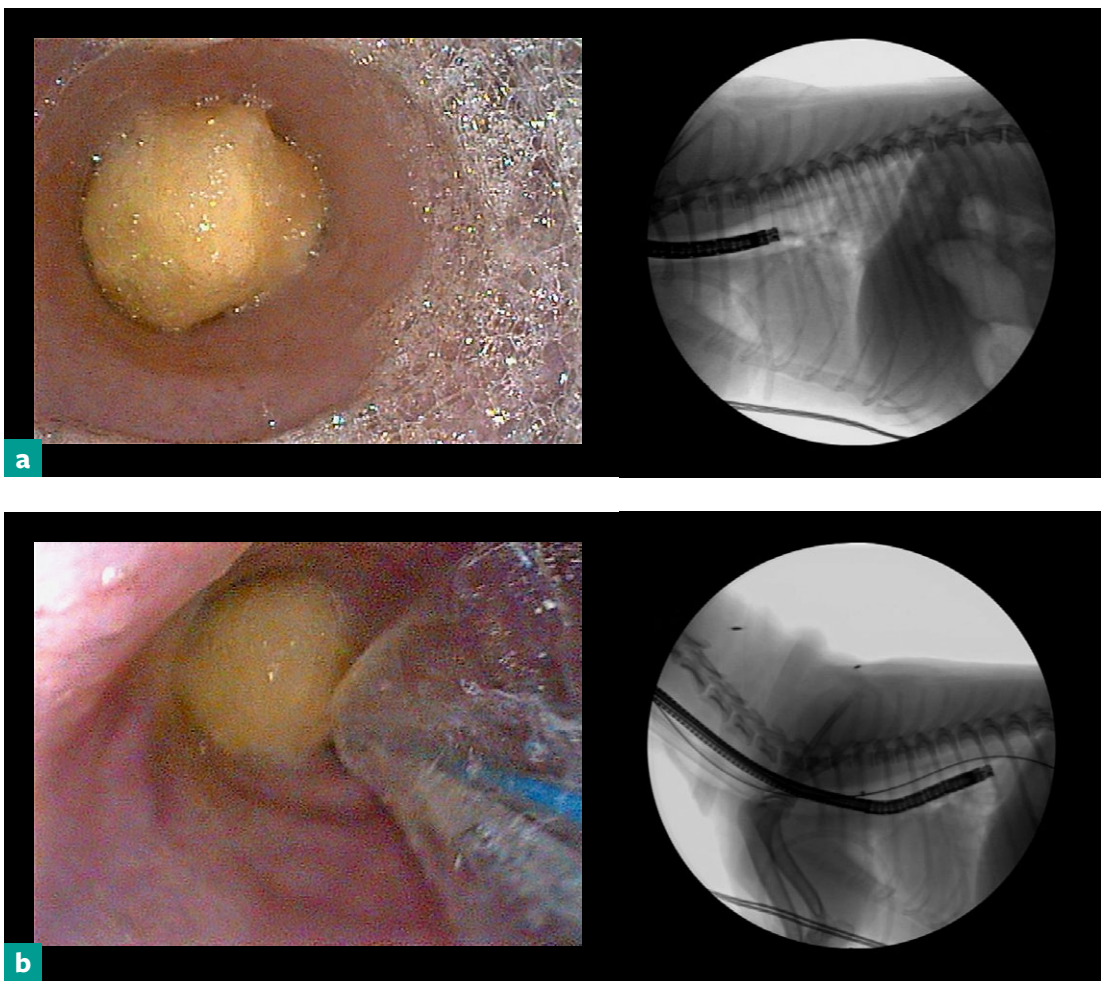
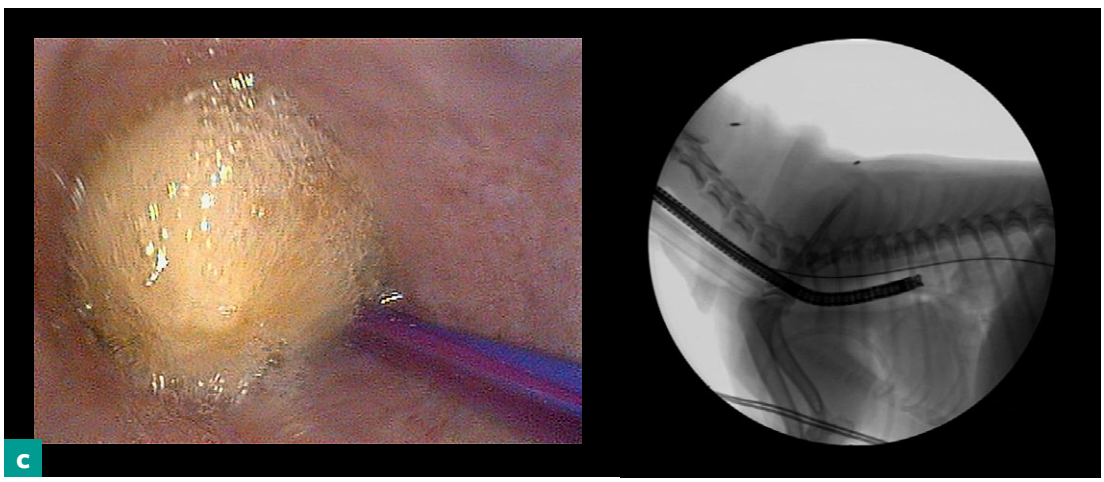
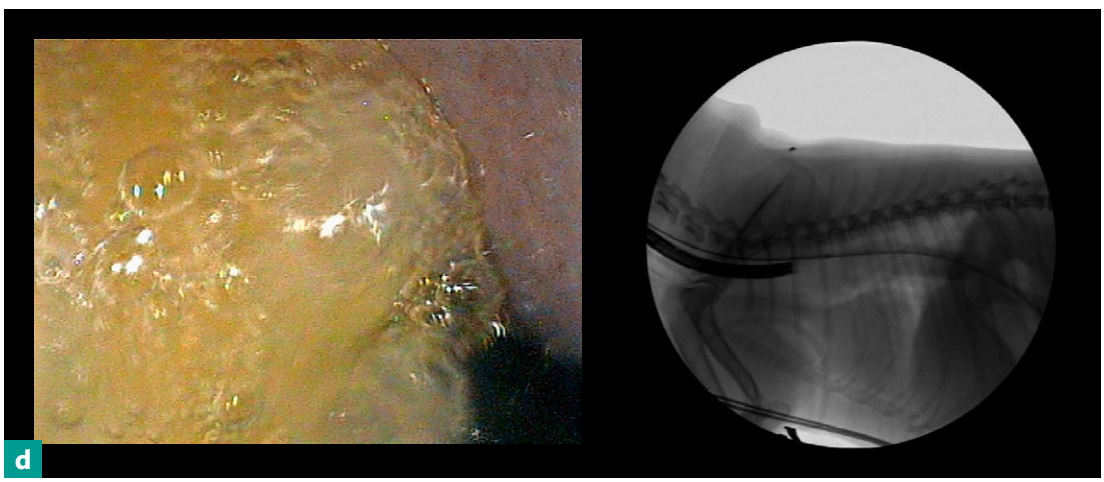



**Fig. 5-8** Balloon-assisted esophageal foreign body removal
Endoscopic and videofluoroscopic side-by-side view of an esophageal foreign body in a 10-year-old female Maltese with retching after eating an apple a few hours prior to presentation (**a**). A 20 mm esophageal balloon was advanced between the foreign body and esophageal wall (**b**), subsequently inflated with saline:iohexol (**c**). The balloon was then removed while inflated, pulling the foreign body orally (**d**).

The author recommends treating all patients with successfully removed esophageal foreign bodies for esophagitis (▶Chap. 5.3.2.2). In the author's experience, many of these patients develop esophagitis post foreign body removal, presumably secondary to esophageal irritation, inflammation, and subsequent gastroesophageal reflux (GER). Proton pump inhibitors (PPI; e.g., omeprazole 1–2 mg/kg q12h for 4 weeks), cisapride (0.5 mg/kg PO q8–12h for 3 weeks), and metoclopramide (0.5 mg/kg PO q8–12h for 2 weeks) can be used concurrently depending on the foreign body and severity of the changes noted during an endoscopic evaluation. If pushing bone foreign bodies into the stomach, PPIs are not recommended as they will interfere with bone digestion time. In addition, broad-spectrum antibiotics may be used if esophageal mucosal barrier function has been lost. Some clinicians recommend the use of anti-inflammatory doses of corticosteroids to reduce the risk of esophageal stricture formation. However, the benefit of this treatment is as of yet unproven, and the author does not recommend it. If esophageal damage is severe, the clinician may elect to rest the esophagus for 2–3 weeks and feed the animal through a gastrostomy tube (▶Chap. 3.2.2.1.3).

The prognosis is generally good; however, some animals may develop complications, the most common of which is esophageal stricture formation.[7,19,20] Esophageal strictures tend to develop if there is circumferential damage to the esophageal mucosa, especially if GER persists after foreign body removal. Overall, esophageal stricture formation is



uncommon and noted in 2–11%, depending on the study.[1,3,13] Death associated with an esophageal foreign body was 5% in one study and associated with the need for surgery, esophageal perforation, and post-procedural esophageal hemorrhage.[1] Major complications are more likely to occur in dogs with a foreign body duration >24 hours.[2]

**KEY FACTS**

- Balloon-assisted esophageal foreign body removal is a very quick and effective method of removing esophageal foreign bodies.
- Esophageal foreign bodies should be removed as soon as possible.

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
svg.to/9842-05-03-04



## 5.3.5 Esophageal strictures

Joao Felipe de Brito Galvao

Esophageal strictures occur secondary to damage of the submucosal and muscular layers of the esophagus. Damage to these layers stimulates the production of fibrous connective tissue.[1] Benign esophageal strictures are often secondary to gastroesophageal reflux (GER) during an anesthetic event.[2–6] Esophageal strictures may also be due to damage from foreign bodies, ingestion of caustic substances, and administration of oral doxycycline or clindamycin (especially in cats), among others.[7–9]

### 5.3.5.1 Clinical presentation and diagnosis

The clinical signs of small animal patients with an esophageal stricture include regurgitation, ptyalism, dysphagia, odynophagia, inappetence, and weight loss.[1,2,5] History of acute development of regurgitation post-anesthesia should raise suspicion for the development of esophagitis and subsequent stricture formation; thus, the importance of aggressive supportive care and subsequent further diagnostics if regurgitation persists.

Thoracic radiographs are often normal (▶Fig. 5-9a). Occasionally, a dilated segment of the esophagus may be seen cranial to the stricture on survey thoracic radiographs. A definitive diagnosis is made via contrast videofluoroscopy (▶Fig. 5-9b) and/or esophagoscopy (▶Fig. 5-10a).[2,3] Esophagoscopy allows the clinician to fully evaluate the esophageal mucosa to aid in treatment decisions. In large dogs, contrast-filled esophageal balloon videofluoroscopy may be needed to document subtle strictures.

**NOTE**

It is important to diagnose and treat even subtle strictures as these tend to become more pronounced over time.

### 5.3.5.2 Treatment

Mechanical dilation is the treatment of choice for esophageal strictures. **Balloon dilation** has been previously commonly done under endoscopic guidance every 4–7 days, averaging 2–4 times per animal.[2,3,5,6,10] Bougienage is also a reported technique but is not as commonly used as balloon catheters are more readily available and used quite successfully.[10] Additionally, the largest bougie available is 20 mm in diameter, which is not wide enough to completely break a fibrous band in a medium-sized dog.

The author believes that completely breaking the fibrous band responsible for the stricture is key to a successful balloon dilation treatment (▶Fig. 5-10b). Contrast-filled balloon dilation videofluoroscopy is essential in determining if the fibrous band has been destroyed (▶Fig. 5-11). Additionally, using a guidewire within the balloon as well as an appropriately sized balloon is a must. A balloon that is too small may not show an obvious fibrous band that leaves a greater diameter than the balloon. Likewise, an oversized balloon will increase the likelihood of esophageal perforation. The author will gradually increase the diameter of the esophageal balloon during the procedure. The esophageal diameter is estimated by filling the esophageal balloon with contrast and sliding it into a normal part of the esophagus. Normal esophagus diameter is achieved when the filled balloon does not slide easily through the normal esophagus. This technique is also used to ensure that subtle strictures are not missed. It is important to use a high-pressure balloon filled with fluid, and even small amounts of air that may become trapped in the balloon catheter should be removed. The saline/contrast solution is not as compressible as air and more effectively provides enough pressure to destroy the fibrous band responsible for the stricture. Often, up to 30 atm (30 bar) pressure may be necessary to break the fibrous band. Unfortunately, it is challenging to find large-diameter balloons that tolerate high pressure without bursting. The author believes that

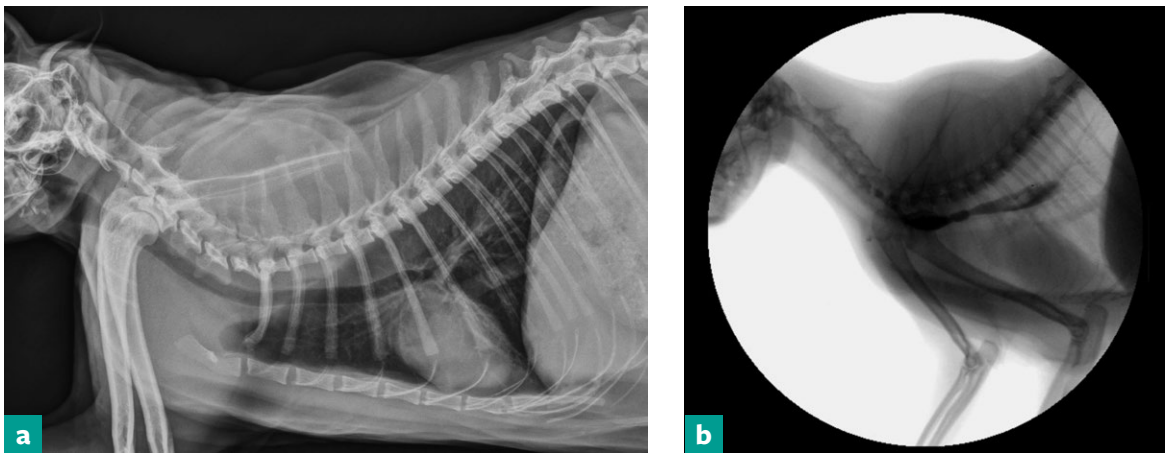


**Fig. 5-9** Esophageal stricture

**a** Lateral thoracic radiograph of an 8-year-old male domestic longhair cat with a history of retching, regurgitation, and anorexia.

**b** Barium esophagram shows a stricture in the thoracic esophagus oral to the heart base. The esophageal stricture was suspected to be secondary to a hairball.

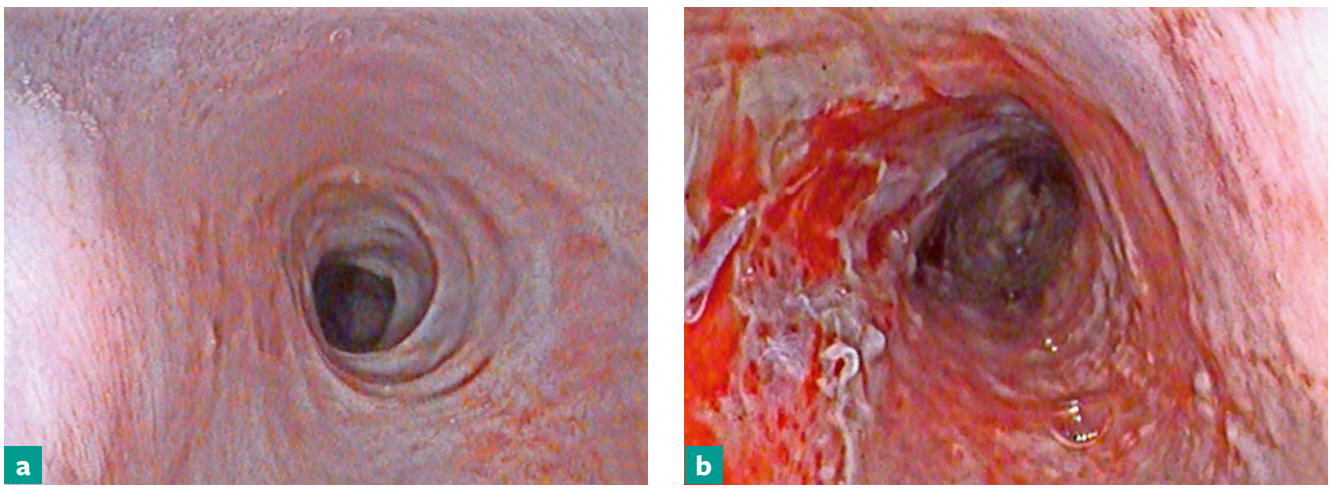


**Fig. 5-10** Esophageal stricture

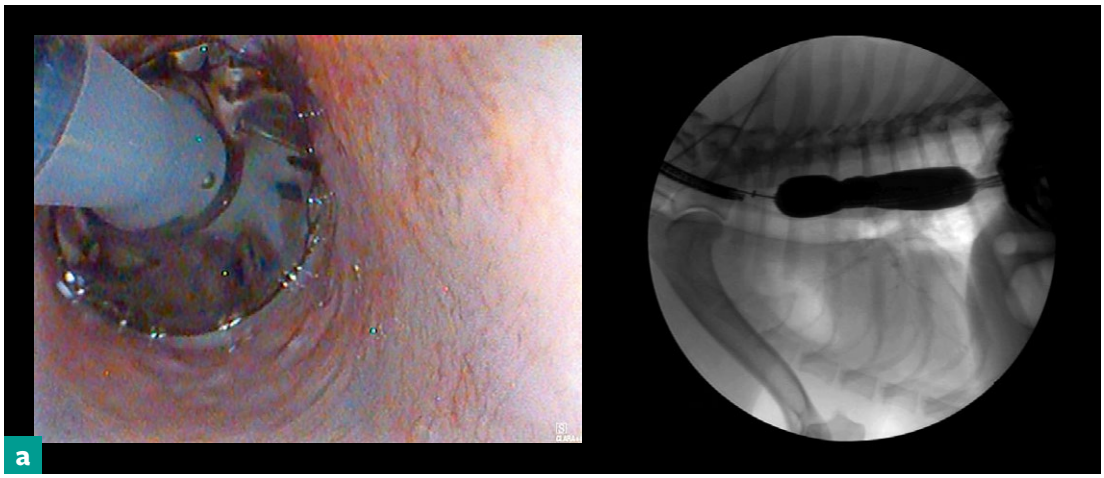
**a** Endoscopic view of multiple esophageal strictures of a 4-year-old male Siberian Husky with regurgitation following an enterotomy procedure to remove an intestinal foreign body. Note the presence of several rings. The diameter of the strictures was approximately 8 mm.

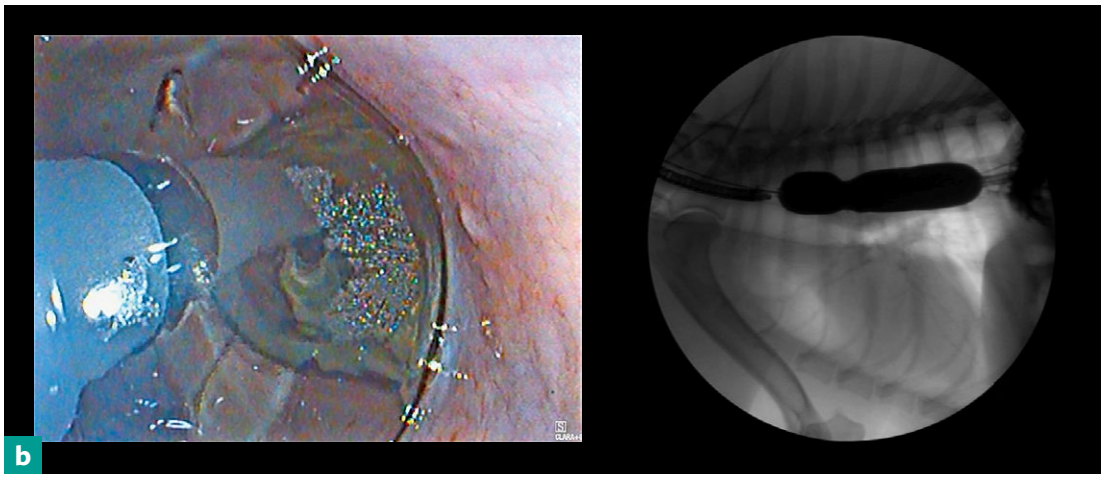
**b** Esophageal stricture after balloon dilation. The strictures were dilated to 30 mm. Note hemorrhage and mucosal tearing, often observed after balloon dilation.

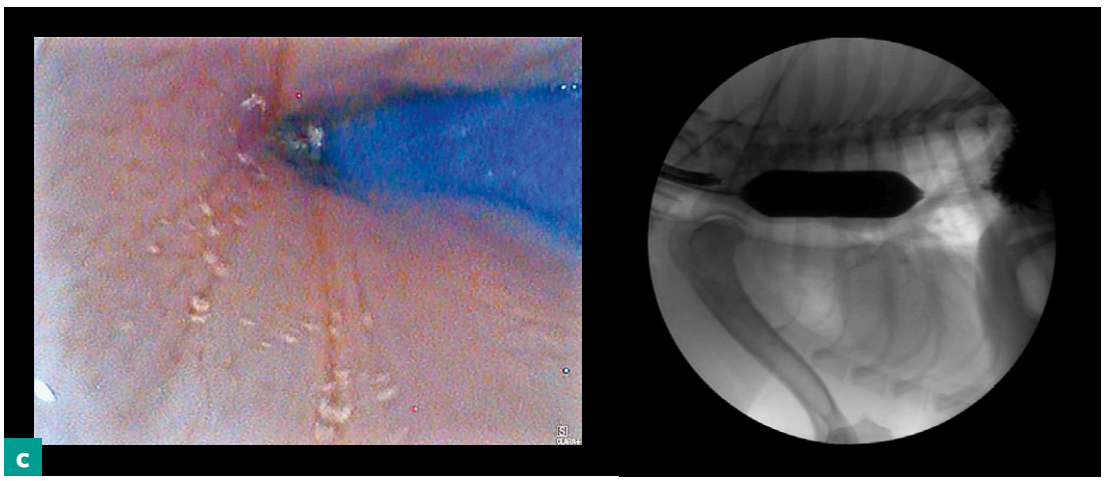
serial balloon dilation procedures may not be needed if the fibrous band is destroyed. It is also suspected that the need to repeat ballooning procedures may be associated with the incomplete destruction of the fibrous band. Using higher diameter and higher pressure balloons may theoretically increase the odds of esophageal perforation, which has been previously reported.[11] Two dogs with esophageal perforation, weighing 3.8 kg and 4.8 kg, underwent dilation with a 30 mm balloon.

**CLINICAL PEARLS**

A rough guideline used by the author suggests ballooning up to 15 mm in patients <7 kg, up to 20 mm for 7–14 kg, 25 mm for 14–24 kg, and 30 mm in patients >24 kg. Giant breed dogs may require 35–40 mm balloons. Again, given the individual patient variation, it is important to first estimate the normal esophageal diameter in each patient.


a


b


c

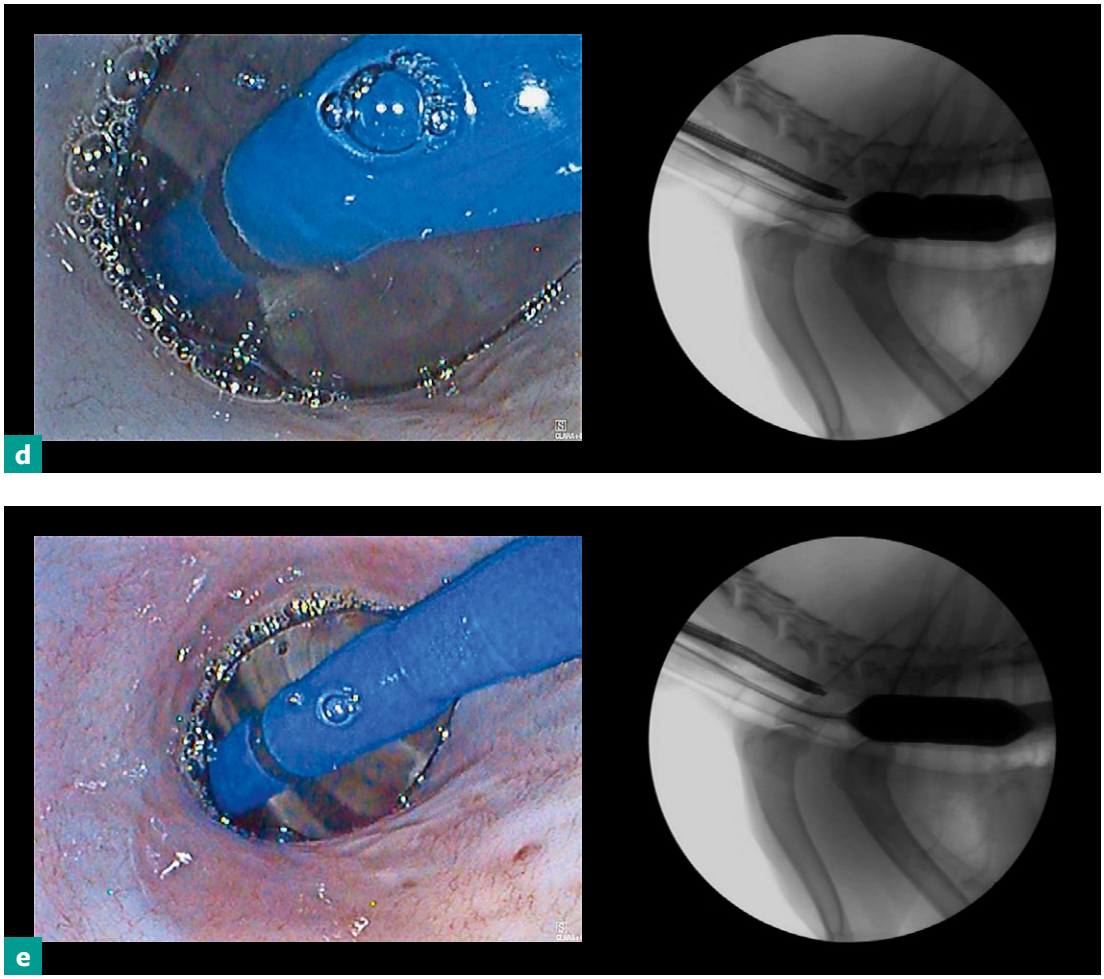



**Fig. 5-11** Esophageal stricture balloon dilation. Endoscopic and videofluoroscopic side-by-side view in the same dog shown in ▶Fig. 5-10.

**a** A 30 mm esophageal balloon dilation showing a waste due to two strictures at a pressure of 2 atm (2 bar).

**b** Continued balloon dilation showing resolution of one of the wastes when applying 3 atm (3 bar) pressure.

**c** Another 30 mm balloon was used at higher pressure (5 atm = 5 bar) showing the resolution of the waste.

**d** A 30 mm balloon dilation in the cervical esophagus showing a small waste, which was not noted endoscopically.

**e** Ballon dilation with higher pressure was able to tear the fibrous band.

Esophageal stents have been successfully used in the past to treat esophageal strictures.[12–14] Esophageal stents potentially offer a single-stage solution to improve esophageal stricture treatment outcomes. These stents have commonly been employed in refractory cases in the past. Although short-term dysphagia improved, a recent study documented major complications in 7 of 9 dogs (78%) after stent placement.[14] Complications included stent migration, hyperplastic tissue ingrowth or overgrowth, dysphagia, gagging and perceived discomfort, and stricture recurrence.

Recently, a **balloon dilation esophagostomy tube** (**B-tube**) was developed to mimic self-dilation described in humans with the purpose of preventing strictures from closing down and avoiding serial balloon dilation procedures.[15] Currently, the author uses the B-tube routinely instead of serial ballooning procedures or esophageal stents (▶Fig. 5-12). The B-tube is placed after a routine balloon dilation that was successful in destroying the fibrous band. The B-tube is kept in place for 6 weeks for the owner to inflate it q12h for the duration of the placement. Patients are briefly anesthetized to remove the B-tube, at which time the esophagus is re-evaluated via contrast videofluoroscopy and endoscopy (▶Fig. 5-13).



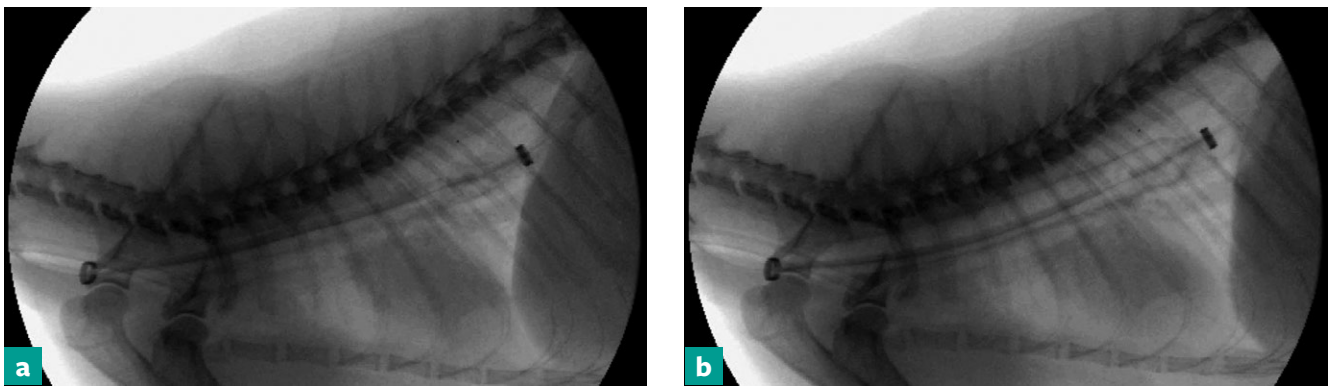



**Fig. 5-12** Videofluoroscopy of a 20 mm × 20 cm balloon dilation esophagostomy tube (B-tube) in the same cat shown in ▶Fig. 5-9

**a** Deflated B-tube

**b** Inflated B-tube

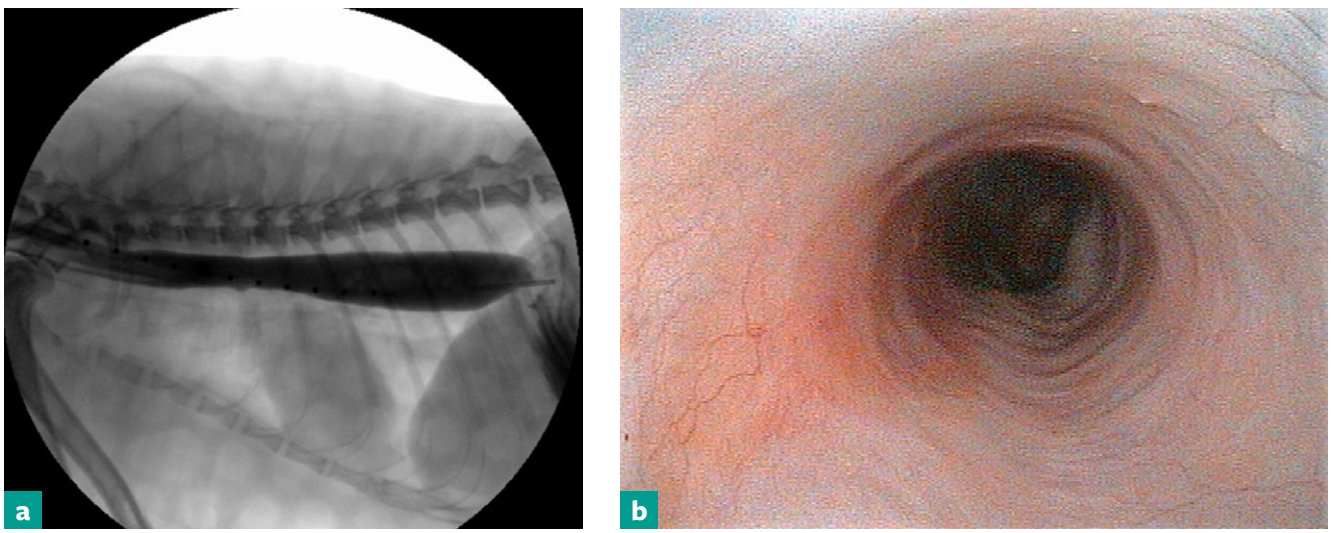



**Fig. 5-13** Diagnostic imaging of the esophagus after balloon dilation esophagostomy tube (B-tube) removal in the same cat shown in ▶Fig. 5-9

**a** Contrast videofluoroscopy after B-tube removal

**b** Endoscopy view after B-tube removal

Note the normal appearance of the esophagus. The narrowest portion of the esophagus was 12 mm, noted with passive contrast dilation.

#### 5.3.5.3 Prognosis

In clinical studies, 70–88% of patients with esophageal strictures had improved outcomes with balloon dilation of the esophageal stricture or bougienage, returning to eating canned or dry dog food with minimal to no regurgitation.[2,3,5,6,16] However, only 14–25% of these patients were able to eat dry food after the balloon dilation treatments,[3,5,16] whereas B-tube patients were commonly able to eat dry food without dysphagia (67%).[15]

Surgical removal of strictures and other surgical techniques have been reported, but surgery is generally reserved for refractory cases where perforation has occurred.[17,18]

Complications associated with balloon dilation include esophageal perforation and esophageal tears.[2,3,5,11] Placement of a gastrostomy tube has been recommended in cases where the esophageal damage is severe, but this is rarely needed.[5,6,19] Treatment for esophagitis should be instituted after the balloon dilation procedure. The use of corticosteroids has been advocated to prevent the reformation of the stricture.[20] However, the efficacy of such corticosteroid therapy has not been proven in a clinical setting, although it has been reported as an adjunct therapy by some authors.[2,5] Intra-lesional triamcinolone[6,13,21] and/or topical mitomycin-C[22–24] can also be considered, but their efficacy is unknown.

**KEY FACTS**

- Regurgitation post-anesthesia should be treated aggressively to help prevent the development of an esophageal stricture.
- Tearing the fibrous band is key in effectively treating esophageal strictures. Fluoroscopy is essential in making sure the fibrous band is completely torn.

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
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### 5.3.6 Esophageal diverticula

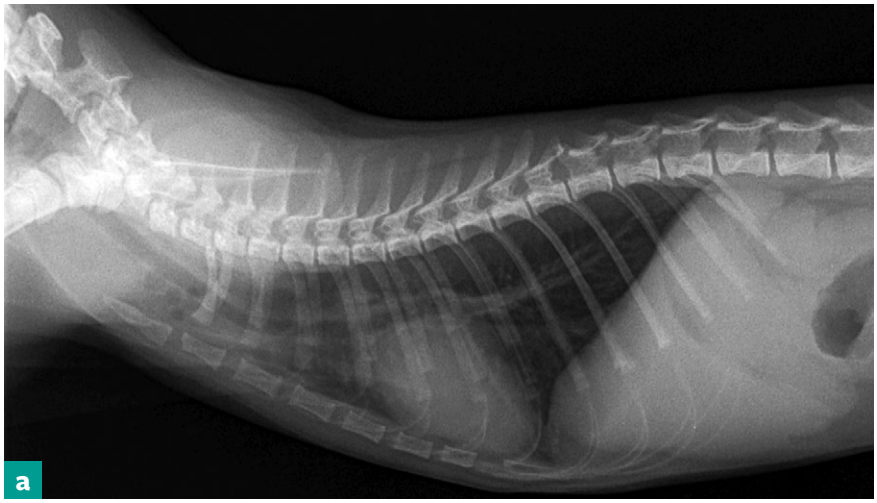
Joao Felipe de Brito Galvao

#### 5.3.6.1 Clinical presentation

Esophageal diverticula are pouch-like sacculations of the esophageal wall that interfere with the orderly movement of ingesta through the esophagus. Diverticula may be congenital or acquired. **Congenital diverticula** are rare abnormalities of embryogenesis that permit herniation of the esophageal mucosa through a defect in the muscularis. **Acquired diverticula** can result from external traction and distortion of the esophagus caused by inflammation in the thoracic cavity near the esophagus. This leads to fibrous tissue formation, which then contracts, pulling the esophageal wall outwards.[1] This type of diverticulum affects all four layers of the esophageal wall and most commonly occurs secondary to a foreign body perforation (▶Chap. 5.3.4).[1] More commonly, diverticula occur from increased intra-luminal pressure and food impaction associated with esophageal injury, hypomotility, or obstruction.[2] This leads to an outpouching of the esophageal mucosa through a defect in the muscular and adventitial layers of the esophagus.[3,4] Predisposing disorders include esophagitis, hypomotility, megaesophagus, esophageal stricture, foreign body, vascular ring anomaly, and neoplasia, among others.[1,2] Both types of diverticula are reported in the dog, while only one case of an esophageal diverticulum has been reported in a cat.[3,5,6] Clinical signs of small diverticula may not be apparent. Large diverticula allow food trapping, leading to postprandial dyspnea, regurgitation, odynophagia, and anorexia.

#### 5.3.6.2 Diagnosis

Survey thoracic radiographs usually reveal an air-, fluid-, or food-filled outpouching of the esophagus (▶Fig. 5-14a). A redundant flexure or deviation of the esophagus at the thoracic inlet that occurs in some animals, especially Chinese shar-peis and brachycephalic breeds, should not be mistaken for a diverticulum.[1,7] Contrast radiography (▶Fig. 5-14b) and fluoroscopy (▶Fig. 5-15) are useful to delineate the diverticulum and to differentiate it from peri-esophageal or mediastinal structures and from a pulmonary mass. Endoscopy can be used to confirm the diagnosis and will allow the identification of any ulceration or scarring.[8]



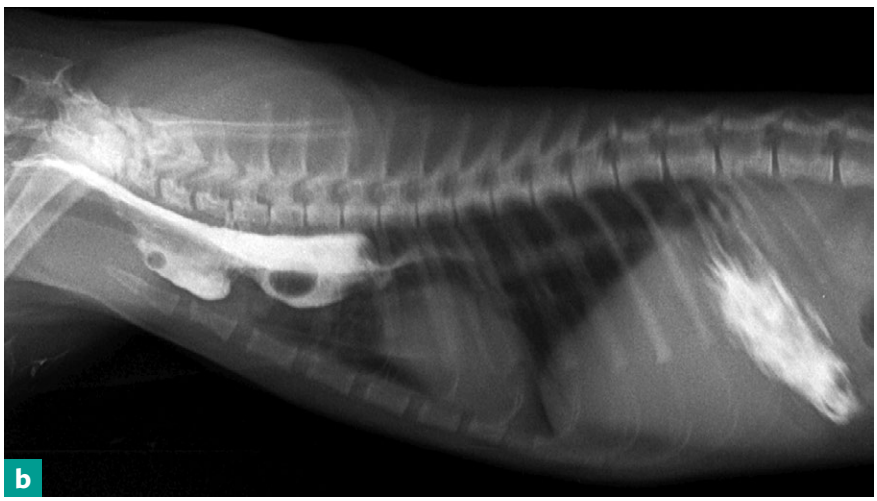




**Fig. 5-14** Esophageal diverticulum

**a** Thoracic radiograph of a 4-month-old female Siamese mix with regurgitation immediately after food intake. Note the ventral deviation of the intra-thoracic portion of the trachea.

**b** An esophagram revealed the extent of the pre-cardial esophageal diverticulum.

(Courtesy of Prof. Romy M. Heilmann, University of Leipzig, Germany.)

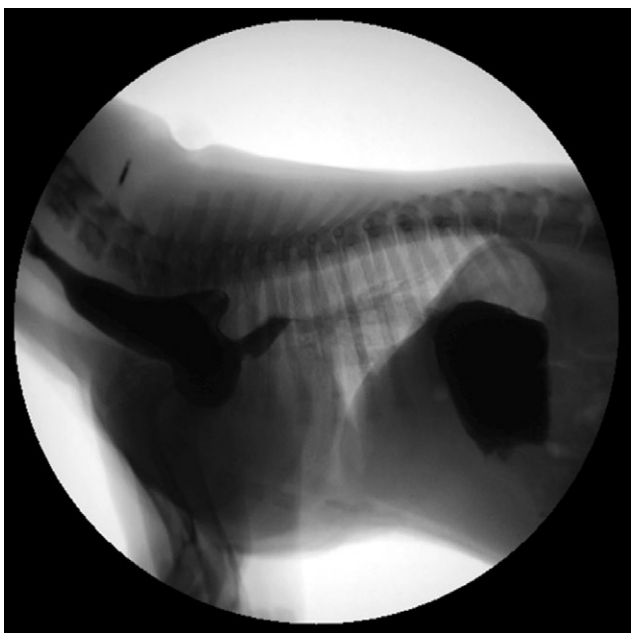


**Fig. 5-15** Esophageal diverticulum

Fluoroscopy image of a 2.5-month-old female Pinscher with regurgitation immediately after food intake and weight loss. Note the esophageal diverticulum localized just proximal to a vascular ring anomaly.

(Courtesy of Prof. Romy M. Heilmann, University of Leipzig, Germany.)

#### 5.3.6.3 Treatment and prognosis

Traction diverticula are commonly managed with broad-spectrum antibiotics, whereas pulsion diverticula are treated for the specific underlying cause. Small diverticula may be managed with a bland, soft diet fed with the patient in an upright position and generally carry a favorable prognosis. Diverticulectomy is recommended for large diverticula. Surgical correction can be associated with a less favorable prognosis as it can induce esophageal stricture formation. Additionally, segmental hypomotility may persist after surgery. Nonetheless, successful surgical management has been reported.[3,5]

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
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### 5.3.7 Airway-esophageal fistula

Joao Felipe de Brito Galvao

An airway-esophageal fistula is a rare abnormal communication between the esophagus and either the trachea or a mainstem bronchus. Such fistulas have been reported in dogs and cats as either congenital or acquired conditions.[1–5] Congenital airway-esophageal fistulae result from incomplete separation of the tracheobronchial tree from the digestive tract during embryological development.[6] Cairn terriers appear to be predisposed to congenital esophageal fistulae.[1,3] Acquired airway-esophageal fistulae most commonly develop secondary to foreign body penetration of the esophagus, especially bones or grass awns.[3]

#### 5.3.7.1 Clinical presentation and diagnosis

The most common clinical sign is coughing or dyspnea, especially after drinking or eating.[1] Other clinical signs include regurgitation and anorexia, fever, or lethargy, with some of these signs related to aspiration pneumonia.

Survey radiographs usually reveal a localized alveolar, bronchial, or interstitial lung pattern or a combination of these.

Most commonly affected lung lobes in dogs: right caudal and middle lobes.[4,7]

Most commonly affected lung lobes in cats: left caudal and accessory lobes.[4,7]

A definitive diagnosis requires a contrast esophagram showing the communication between the esophagus and the airway. Iodinated contrast agents are not recommended, given their high osmolality, leading to pulmonary edema if they reach the airway.[1–3,6]

#### 5.3.7.2 Treatment and prognosis

Treatment requires surgical correction. Lung lobectomy is usually necessary with repair of the esophageal wall defect.[1,3] The prognosis for a full recovery is good if the animal survives the surgical procedure. Otherwise, the prognosis is guarded if severe complications such as marked pleural effusion, pneumonia, or pulmonary abscessation are present.

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
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### 5.3.8 Esophageal hypomotility/megaesophagus

Joao Felipe de Brito Galvao

**Esophageal hypomotility or dysmotility** may occur without megaesophagus, and young terrier dogs appear to be overrepresented.[1] Esophageal dysmotility can be segmental or global. Not all dogs are symptomatic and may improve over time. It is suspected that some of these dogs have a syndrome of delayed esophageal maturation. Cats are also described to have esophageal dysmotility,[2] with idiopathic dysmotility noted in many cats. 78% of the cats treated medically showed an improvement in clinical signs. Other considerations for esophageal dysmotility include critically ill dogs and cats. Esophageal dysmotility in these patients is associated with increased mortality.[3] Esophageal dysmotility has also been associated with laryngeal paralysis,[4,5] and the severity of esophageal dysmotility is a prognostic factor for the development of postoperative aspiration pneumonia in affected dogs. Esophagrams and neurologic examinations are recommended in all dogs with laryngeal paralysis.

**Megaesophagus** is a dilation of the body of the esophagus associated with poor to no esophageal peristalsis. Megaesophagus has been described as an idiopathic congenital, idiopathic acquired, or secondary acquired disorder.[6–20] Congenital disease has been reported in both the dog and the cat, and an inherited component has been suggested.[8,9,16] The most common underlying disease process that results in a secondary megaesophagus is myasthenia gravis.[11,14,21,22] Other underlying conditions reported include hypoadrenocorticism, hypothyroidism, polyneuropathies, lead toxicity, polymyopathies, thymoma (causing a paraneoplastic form of myasthenia gravis), dysautonomia, and possibly diet-induced, among others.[7,10,12,13,15,17,18,20,23] The exact etiology and pathogenesis of primary megaesophagus remain unknown. Some dogs have a normal lower and upper esophageal sphincter response to swallowing but an absent or decreased response of the esophageal sphincters to intra-luminal stimuli.[24] This study, along with others, suggests that the underlying defect in dogs with idiopathic megaesophagus may lie in the vagal afferent innervation to the esophagus.[25]



#### 5.3.8.1 Clinical presentation and diagnosis

The most common clinical sign, regardless of the cause of the megaesophagus, is regurgitation. Patients with megaesophagus generally maintain their desire to eat unless they develop concurrent aspiration pneumonia. Regurgitation may occur immediately or several hours after eating. Ptyalism and weight loss are common. Physical examination is often unremarkable unless an underlying condition is present (e.g., systemic weakness may be seen with myasthenia gravis). Thoracic radiographs usually show a diffusely dilated esophagus filled with air, food, and/or fluid. In questionable cases, contrast videofluoroscopy will help determine the extent of esophageal motility and whether any obstructive lesions are present. A definitive diagnosis involves ruling out other known causes of megaesophagus with appropriate testing, including serum acetylcholine receptor antibody titers, adrenocorticotrophic hormone (ACTH) stimulation testing, thyroid function testing, and lead concentrations.[21] Endoscopy may help rule out an obstructive disease such as an occult lower esophageal stricture[26] but is not generally necessary.

#### 5.3.8.2 Treatment and prognosis

If an underlying disease is present, it should be treated appropriately. For example, animals with myasthenia gravis often respond well to immunosuppression and anticholinesterase drugs.[11,27] Other patients, especially those with a focal form of megaesophagus, may have spontaneous regression of clinical signs with supportive care.[22] Sildenafil at 1 mg/kg PO q12h has been successfully used in dogs with congenital idiopathic megaesophagus.[28] Sildenafil is thought to decrease the lower esophageal sphincter tone, presumably increasing in congenital idiopathic megaesophagus. Treatment for acquired idiopathic forms of megaesophagus is via supportive care. Aspiration pneumonia should be treated as it arises. Decreased appetite and/or lethargy may be an early sign of aspiration pneumonia in these dogs, and clinical signs may occur prior to radiographic changes becoming apparent. Dietary support should be provided in the form of a high-quality, high-calorie diet either via frequent, small upright feedings (e.g., Bailey chair) or through a gastrostomy tube. It is important to evaluate different food consistencies to determine the best one for each individual patient (e.g., gruel, canned meatballs, and kibble). Surgical treatment of megaesophagus (gastroesophageal myotomy) is associated with poor results.[29]

The prognosis for congenital or acquired idiopathic megaesophagus is guarded. Some young dogs may recover esophageal function as they mature.[9] Although adult-onset megaesophagus carries a poor prognosis, mortality is typically associated with poor quality of life due to recurrent bouts of aspiration pneumonia. There have been rare reports of transient cases of megaesophagus.[30] A small case series showed that intermittent esophageal suctioning in dogs with megaesophagus that continue to regurgitate despite gastrotomy tube feedings can reduce or resolve bouts of recurrent aspiration pneumonia.[31]

### References

The complete list of references for this chapter can be downloaded from vetline.de:
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## 5.3.9 Hiatal hernia

Harry Cridge

### 5.3.9.1 Etiology and pathogenesis

A hiatal hernia is a protrusion of abdominal contents through the esophageal hiatus into the thoracic cavity in the presence of an intact, albeit abnormal or lax, phrenicoesophageal ligament.

Four types of hiatal hernias have been described[1]:

- **Type I** (sliding) hiatal hernias are the most common and occur when the gastroesophageal junction displaces cranially into the thoracic cavity through the esophageal hiatus.[2,3]
- **Type II** (paraesophageal) hiatal hernias occur when part of the stomach moves cranially into the thoracic cavity, adjacent to the gastroesophageal junction, which remains in its normal anatomic position.[4]
- **Type III** (mixed) hiatal hernias include elements of both types I and II hiatal hernias.[5]
- **Type IV** hiatal hernias involve the herniation of organs other than the stomach.[6]

The etiology and pathogenesis of hiatal hernias are poorly understood.[1] Hiatal hernias can either be congenital or acquired.

#### 5.3.9.1.1 Congenital hiatal hernias

Many brachycephalic breeds are predisposed to congenital hiatal hernias, including English bulldogs, French bulldogs, pugs, and Boston terriers.[7–9] Chinese shar-peis are predisposed to congenital hiatal hernias due to a malformation of the esophageal hiatus.[10,11]



Congenital hiatal hernias appear to be the most common type of hiatal hernias in dogs.[2,3]

#### 5.3.9.1.2 Acquired hiatal hernias

Hiatal hernias may also occur secondary to many acquired disorders, including neurologic/neuromuscular disease, trauma, or respiratory disease. Increased negative intra-thoracic pressure, as seen in dogs with severe upper airway obstruction (e.g., laryngeal paralysis or brachycephalic upper airway syndrome), can lead to the development of an acquired hiatal hernia during inspiration. Subsequent esophagitis further decreases lower esophageal sphincter (LES) tone, aggravating reflux and resulting in a vicious perpetuation of disease.[12]



Acquired hiatal hernias are suspected to be the most common type of hiatal hernias in cats.[2,3]

### 5.3.9.2 Clinical presentation and diagnosis

Animals with a congenital hiatal hernia often display clinical signs shortly after weaning and typically before 1 year of age, whereas clinical signs of acquired disease occur later in life. Clinical signs develop secondary to esophagitis (▶ Chap. 5.3.2) and associated esophageal dysmotility. Signs may include regurgitation, vomiting, dysphagia, ptyalism, anorexia, weight loss, and/or respiratory distress. Other animals may be asymptomatic.[2]

Physical examination is generally unremarkable unless the patient has concurrent aspiration pneumonia. Poor body and muscle condition can be seen with chronic disease.

#### 5.3.9.2.1 Radiographs

Survey thoracic radiographs can reveal a caudo-dorsal soft tissue opaque or gas-filled structure in the region of the esophagus and overlying the diaphragm (▶ Fig. 5-16). Concurrent esophageal dilation is frequently noted. Positive contrast esophagrams or gastrograms may aid in the detection of this disorder.[4] Unfortunately, false negatives are common due to the dynamic nature of the disease.

#### 5.3.9.2.2 Videofluoroscopy

Videofluoroscopy is more useful than survey radiographs for the diagnosis of cases with intermittent herniation and may allow for the identification of concurrent gastroesophageal reflux and dysmotility. Videofluoroscopy frequently reveals acquired hiatal hernias in brachycephalic animals with obstructive airway disease, and the prevalence is greater than previously suspected based on survey radiographs.[13]

#### 5.3.9.2.3 Esophagoscopy

Reflux esophagitis and an open LES during esophagoscopy should prompt consideration of a sliding hiatal hernia.[14] If this is observed, the endoscope should be passed into the stomach and then retroflexed to allow for retrograde evalua-

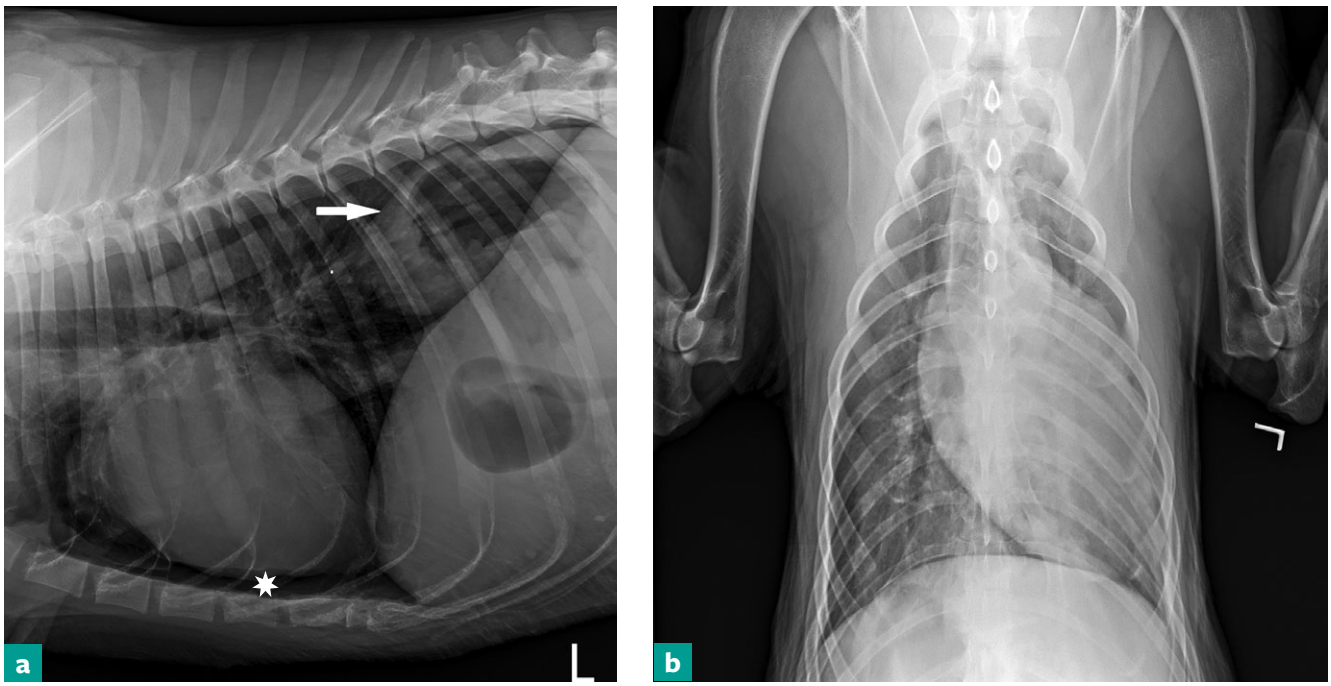



**Fig. 5-16** Hiatal hernia as observed by survey radiographs in a 2-year-old German shepherd dog that presented following vehicular trauma

**a** A gas-filled structure is seen in the caudo-dorsal thorax (**arrow**) in the region of the esophagus and overlying the diaphragm. This is best visualized on the left lateral projection. A mild pneumothorax can also be seen (**asterisk**).

**b** Ventrodorsal projection of the same dog

(Courtesy of Dr. Marc Seitz and Dr. Alison Lee, Mississippi State University, Starkville, MS, USA.)

tion of the LES and gastroesophageal junction.[14] Imprints of the esophageal hiatus should be identified against the gastric mucosa.[14] Alternatively, ballooning of the esophageal wall into the esophageal lumen may be seen, and various manipulations have been proposed to increase the detection of a hiatal hernia (▶ Fig. 5-17). A recent study indicated that two manipulation techniques could be used to increase the detection of sliding hiatal hernias in brachycephalic dogs; however, only hernias detected by temporarily occluding the endotracheal tube appeared to correlate with gastrointestinal clinical signs (as determined by a scoring system).[15] Temporary endotracheal tube obstruction for three spontaneous inspirations, or a maximum of 30 seconds, is thought to promote deep inspirations that mimic the effects of an upper airway obstruction that would otherwise be masked by the intubation of an anesthetized patient.[15] Manual compression of the cranial abdomen was also reported to increase the detection of hiatal hernias but did not correlate with clinical scores.[15] Thus, temporary endotracheal tube obstruction may be beneficial in the detection of abnormalities at the gastroesophageal junction, such as hiatal hernias. Importantly, this maneuver does not lead to false positive diagnoses in healthy control animals.[16] Anesthetic risk for esophagoscopy should be considered.

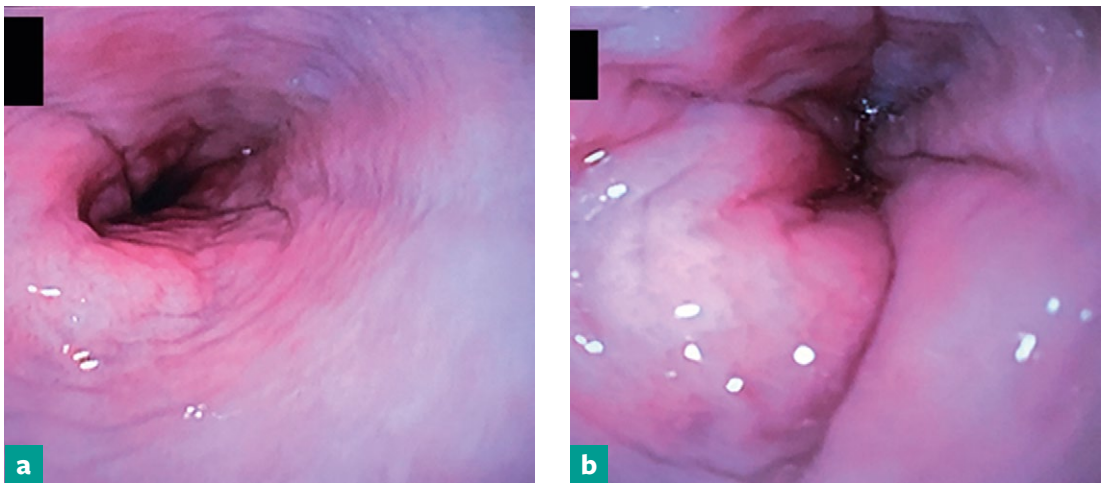



**Fig. 5-17** Hiatal hernia in a 3-year-old French bulldog that presented for stertor and regurgitation

In esophagoscopy before (**a**) and after (**b**) application of manual abdominal pressure ballooning of the esophageal wall into the esophageal lumen can be seen. (Courtesy of Dr. Katie Cooley Lock, Charlotte Animal Referral & Emergency, Charlotte, South Carolina, USA.)

#### 5.3.9.3 Management

An important consideration before pursuing medical or surgical management is that not all dogs with radiographic evidence of a hiatal hernia require intervention. Dietary fat restriction (▶Chap. 3.2.1.3) is often sufficient for the management of mildly affected cases.

The goals of medical management include increasing gastric emptying, increasing LES tone, and managing concurrent esophagitis (▶Chap. 5.3.2.2). Cisapride is the prokinetic of choice for this indication in dogs.[17] Small, frequent fat-restricted meals are also recommended to further promote gastric emptying. Upright feeding may assist animals with concurrent esophageal dysmotility (▶Chap. 5.3.8). Proton pump inhibitors administered q12h are preferred to oral H2-receptor antagonists for gastric acid suppression.[18,19] Cytoprotective drugs, such as sucralfate, are also frequently prescribed. Proton pump inhibitors, cisapride, and sucralfate have also been proposed for the medical management of hiatal hernias in cats.[3]

Surgery is generally considered in patients with congenital hiatal hernias and those with significant clinical signs that fail to respond to medical management.[20] If an underlying disorder (e.g., brachycephalic upper airway syndrome) is noted, it should be corrected first.[20] Potential surgical techniques for the management of a hiatal hernia include phrenoplasty, esophagopexy, and left-sided gastropexies.[7,10,11,20–22]

##### 5.3.9.3.1 Prognosis

Overall prognosis is generally good, with most cases responding to medical management. When medical management fails, surgery often improves but may not resolve clinical signs.

**KEY FACTS**

- A hiatal hernia is a congenital or acquired protrusion of abdominal contents through the esophageal hiatus into the thoracic cavity in the presence of an intact, albeit abnormal or lax, phrenicoesophageal ligament.
- Not all dogs with hiatal hernias require intervention.

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
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### 5.3.10 Gastroesophageal intussusception

Joao Felipe de Brito Galvao, Lars F.H. Theyse

Gastroesophageal intussusception occurs when the proximal parts or all of the stomach invaginate into the caudal portion of the thoracic esophagus without displacing the gastroesophageal junction.[1] In very rare cases, additional organs such as the spleen, pancreas, duodenum, and omentum may also invaginate.[2] Being a true invagination, it is clearly distinguishable from a hiatal hernia. In general, gastroesophageal intussusception is a rare disorder, most frequently seen in puppies or kittens, but it also affects adult dogs and cats.[3–15] According to one report, over 80% of puppies were <3 months of age.[5] German shepherd dogs appear to be overrepresented (>30% of affected dogs),[5,10,13,15] with a predisposition in male dogs.[10] The exact pathogenesis remains unclear, but an abnormal function of the thoracic esophagus, gastroesophageal junction, and stomach seem to play a critical role. Megaesophagus (▶Chap. 5.3.8) is often diagnosed concurrently with gastroesophageal intussusception.[7,16]

#### 5.3.10.1 Clinical presentation and diagnosis

The most common clinical signs reported include vomiting, regurgitation, anorexia, and hematemesis.[10] Clinical signs can be either chronic or acute. Chronic cases usually show recurrent vomiting and regurgitation as the most obvious signs. In contrast, acute cases present with respiratory and cardiovascular collapse, presumably resulting from intra-thoracic compression of lung lobes and the posterior vena cava resulting in a decreased venous return.

**NOTE**

Acute gastroesophageal intussusception constitutes a life-threatening condition.

A tentative diagnosis is based on survey radiographs, showing a soft tissue mass caudal of the heart and cranial of the diaphragm in the area of the distal esophagus and a dilated proximal esophagus (▶Fig. 5-18). Endoscopy can confirm the diagnosis, showing intra-luminal gastric folds.[17] Computed tomography (CT) can exclude other intra-thoracic soft tissue-attenuating conditions such as a paraesophageal abscess or esophageal diverticulum.

#### 5.3.10.2 Treatment and prognosis

Surgery is usually recommended as the treatment of choice both in acute and chronic cases.[3] In severe acute cases, presurgical stabilization of the cardiovascular system is essential. The goal of surgical treatment is repositioning the invaginated stomach wall, evaluating viability, and preventing recurrence using a left-sided or bilateral incisional gastropexy.[3] Endoscopic repositioning of the gastroesophageal intussusception and placement of a percutaneous endoscopic gastrostomy (PEG) tube (▶Chap. 3.2.2.1.3) to stabilize the stomach wall

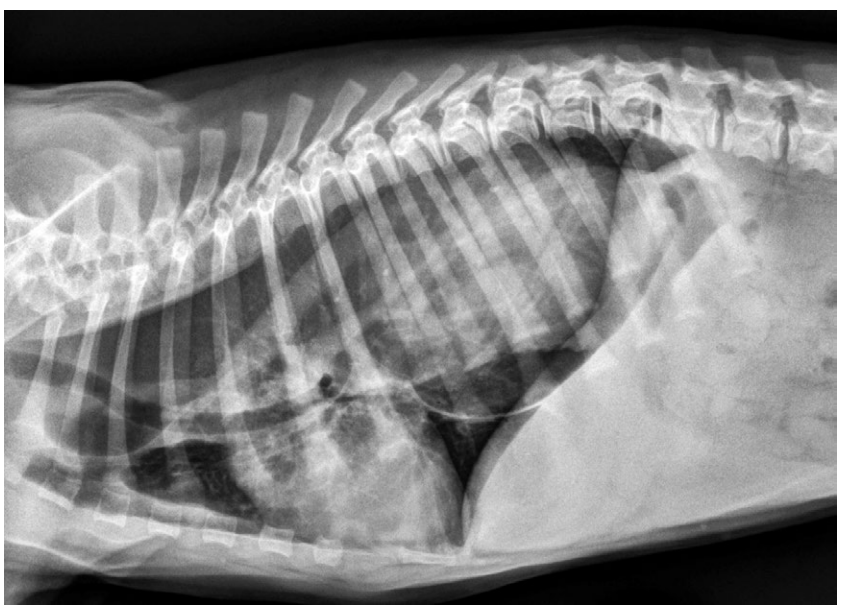


**Fig. 5-18** Gastroesophageal intussusception
Lateral thoracic radiograph of a 2-month-old female German shepherd dog showing a soft tissue mass in the area of the distal esophagus. The puppy had been acquired 4 days prior to presentation and had a history of regurgitation since.

have been reported.[10,11,14] Persistent regurgitation was common after treatment, especially in dogs previously diagnosed with megaesophagus, requiring managed feedings and medication.[10] Prognosis of surgical intervention is reasonable, with reported long-term survival (median follow-up time of 1 year) of 65% of cases, whereas one-third of affected dogs without treatment were euthanized in that study.[10]

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
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## 5.3.11 Vascular ring anomalies

Lars F.H. Theyse

Vascular ring anomalies are developmental conditions resulting in a complete or incomplete ring of major vessels encircling the esophagus and trachea. Several types of vascular ring anomalies have been described in the dog and cat.[1] The most common type is a **persistent right aortic arch with a normal left ligamentum arteriosum,** resulting in a complete ring. This type accounts for 95% of clinical cases in dogs.[2] With a double aortic arch, both the esophagus and trachea are encircled, which may result in additional respiratory signs.[3] A left aortic arch with a persistent right ligamentum arteriosum also results in a complete ring.[4] Right aortic arch with an aberrant left subclavian artery and left aortic arch with an aberrant right subclavian artery result in incomplete rings. The aberrant left or right subclavian arteries pass dorsal to the esophagus, thus compressing the esophageal lumen.[5,6] Although vascular ring anomalies are reported less frequently in cats, the subclassification is similar to that in dogs.

### 5.3.11.1 Clinical presentation and diagnosis

Clinical signs of vascular ring anomalies typically start after weaning, during the transition phase from ingesting liquid to solid food. Because esophageal obstruction is the major problem, affected patients initially present with regurgitation. Esophageal dilation proximal to the obstruction may extend proximally to the cervical region. Coughing and respiratory distress can be caused by aspiration pneumonia and tracheal compression.

CT allows for the identification of esophageal obstructions, and when combined with CT angiography, it can determine the type of vascular ring anomaly.[5,7] Esophagoscopy can support both the diagnosis and surgical intervention.[8]

### 5.3.11.2 Treatment and prognosis

Surgical release of the encircling vessels is the treatment of choice. Depending on the type of anomaly, a thoracotomy or thoracoscopy should be performed with either a left- or right-sided approach.[6,9] After ligating and transecting the obstructing vessels, the esophagus is checked for any remaining fibrotic bands using a large bore tube or balloon catheter. Adequate dilatation of the esophagus should be reached. Prognosis is considered good in most patients, although esophageal dilation and dysmotility are usually irreversible and responsible for persistent clinical signs.[2,10]

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
svg.to/9842-05-03-11

## 5.3.12 Neoplastic conditions of the esophagus

Katie Z. Wright, Ann E. Hohenhaus

### 5.3.12.1 Introduction

Information on the occurrence of esophageal tumors in dogs and cats is sparse. An incidence of <0.5% of all neoplasms and <5% of the alimentary neoplasms in both species has been previously reported.[1–3] This older literature is consistent with several more recent tumor registry surveys from Europe, which report an incidence of alimentary tract neoplasia (including esophageal tumors) from 1.9–12% in dogs and 2.9–8% in cats.[4–6] Epithelial tumors are the most commonly reported histology in both species, followed by mesenchymal tumors in dogs and lymphoid tumors in cats.[5,7]

In a report from the United States, squamous cell carcinoma was the most common primary esophageal neoplasia in cats.[8] There is no male or female predominance in cats diagnosed with alimentary tract tumors, but Siamese, Chartreux, and Somali cats are over-represented compared to European shorthair cats.[7] The occurrence of alimentary tract tumors increases with increasing age in both dogs and cats.[9] The median age of occurrence in cats is 10 years.[6]

A well-established median age of dogs with squamous cell carcinoma has yet to be reported, but a range of 6–11 years old has been suggested in older dogs.[10]

Because esophageal tumors in dogs and cats are rare, reliable and well-established information about their cause remains limited.

A strong causal relationship has been reported in the dog between infection by the nematode *Spirocerca lupi* and esophageal sarcoma in geographical regions where the parasite is prevalent (Africa, Israel, southeastern USA).[10–12]

**Barrett's esophagus** is defined as metaplastic columnar mucosal changes that replace the normal esophageal squamous mucosa and has been reported in dogs and cats.[13–18] In people, this morphologic change is a known predisposition to cancer and occurs secondary to chronic gastroesophageal reflux disease (GERD ▶Chap. 5.3.3).[13] GERD and Barrett's esophagus are major risk factors in people for esophageal adenocarcinoma, but their role in neoplastic development of domestic animal species is unreported.[13]

### 5.3.12.2 Histopathology

Many histologic types of primary esophageal tumors have been described, including squamous cell carcinoma, adenosquamous carcinoma, adenocarcinoma of the esophageal glands, carcinoma in situ, fibrosarcoma, sarcoma, osteosarcoma, neuroendocrine carcinoma, plasma cell tumor, rhabdomyosarcoma, and angioleiomyosarcoma.[2,11,12,14,19,20–28] Benign esophageal tumors, such as leiomyomas and plasma cell tumors, have been reported in dogs.[20,30–31] Secondary esophageal tumors originating from locally invasive tumors such as thyroid carcinoma, gastric carcinoma, or via distant metastasis have also been documented.[2,32] In one study, tumors metastatic to the esophagus were three times more common than primary esophageal tumors.[2]

Different histologic types of esophageal tumors affect different portions of the esophagus. Squamous cell carcinoma in dogs and cats often occur at the middle third of the esophagus at the level of the first two ribs, cranial to the aortic arch.[10] In one case series, 24 of the 29 reported cases of feline esophageal squamous cell carcinoma occurred at this location.[33]

Canine leiomyosarcoma secondary to *Spirocerca lupi* is often located in the caudal thoracic esophagus, and the tumors are pedunculated, nodular, or fungiform masses extending into the lumen of the esophagus.[10] Occasionally, the nodules may contain the parasites, and the surface is often ulcerated.[10] On histopathologic evaluation, areas of fibroblastic tissue with high mitotic rates are reported.[10] It is thought that, with continued growth, these areas eventually develop into typical invasive fibrosarcoma.[10]

### 5.3.12.3 Clinical presentation

The clinical signs associated with esophageal neoplasia in dogs and cats can often be explained by obstruction of the esophageal lumen by tumor, stricture, or because of pain during swallowing. These signs include regurgitation, dysphasia, ptyalism, halitosis, and weight loss.[1,8,34,35] Secondary aspiration pneumonia is reported.[21] An association has been made between chronic upper respiratory signs and papillomatous esophagitis in a cat.[36] This cat was believed to have had chronic reflux into the pharynx and nasal passages resulting in chronic upper respiratory signs. Esophageal tumors should be on the differential list in cases of unexplained chronic upper respiratory signs.

### 5.3.12.4 Diagnosis

Physical examination does not typically contribute to the diagnosis of esophageal neoplasia unless a cervical mass is palpable. Routine blood tests, while recommended, are often not suggestive of esophageal neoplasia. Diagnostic imaging is required to localize the esophageal tumor and determine the best approach for biopsy and treatment.[1,32]

The diagnosis of esophageal neoplasia is typically made with a combination of plain film radiography, a positive contrast esophagogram (with or without fluoroscopy), and endoscopy.[37] Computed tomography (CT) imaging may prove beneficial in these patients, though sparsely reported.[35,37] Plain radiographs have the added benefit of ruling out other esophageal disorders with similar clinical signs, such as foreign bodies and megaesophagus. Lateral films have been described as the most useful view to identify esophageal tumors.[37] A contrast esophagogram will frequently show esophageal dilation proximal to a tumor, a filling defect in the tumor area, or leakage of contrast material from an esophageal defect caused by the tumor (▶Fig. 5-19).[8] When interpreting contrast esophagograms, it is important to remember that the

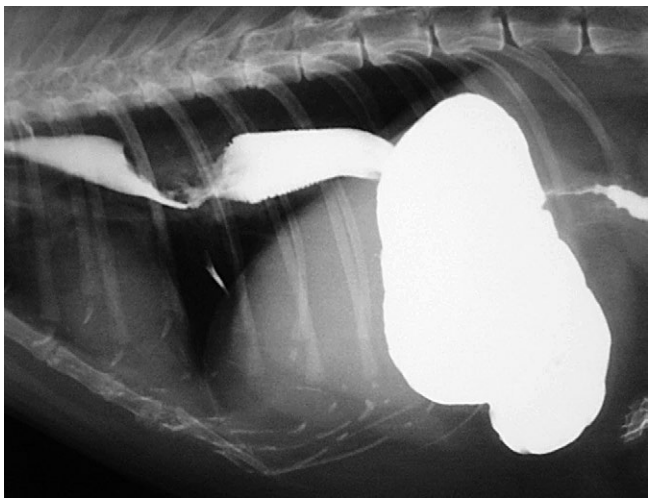


**Fig. 5-19** Esophageal tumor in a cat

This contrast esophagogram demonstrates a filling defect caused by an esophageal tumor in a cat.

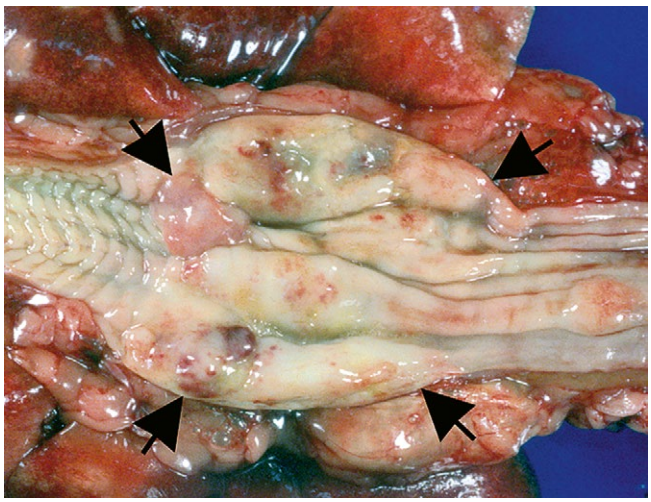


**Fig. 5-20** Appearance of striated muscle in a feline esophagus

This figure shows a metastatic renal sarcoma in the esophagus (**arrows**) of a cat. Note the normal striated muscle of the distal feline esophagus on the left.

distal portion of the feline esophagus consists of striated muscle and typically has a regular herringbone appearance (▶Fig. 5-20). Fluoroscopic evaluation of the esophagus is not always needed to diagnose an esophageal tumor. This imaging modality is beneficial if esophageal motility is required to visualize a dynamic mass.

Esophageal tumors are typically intra-luminal.[10] Thus, esophagoscopy is a less invasive option than thoracotomy for biopsy acquisition (▶Fig. 5-21). Multiple tissue samples should be obtained with the biopsy forceps to ensure adequate tissue for histological evaluation, given the anticipated surrounding inflammation.[35] Leiomyomas appear as circumscribed submucosal masses with a normal and freely movable mucosa making endoscopic biopsy unrewarding. Advanced imaging, such as CT, may help determine the extent of the lesion, especially when minimal mucosal involvement is evident on endoscopic evaluation.[37] In dogs with esophageal sarcoma induced by *Spirocerca lupi* infection, ova may be detected in the feces.[38]

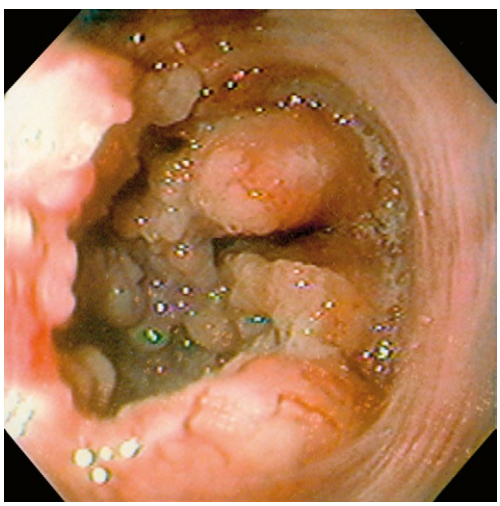


**Fig. 5-21** Esophageal squamous cell carcinoma in a dog

This figure shows the endoscopic view of a squamous cell carcinoma in the esophagus of a dog.

### 5.3.12.5 Treatment

Successful marginal and complete surgeries are reported in the literature, leading to long-term survival and resolution of clinical signs.[31,37] Reconstruction of the esophagus has been attempted by microvascular colon transfer, and a vascular skeletal muscle graft.[39,40] Although surgical resection of esophageal tumors has been the treatment modality of choice, it is uncommon for an esophageal tumor to be amenable to complete resection because the esophagus is incapable of longitudinal stretching and heals poorly under tension.

Effective adjuvant therapy following surgery, or therapy in lieu of surgery, for esophageal neoplasia is lacking. Various case reports of other treatment modalities, such as chemotherapy, radiation therapy, and photodynamic therapy for esophageal tumors, are reported. Doxorubicin chemotherapy following surgical excision of *Spirocerca lupi*-induced esophageal sarcomas led to a median survival time of 267 days.[41] The utility of radiation therapy for treating esophageal tumors is

limited by the poor tolerance of normal structures in the thoracic cavity for radiation-induced side effects. Photodynamic therapy, using a photosensitizing dye activated by a laser light source, was administered to a dog with esophageal squamous cell carcinoma.[42] The tumor underwent partial remission, and the dog survived for 9 months before recurrent regurgitation and aspiration pneumonia resulted in euthanasia.[42] It would be reasonable to expect chemotherapy to benefit pets with esophageal lymphoma; however, no published data currently exist.

Esophageal tumors compromise oral alimentation, and a gastrostomy tube (▶Chap. 3.2.2.1.3) can be considered to provide adequate nutrition and decrease the risk of aspiration pneumonia from regurgitation. Naso-esophageal or esophagostomy tubes (▶Chap. 3.2.2.1.2) are not appropriate in patients with esophageal tumors. Palliative care has been described in a cat with esophageal squamous cell carcinoma, which included a COX-2 inhibiting medication (piroxicam) and feeding tube, leading to a 4-week survival.[35] COX-2 inhibiting therapy has suggested efficacy in dogs and cats with oral squamous cell carcinomas.[35,43,44] While its efficacy in esophageal squamous cell carcinoma is unknown, it is reasonable to consider on it a case-specific basis. Medication for the treatment of esophagitis may be of benefit.

### 5.3.12.6 Systemic complications

Paraneoplastic syndromes are sequelae of cancer occurring remotely from the site of the primary tumor. Hypertrophic osteopathy (▶Fig. 5-22) is a paraneoplastic syndrome of unknown cause associated with esophageal osteosarcoma and *Spirocerca lupi* lesions.[1,22,45] In some cases, painful, swollen limbs may be the first sign of disease.[1] Radiographs of the distal extremities reveal extensive diaphyseal and metaphyseal periosteal bony proliferation on long bones. The metacarpal and metatarsal regions are often most severely affected.[1]

Passive congestion of the liver causing ascites and hindlimb edema has been attributed to caudal vena caval compression by an esophageal leiomyoma of the caudal esophagus.[46] Two other complications of esophageal tumors reported include tracheal invasion and aspiration pneumonia.[2,21]

### 5.3.12.7 Prognosis

Pets with esophageal neoplasia amenable to surgery can enjoy long-term survival.[20,31,37,41] More often, esophageal tumors are too advanced at the time of diagnosis to allow successful treatment. Most cases have a reported survival time of <1 month.[1]



**Fig. 5-22** Hypertrophic osteopathy, a paraneoplastic syndrome in a dog

Orthogonal radiographs of the pes and tarsus of a dog with esophageal neoplasia leading to the secondary characteristic of periosteal proliferation of new bone growth along the existing metatarsal bones (**arrows**).

**KEY FACTS**

- Esophageal tumors are very rare in both dogs and cats.
- Esophageal metastatic tumors are more common than primary esophageal tumors.
- *Spirocerca lupi* is a known cause of esophageal tumors in dogs, and infection can be detected on fecal testing.
- Clinical signs are most frequently related to esophageal obstruction.
- Resection of the esophageal tumor is rarely possible because the tumor is advanced at the time of diagnosis, making survival times short.

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
svg.to/9842-05-03-12

# 6 Stomach

## 6.1 Anatomy

Panpicha Sattasathuchana

Enzymatic digestion of ingesta initially occurs in the stomach. The stomach consists of five anatomical regions: the cardia, fundus, corpus (body), antrum, and pylorus (▶Fig 6-1). The cardia, the fundus, and one-third of the corpus constitute the proximal stomach, whereas the antrum, the pylorus, and the other two-thirds of the corpus make up the distal stomach. The proximal portion of the stomach is mainly responsible for the production of gastric juice. The distal stomach is primarily responsible for the mechanical digestion of ingesta.

The gastric wall has four layers: the mucosa, submucosa, muscularis externa, and serosa. Each layer differs in function according to its anatomical region. The **mucosa** is the innermost layer. It faces the lumen and contains epithelial cells, glandular cells, and the lamina propria. The gastric mucosa has gastric pits and glands. The mucosa in the fundus and corpus is thicker and more glandular than in the cardia and pylorus. The **submucosa** layer contains collagen, elastin, glands, and blood vessels. The **muscularis externa** has three layers of smooth muscle, which are longitudinal (in the middle part of the stomach), circular (across the whole area of the stomach), and oblique (not well developed). These three muscle layers help mechanically crush and propel ingesta out of the stomach. The **serosa** is the outermost layer and consists of a connective tissue layer known as the adventitia.

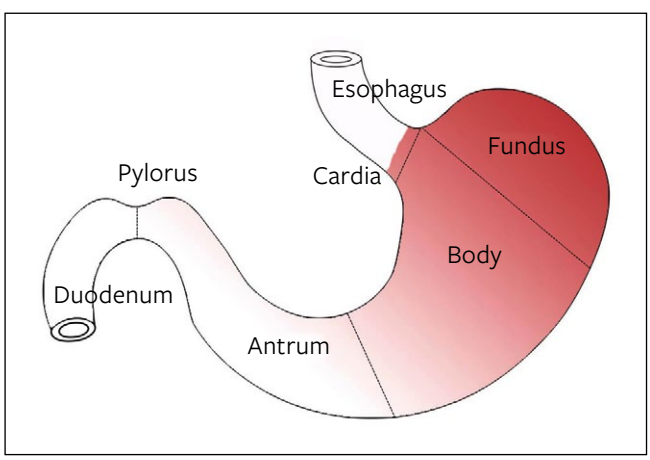



**Fig 6-1** Major anatomical regions of the stomach

The gastric mucosa and submucosa form invaginations called gastric pits, and gastric glands open into the base of these. Three different types of glands are named based on their localization; cardiac glands are located in the gastric cardia, fundic glands (also called oxyntic glands) in the fundus and corpus, and pyloric glands in the pyloric portion of the stomach. Each of these glands contains different secretory cells, which differ in their localization within the gastric glands as well as in the type of products they secrete:

**Cardiac glands** consist mainly of mucus-secreting cells.

**Fundic glands** contain mucous neck cells, chief cells, parietal (oxyntic) cells, enterochromaffin-like cells, and somatostatin-producing cells (D cells) (▶Fig. 6-2). Mucous neck cells produce mucus, gastric lipase, and pepsinogen A.[1,2] In the presence of hydrochloric acid, pepsinogen is activated to the endopeptidase pepsin. Chief cells, located at the base of the fundic glands, produce both pepsinogen A and B isoforms.[2] Parietal cells are found in the upper third of the fundic gland. These glands produce protons ($H^+$), pepsinogen A, intrinsic factor (in dogs), and R-protein. Intrinsic factor binds to cobalamin (vitamin $B_{12}$) and is necessary for its absorption in the ileum. Unlike humans, dogs have limited secretion of intrinsic factor from the stomach, and cats have no intrinsic factor secretion from the stomach. Ghrelin is a peptide "hunger hormone" produced by epithelial cells in the gastric fundus. Ghrelin stimulates appetite, the release of growth hormone, the secretion of gastric acid, and gastric motility. Trefoil factors 1 and 2 (TFF 1 and TFF 2) are peptides synthesized in and secreted by mucous neck cells, in the gastric fundus and antrum, and pyloric gastric glands. Trefoil factors co-function with mucins to maintain the mucosal surface.

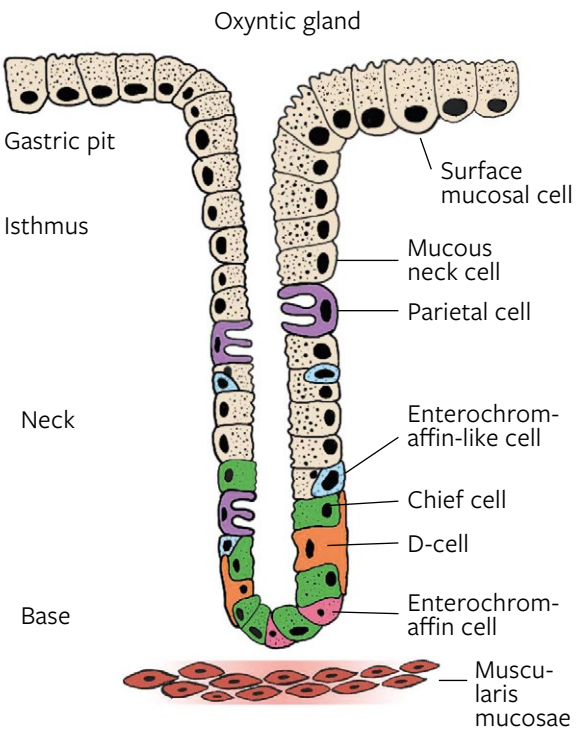



**Fig. 6-2** Structure of a gastric fundic gland

Fundic glands are found in the corpus and fundus of the stomach and consist of various cells responsible for regulating acid and mucus secretion.

**Pyloric glands** contain mucus-secreting cells and gastrin-producing endocrine cells (G-cells). Gastrin stimulates parietal cells to produce gastric acid and is a trophic factor for the gastric mucosa.

**KEY FACTS**

- There are five anatomical regions of stomach that play varying roles in enzymatic and mechanical digestion.
- Gastric glands produce important chemical agents, including gastric lipase, gastrin, ghrelin, hydrochloric acid, pepsinogen, R-protein, and trefoil factors.

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
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## 6.2 Physiology

Panpicha Sattasathuchana

### 6.2.1 Gastric emptying and motility

Ingesta pass to the stomach from the esophagus through the lower esophageal sphincter. The first part of the stomach that contacts the ingesta is the cardia. The fundus and the corpus can actively expand to accommodate the ingesta. In the postprandial phase of gastric motility, the antrum functions to mechanically crush and reduce the size of the ingesta. The pylorus acts as the "gatekeeper," preventing any particles >2 mm from entering the duodenum.[1] Ingesta-particles >2 mm are propelled back into the antrum. This repeating a to-and-fro movement of ingesta in the antrum leads to the mechanical breakdown and stirring of food known as trituration, resulting in the passage of digestible solids into the duodenum. The rate of gastric emptying of solid food depends on the size of the particles and caloric density. Liquids empty from the stomach more rapidly than digestible solids.[1] Non-digestible solids are emptied later in the interdigestive phase of gastric motility.

### 6.2.2 Gastric acid secretion

Acidic gastric juice with a pH of 1–2 is required for digestion in the stomach. The acidic conditions in the stomach result from hydrochloric acid secreted by parietal cells in the fundus and corpus (▶Fig. 6-3, ▶Fig. 6-4). This low gastric luminal pH also helps control the microbiota of the stomach, activates pepsinogen, and helps digest protein. Secretion of hydrochloric acid is stimulated by acetylcholine, gastrin, and histamine.[2] Activation of acetylcholine ($m_3$), gastrin (G), and histamine ($H_2$) receptors increase the accumulation of cyclic adenosine monophosphate (cAMP) and intracellular $Ca^{2+}$ in parietal cells. The accumulation of cAMP activates protein kinase A, which increases protein phosphorylation. Protein phosphorylation activates $H^+$, $K^+$, and ATPases (proton pumps), which hydrolyze ATP leading to the active transport of $H^+$ into the gastric lumen.

There are three phases of gastric acid secretion: cephalic, gastric, and intestinal. The **cephalic phase**, which accounts for 15–30% of total gastric secretion, is stimulated by vagal neurons and neuropeptides in response to taste, smell, or the sight of food. Acetylcholine released from cholinergic neurons of the vagal nerve stimulate muscarinic receptors ($m_3$) on the apical surface of parietal cells, activating their proton pumps and acid secretion. Acetylcholine also activates histamine secretion from enterochromaffin-like cells

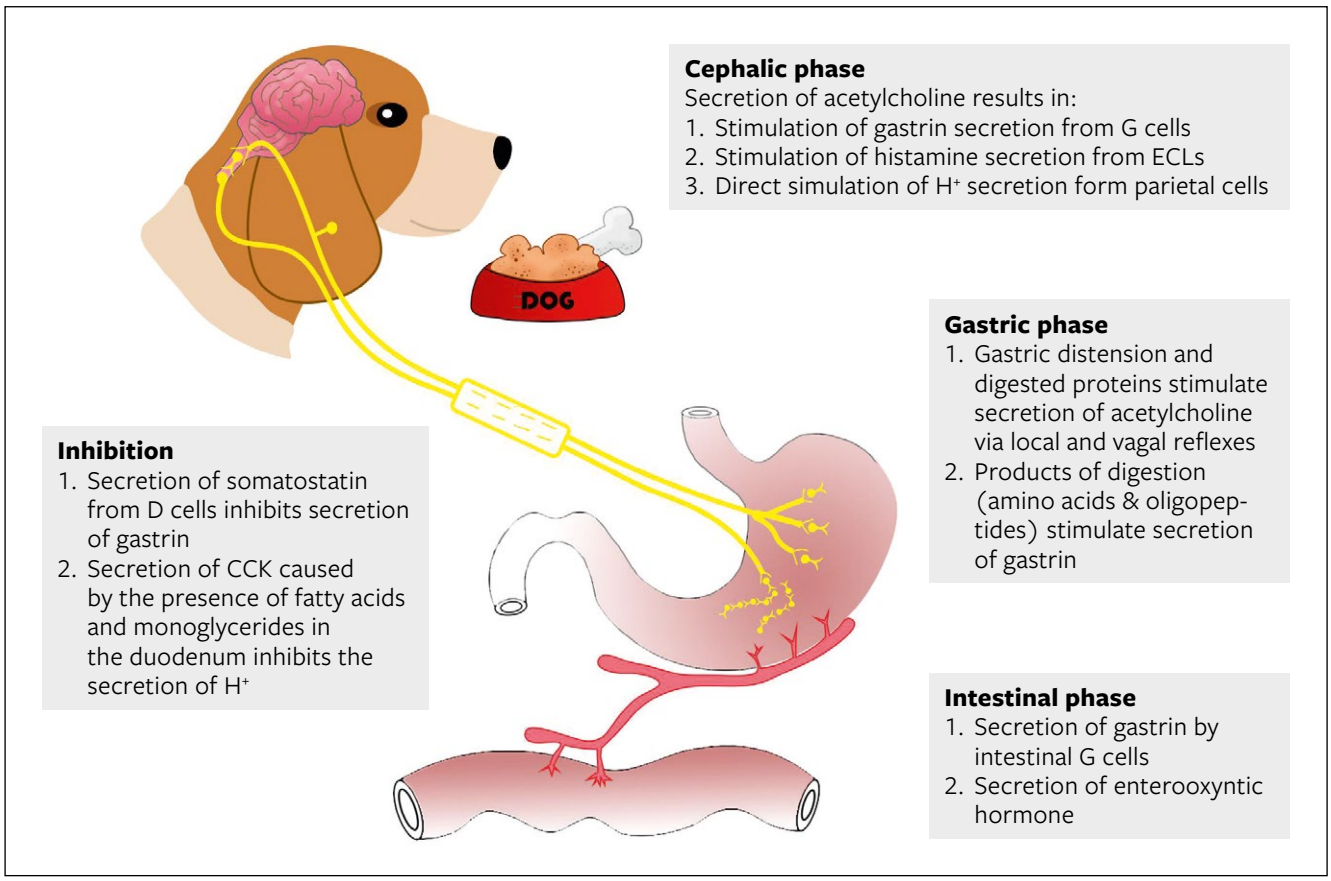



**Fig. 6-3** Regulation of gastric acid secretion

Gastric acid secretion consists of three digestive phases (cephalic, gastric, and intestinal phase).

**ECLs** = enterochromaffin-like cells, **CCK** = cholecystokinin

in the gastric fundus. Histamine enhances the acid secretory response of parietal cells to gastrin and acetylcholine. Acetylcholine also stimulates gastrin secetion via bombesin and inhibits somatostatin secretion. The **gastric phase** accounts for 50–60% of total gastric secretion. This phase is initiated by gastric distention and gastrin-producing endocrine cell (G cell) stimulation by amino acids and peptides in the gastric lumen. Stretching of the stomach wall activates local reflexes (mediated by acetylcholine) and vasovagal reflexes (mediated by acetylcholine and bombesin). Both acetylcholine and bombesin activate G cells to secrete gastrin. Both acetylcholine and gastrin activate $H^+$ secretion from parietal cells. The **intestinal phase** accounts for 5% of total gastric secretion. Stimulation of gastric secretion occurs when the duodenal pH is >3. Gastrin from intestinal G cells and enterooxyntic hormone from the duodenum are released and stimulate $H^+$ secretion from parietal cells.

When the gastric pH is <3, somatostatin is released by D cells, initiating a **negative feedback** mechanism on G cells that inhibits gastrin secretion. At a gastric pH <2, the secretion of gastrin is completely inhibited. Cholecystokinin (CCK) is released by enteroendocrine cells (I cells) when amino acids, fatty acids, and peptides are present in the duodenum. CCK inhibits parietal cell secretion and activates exocrine pancreatic secretion and gall bladder contraction.

Gastric acid secretion also occurs during the interdigestive phase, which is a phase between meals. Gastric acid secretion in the **interdigestive phase**, which is important for cleaning the empty stomach in preparation for the next meal, is regulated by acetylcholine and histamine. This phase accounts for 15% of total gastric acid secretion.

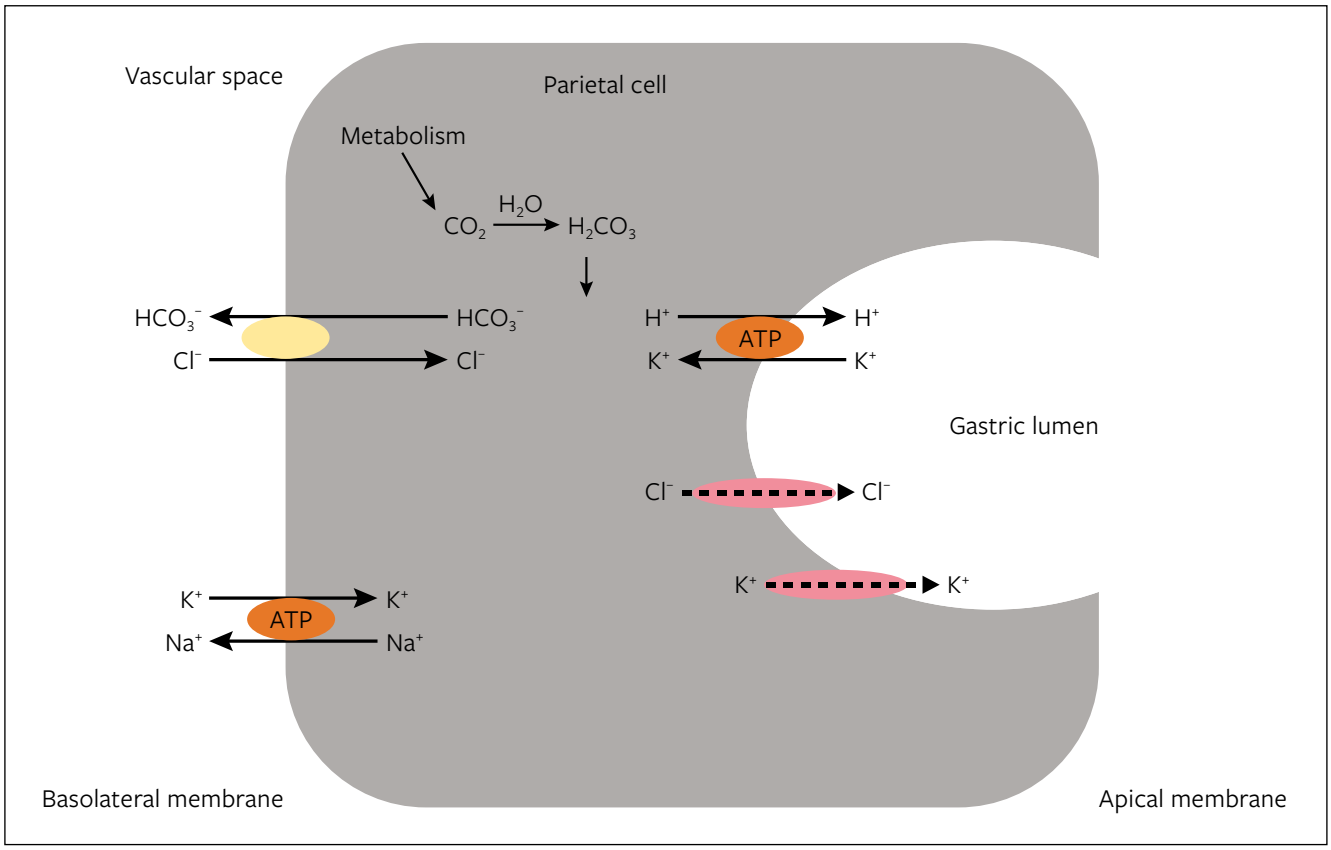



**Fig. 6-4** Hydrochloric acid secretion by parietal cells

$CO_2$ from intracellular aerobic metabolism reacts with $H_2O$ to form $H_2CO_3$, which dissociates into $HCO_3^-$ and $H^+$. At the apical membrane, $H^+$ is pumped into the gastric lumen via $H^+$, $K^+$-ATPase against their electrochemical gradients. $Cl^-$ also accompanies $H^+$ into the gastric lumen via a $Cl^-$ channel to create HCl in the gastric lumen. At the basolateral membrane, the downhill efflux of $HCO_3^-$ into vascular space occurs via the $Cl^-$-$HCO_3^-$ exchange, which is responsible for an alkaline tide or high blood pH after a meal. This $HCO_3^-$ is secreted back into the duodenum in pancreatic secretion. $Na^+$, $K^+$-ATPase is also found at the basolateral membrane to pump $Na^+$ out of cells and move $K^+$ into cellular space. $K^+$ is passively diffused out of cells into the gastric lumen at the apical membrane.

### 6.2.3 Gastric mucosal barrier

Without a functional gastric mucosal barrier, the highly acidic conditions and potent digestive enzymes in the gastric lumen severely damage the gastric mucosa.

The first layer of defense against autodigestion is the **secretion of bicarbonate and mucus**.[3] Secretion of both is increased by acetylcholine from parasympathetic stimulation. Mucous neck cells secrete a viscous and sticky glycoprotein gel. This mucus gel is subject to proteolysis by pepsins, forming a protective layer covering the gastric mucosa. The formation of bicarbonate from the gastric parietal cells occurs in conjunction with the formation of $H^+$ and works with the gastric mucus to prevent damage to the gastric mucosa by gastric contents. The pH at the surface of the gastric epithelium is nearly 7.

The **structure of epithelial cells** also plays a role in the mucosal protectant mechanism.[4] The hydrophobic phospholipid structure at the apical surface of epithelial cells helps prevent acidic gastric juice in the lumen from breaching the epithelial surface. Additionally, the gastric epithelial cells are bound together by tight junctions to prevent the back diffusion of hydrochloric acid and pepsin via the paracellular pathway. The gastric epithelial cells also have a relatively high bicarbonate content that neutralizes acid that back diffuses into them.

When the gastric mucosal barrier fails to protect the gastric surface, **gastric epithelial cells can rapidly regenerate** because of their high cellular turnover rates. Moreover, epidermal growth factor, transforming growth factor-alpha, trefoil peptides, and nitric oxide increase the proliferation of adjacent epithelial cells to cover the lesion.

**Prostaglandins**, particularly prostaglandin E2 and prostacyclin, play a major role in maintaining the integrity of the gastric mucosal barrier. They stimulate mucus and bicarbonate secretion, increase gastric mucosal blood flow, and promote the regeneration of epithelial cells.

**KEY FACTS**

- The digestive function of the stomach is due to the combined effects of gastric motility and gastric acid secretion.
- Gastric mucosal barrier protections involve mucous secretion, bicarbonate secretion, and the rapid regeneration of epithelial cells.

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
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# 6.3 Diseases of the stomach

## 6.3.1 Acute and chronic gastritis

M. Katherine Tolbert

### 6.3.1.1 Classification

By definition, gastritis is an inflammatory disease of the stomach. Many patients with clinical signs suggestive of a gastric disorder, most commonly vomiting or gastric distension, are presumed to have inflammation or some type of mucosal injury; however, as infiltration of the gastric mucosa with inflammatory cells is rarely definitively proven with biopsy in the acute setting and can be minimal even with severe signs, it might be more accurate to use the term gastropathy for these cases. Inflammation, when present, is also rarely limited to the stomach and often extends into the small intestine.

Classification schemes for gastritis in humans, such as the Sydney Classification System for chronic gastritis,[1] are used to streamline terminology and approach amongst clinicians and researchers. To this end, guidelines for the evaluation of gastrointestinal inflammation, including gastritis, were created by the World Small Animal Veterinary Association (WSAVA) International Gastrointestinal (GI) Standardization Group.[2] Since histopathologic evaluation is not always performed, gastritis in dogs and cats is commonly categorized by the duration of clinical signs and not on histological parameters, although the latter can be helpful in the determination of etiology and chronicity as outlined for chronic gastritis.

### 6.3.1.2 Acute gastritis/gastropathy

Acute gastritis, defined by the presence of clinical signs for <2 weeks, is often self-limiting and responds to supportive care. A variety of etiologies has been implicated in the development of gastritis or vomiting in dogs and cats (▶Tab. 6-1). Acute gastritis can affect a dog or cat of any age or breed. The most common causes include foreign bodies, dietary indiscretion ("garbage gut"), food intolerance, drugs, household chemicals, pesticides/herbicides, plants, systemic illness, and infectious agents. A list of common plants and household chemicals associated with gastritis may be found in an excellent review by Webb and Twedt.[3] Among drugs, non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics, and chemotherapeutics are leading causes of gastritis in dogs and cats. NSAIDs are injurious to the gastrointestinal epithelium, both directly and indirectly, as a result of being weak acids and inhibiting the synthesis of protective prostaglandins. The majority of NSAIDs used in dogs and cats have been associated with the development of gastric lesions.

Acute metabolic illness (e.g., acute hepatic or renal injury, hypoadrenocorticism) or conditions causing poor gastrointestinal (GI) perfusion (e.g., gastric dilatation-volvulus ▶Chap. 6.3.3, thromboembolic disease, extreme exercise) may also acutely trigger gastric inflammation, although the majority of these conditions are also accompanied by systemic signs.

Infectious agents can be causes of both acute and chronic gastritis and include a variety of helminths (e.g., *Physaloptera* spp., *Ollulanus*), oomycetes (e.g., *Pythium*), fungi (e.g., *Histoplasma*), bacteria (e.g., *Salmonella* spp., *Campylobacter jejuni*, *Helicobacter*), and rarely, viruses (Parvovirus, Distemper virus).



In cats, heartworm infection may cause vomiting and gastritis, although this tends to present more chronically.

Enteropathogenic bacteria are rarely primary causes of acute gastritis except in dogs and cats with exposure to uncooked foods, treats, or roadkill or those with a history of hunting. As with metabolic disease, most non-parasitic, infectious agents are generally accompanied by systemic signs such as fever. Often the cause of acute gastritis/gastropathy is undetermined and symptomatic treatment, as outlined later, is initiated.

**Tab. 6-1** Causes of gastropathy in dogs and cats

| Category | Dogs | Cats |
|---|---|---|
| Structural/inflammatory | • Dietary indiscretion<br>• Food intolerance<br>• Foreign body<br>• Inflammatory bowel disease<br>• Gastric neoplasia<br>• Pyloric hypertrophy<br>• Bilious vomiting syndrome | • Dietary indiscretion<br>• Inflammatory bowel disease<br>• Foreign body<br>• Gastric neoplasia |
| Infectious | • Viral<br>• Bacterial (*Helicobacter*)<br>• Fungal (*Histoplasma*)<br>• Helminth<br>– *Gnathostoma binucleatum*<br>– *Physaloptera spp.*<br>– *Toxocara canis*<br>• Oomycete (*Pythium*) | • Bacterial (*Helicobacter*)<br>• Helminth<br>– *Ollulanus tricuspis*<br>– *Gnathostoma binucleatum*<br>– *Toxocara cati*<br>• Dirofilariasis |
| Drugs/Toxins | • NSAIDs<br>• Antibiotics<br>• Chemotherapeutics<br>• Proton pump inhibitors<br>• Household and outdoor plants | Same as dogs |
| Breed related | • Basenji: immunoproliferative enteropathy<br>• Norwegian lundehund: atrophic gastritis, lymphangiectasia<br>• Rottweiler: eosinophilic enteropathy<br>• Racing breeds | None known |

**NSAIDs** = non-steroidal anti-inflammatory drugs



#### 6.3.1.2.1 Clinical presentation and diagnosis

Obtaining a **detailed history** and performing a comprehensive physical exam are critical to determining the best diagnostic and therapeutic approach. Standardized checklists[4] can be used to facilitate the acquisition of a complete history in the face of a busy clinic day for both acute and chronic vomiting. Dogs and cats with vomiting from dietary indiscretion can have rapidly resolving clinical signs with supportive care. Animals with a history of more severe signs such as protracted vomiting, hiding behavior, hematemesis, or physical exam abnormalities such as dehydration, hypovolemia, or abdominal pain need more extensive evaluation. Owners should be questioned regarding the possibility of exposure of their pet to yarn, string, tinsel, needles, or hair ties. A full drug history should be obtained for any dog (or cat) presenting with signs of gastric disease.

**CLINICAL PEARLS**

Intoxications secondary to chocolate (theobromine), macadamia nuts, mycotoxins (e.g., mushrooms, sago palms, blue-green algae, molds), and marijuana should be considered in dogs or cats exhibiting vomiting in association with an acute onset of neurologic abnormalities.

Viral etiologies rarely cause vomiting alone but should be suspected when there is an outbreak of GI signs in multiple dogs or cats from the same shelter or household or when signs are severe, particularly in young animals. Viral gastroenteritis may cause inappetence, fever, lethargy, vomiting, and diarrhea.

**Physical examination findings** in animals with acute gastritis/gastropathy vary. Animals may have mild symptoms and, therefore, no abnormalities or have severe symptoms accompanied by hunched posture, abdominal pain, facial grimace, dehydration, ptyalism, or signs of hypovolemia and shock, including weak pulses, hypo- or hyperthermia, tachycardia, pale mucous membranes, and prolonged capillary refill time. Cranial abdominal pain may be appreciated on physical examination in cases of foreign body ingestion, gastric dilatation-volvulus, pancreatitis, or severe GI ulceration. Linear foreign bodies may become anchored to the base of a patient's tongue, and careful inspection of this area on physical examination is recommended when possible. Rectal and fecal examination should be performed to evaluate for frank blood, tarry stools, and parasites. Examination of the vomitus for the presence of blood or parasites is also recommended. Body and muscle condition scores (▶Chap. 3.1.1) are expected to be normal in cases of acute gastritis and are often normal in animals with chronic gastritis in the absence of co-morbidities.[5]

The need for an extensive **diagnostic evaluation** and therapeutic intervention depends on the severity of clinical signs, as well as physical exam findings. For dogs and cats with mild signs, supportive care may be all that is needed. In the absence of a known cause such as dietary indiscretion, young dogs and cats, especially those with outdoor exposure or access to foreign objects, a centrifugal fecal flotation, fecal nematode antigen testing, and abdominal radiographs are generally recommended to evaluate for the presence of parasitic disease or foreign material. For those dogs and cats with concerning historical findings (e.g., hematemesis, prolonged dysrexia, possible foreign body ingestion) or moderate to severe physical exam abnormalities (e.g., pale mucous membranes, signs of hypovolemia, abdominal pain, tarry or frank blood on rectal examination), additional diagnostic workup including a complete blood count (CBC), biochemical panel, urinalysis, and coagulation panel in addition to further imaging such as abdominal ultrasound may be indicated. Other diagnostics are considered based on the history, physical exam, and results of the initial diagnostic workup.

#### 6.3.1.2.2 Treatment

For dogs and cats with mild signs, a short period (<12 hours) during which food is withheld along with supportive care and introduction of oral fluids followed by a low residue food for several days might be all that is needed.

**NOTE**

Prolonged fasting of patients is not recommended because of the positive benefits of early enteral nutrition.

If the signs are more severe, (i.e., dehydration, continuous vomiting), the animal will need **fluid replacement** with intravenous replacement crystalloids (e.g., lactated Ringer's solution). Correction of electrolyte abnormalities (e.g., hypokalemia) is often required in patients with severe vomiting. If the animal tolerates oral water, a bland, low residue commercial or home-cooked **diet** (e.g., white fish or chicken and rice, cottage cheese and rice), given in small amounts multiple times during the day, can be introduced. The animal's regular food can be slowly reintroduced over a 3–5-day period after vomiting has ceased. In some patients, **symptomatic treatment with antiemetic drugs** may be needed while evaluating the cause of vomiting. Antiemetics can be prescribed once the practitioner is confident that a mechanical obstruction or toxicity, in which emesis might be induced, is not the cause of vomiting. Commercially available antiemetics commonly used in veterinary medicine include maropitant, serotonin antagonists, and metoclopramide (▶Tab. 6-2). The choice of antiemetic drug is dictated by the likely stimulus of vomiting (e.g., motion sickness or vestibular disease, abdominal disease) and the species. **Anthelminthic treatment** is recommended, especially in young animals and those without an anthelminthic preventative history. An infestation with gastric nematodes (i.e., *Physaloptera* spp. in dogs and *Ollulanus tricuspis* in cats) may be challenging to diagnose, and routine therapy with a broad-spectrum anthelminthic agent is effective in eradicating stomach worms (in dogs: pyrantel pamoate at 15 mg/kg PO repeated in 2–3 weeks; in cats: fenbendazole at 50 mg/kg PO q24h for 3 days) is prudent before recommending more expensive diagnostic tests. Gastric acid suppressant drugs (e.g., histamine-2 receptor antagonists, proton pump inhibitors, sucralfate) are reserved for patients in which gastric erosion or ulceration is suspected due to the presence of hematemesis or melena, as discussed in a later section.

**Tab. 6-2** Drugs and doses for the treatment of vomiting in dogs and cats

| Class | Drug | Mechanism of action | Doses | Side effects and additional information |
|---|---|---|---|---|
| **Antiemetics** | **Ondansetron, Dolasetron** | Serotonin ($5\text{-}HT_3$) receptor antagonist | 0.5–1.0 mg/kg q8–24h PO or IV | • Sedation<br>• Slows gastrointestinal motility<br>• Poor bioavailability<br>• Oral administration is not recommended in cats due to poor bioavailability and short half-life |
| | **Maropitant citrate** | Neurokinin ($NK_1$) receptor antagonist | • 1 mg/kg q24h IV, SC<br>• 2 mg/kg q24h PO | • Caution in puppies <11 weeks old due to a higher frequency of bone marrow hypoplasia<br>• Caution in animals with liver dysfunction |
| | **Metoclopramide** | Dopamine-2 receptor (low doses) and $5\text{-}HT_3$ (high doses) antagonist | • 0.2–0.5 mg/kg q6–8h PO, SC, IV<br>• CRI: 1 mg/kg/day IV | • Monitor for extrapyramidal signs<br>• Not an effective antiemetic in cats |
| **Gastroprotectants** | **Proton pump inhibitors (omeprazole, pantoprazole, esomeprazole)** | Inhibition of parietal cell $H^+\text{-}K^+$-ATPase | 1 mg/kg q12h PO, IV | • Vomiting, diarrhea<br>• Long-term prophylaxis not recommended<br>• Esomeprazole may be effective q24h in dogs<br>• Drug interactions |
| | **Histamine-2 receptor antagonists (famotidine, ranitidine)** | Competitive inhibitor of parietal cell histamine-2 receptor | • 1 mg/kg q12h PO, IV, SC<br>• 8 mg/kg/day IV as a CRI | Diminished effect with prolonged use |
| | **Sucralfate** | Coating agent | 0.25–1g q6–8h PO as a slurry | Drug interactions |
| | **Misoprostol** | Prostaglandin E1 analog | Dogs: 3 µg/kg PO q8–12h | • Cramping, diarrhea<br>• Do not use in pregnant animals<br>• Not recommended for cats |

**PO** = per os, **IV** = intravenous, **SC** = subcutaneous, **CRI** = continous rate infusion



## KEY FACTS

- Acute gastritis, defined by the presence of clinical signs for <2 weeks, is often self-limiting and responds to supportive care. The most common causes include foreign bodies, dietary indiscretion or intolerance, drugs, household chemicals or pesticides/herbicides, plants, systemic illness, and infectious agents.
- Obtaining a detailed history and performing a comprehensive physical examination are critical to determining the best diagnostic and therapeutic approach.
- For dogs and cats with mild signs, a short period (<12 hours) during which food is withheld along with supportive care and introduction of oral fluids followed by a low residue food for several days might be all that is needed.
- If the signs are more severe, the animal will need fluid replacement. Symptomatic treatment with antiemetic drugs may be needed. Antiemetics can be prescribed once the practitioner is confident that a mechanical obstruction or toxicity, in which emesis might be induced, is not the cause of vomiting. Anthelminthic treatment is recommended especially in young animals and those without an anthelminthic preventative history.

### 6.3.1.3 Chronic gastritis

#### 6.3.1.3.1 Etiology and classification

The pathogenesis of chronic gastritis in dogs and cats is also not always determined. In some cases, a cause, such as parasitism, neoplasm, infectious agent, or a metabolic disorder (e.g., uremia, hepatopathy), can be identified. Once more common causes are determined to be unlikely, chronic gastritis is deemed idiopathic, and food intolerance or immune-mediated condition is often considered to be responsible.



Several breeds are at risk for chronic gastritis, including the basenji, the Drentse patrijshond, and the Norwegian lundehund.

Clinical signs in dogs and cats with chronic gastritis are characterized by persistent or intermittent vomiting of variable frequency and character that has been present for >2 weeks. Because inflammation can impair gastric motility and delay gastric emptying, animals with chronic gastritis may retain food in the stomach for long periods of time. Determining the cause of chronic gastritis may require the acquisition of a mucosal tissue sample via endoscopy (▶Chap. 1.5) or laparotomy (▶Chap. 1.6). Gastritis can then be classified based on the cellular infiltrate (i.e., lymphoplasmacytic, eosinophilic, pyogranulomatous, suppurative, lymphoid follicular hyperplasia, neoplastic), the presence of morphologic changes (i.e., hypertrophy, atrophy, mineralization, ulceration, edema, glandular nesting, and fibrosis), and lesion severity (i.e., normal, mild, moderate, marked, severe). More details on histopathologic evaluation and nomenclature can be found in publications by the WSAVA GI Standardization Group.[2]

##### Lymphoplasmacytic and lymphocytic gastritis

Lymphoplasmacytic (LP) gastritis is the most common histologic type of chronic gastritis in dogs, representing 51% of dogs in one study.[5] Mild to moderate LP gastritis can be observed in dogs and cats in good health, and thus the presence of clinical signs should be considered when determining the importance and requirement for treatment of gastric inflammation.[5,6] Causes of LP and lymphocytic gastritis can include inflammatory bowel disease (▶Chap. 11.2), food responsive disease, *Helicobacter* spp. colonization (▶Helicobacter-associated gastritis), exercise and breed predisposition (Alaskan racing sled dogs).[7] *Helicobacter* spp. are frequently identified in the stomachs of dogs with and without both gastric inflammation and clinical signs of disease; therefore, their role as a potential pathogen in dogs remains unclear.[8] Indeed, some researchers propose that loss of tolerance to *Helicobacter* rather than pathogenicity of the organism may be responsible for the development of inflammation and clinical signs. *Helicobacter* spp. colonization is also frequently present in healthy cats; however, *Helicobacter* organisms have been associated with gastric lymphoid follicles and epithelial proliferation[9] as well as gastric lymphoma in cats.[10] Thus, the role of *Helicobacter* spp. as a causative agent of inflammation in companion animals is often difficult to determine but treatment is often recommended where organisms are associated with inflammation in animals that fail initial therapies such as dietary modification. More information is provided in a subsequent section. Severe LP infiltration may be difficult to distinguish from gastric lymphoma (▶Chap. 6.3.4), especially when the biopsy specimens are endoscopically obtained.[6] The use of immunophenotyping, as outlined in diagnostics, may help support a diagnosis of lymphoma.

##### Eosinophilic gastritis

According to the WSAVA GI Standardization Group, the mucosa of the normal gastric body and gastric antrum may have 0–2 and 0–6 eosinophils/10,000 $mm^2$, respectively. Eosinophil counts beyond these numbers would suggest the presence of eosinophilic gastritis. Eosinophilic gastritis is often accompanied by small or large intestinal eosinophilic infiltration. In the absence of a food allergy/intolerance or parasitic disease, eosinophilic gastritis is included under the umbrella of idiopathic inflammatory bowel disease.[11] Dogs with eosinophilic gastritis tend to be younger (<5 years)[11], and Rottweilers are likely a predisposed breed. Gastric infiltration is usually restricted to the mucosa, but in some patients, it may extend into the muscularis and even the serosa. Mucosal involvement can cause enlargement of the rugal folds. The diseased mucosa may become ulcerated, which leads to bleeding or leakage of plasma proteins into the gastric lumen. Peripheral eosinophilia is a common finding, but its severity can vary markedly. Some dogs also have a history of either urticaria or dermatologic changes or vomiting that may be associated with the ingestion of a specific diet. The treatment of eosinophilic gastritis is usually centered on dietary modification (e.g., hydrolyzed or limited ingredient diet, ▶Chap. 3.2) and anthelminthic therapy. Several dietary trials in which the client feeds the diet exclusively may be needed before clinical signs resolve. Dogs that fail anthelminthic and dietary therapy may have a positive response to immunomodulatory therapy (e.g., corticosteroids). A detailed review of the pathophysiology and management strategies

for eosinophilic gastrointestinal disorders is provided elsewhere.[11] Eosinophilic gastritis appears to be rare in cats, including those with eosinophilic enteritis.[12]

### Hypertrophic gastropathy/gastritis

Chronic hypertrophic gastropathy/gastritis is a rare disorder that appears either as diffuse, generalized mucosal hypertrophy or, more frequently, as localized hypertrophy of the antral mucosa that may cause intermittent or chronic pyloric obstruction. Clinical signs of hypertrophic gastropathy include delayed gastric emptying, abdominal distension, vomiting, dysrexia, and lethargy. Although vomiting is most common, some animals may regurgitate if the abdominal distension is severe enough to overcome the lower esophageal sphincter pressure. Causative factors that may lead to gastric mucosal hypertrophy include chronic inflammation, foreign bodies, or long-term use (i.e., years) of proton pump inhibitors. Boxers and basenjis have a predilection for the diffuse form of hypertrophic gastritis. In contrast, the localized form is over-represented by young to middle-aged small breed dogs. Dogs with hypertrophic pyloric gastropathy often have fluid or gas-filled stomachs on radiographs. Contrast radiography can be useful to confirm outflow obstruction. Documentation of delayed gastric emptying and increased pyloric wall thickness on ultrasound supports the diagnosis (▶Fig. 6-5). Definitive diagnosis is confirmed by endoscopic or surgical identification of enlarged mucosal folds that make pyloric intubation difficult.[13] Surgical resection of the affected area is considered to be the treatment of choice. The disease is characterized microscopically by mucosal hyperplasia with glandular and foveolar hyperplasia, edema, microscopic foci of ulceration, or cystic glandular dilation. Varying degrees of inflammatory cell infiltration are often present. Dogs with pyloric hypertrophy from Ménétrier disease, in which the gastric mural thickening is due to hyperplasia of the mucous cells with concurrent loss of chief and parietal cells, may be predisposed to gastric carcinoma.[14]

### Atrophic gastritis

Atrophic gastritis is a rare disorder in which the gastric mucosa atrophies. The presence of inflammation tends to be minimal. The fundic mucosa is often involved leading to loss of gastric acid-secreting function. Atrophic gastritis is most commonly reported in the Norwegian lundehund, where a genetic predisposition is suspected. The cause is unknown, but the condition occurs mainly in older dogs and may be immune-mediated in origin. Atrophic gastritis may also be a sequel to chronic biliary reflux gastritis in dogs. The predominant complaint is chronic intermittent vomiting. The achlorhydria may predispose to bacterial overgrowth from ingested microorganisms that would normally be destroyed by the acidic stomach contents. This can lead to malabsorption, chronic diarrhea, and loss of body weight and condition. An association between atrophic gastritis and gastric carcinoma has been recognized and is thought to occur secondary to enterochromaffin-like cell hyperplasia from chronic hypergastrinemia.[15]



**Fig. 6-5** Abdominal ultrasound showing increased circumferential pyloric wall thickness (✱) consistent with pyloric hypertrophy in a 1-year-old French bulldog.

### Helicobacter-associated gastritis

*Helicobacter* spp. are gram-negative, microaerophilic, curved to spiral-shaped, motile bacteria. *Helicobacter* spp. are predominantly identified in the stomach; however, they can also be found in the oral cavity, intestine, and hepatobiliary system.[16,17] Most gastric Helicobacter-like organisms (GHLO) found in dogs and cats are large spiral organisms (0.5 × 5–10 µm) that cannot be distinguished by light microscopy. To date, *H. felis*, *H. bizzozeronii*, *H. salomonis*, *Flexispira rappini*, *H. bilis*, *H. heilmannii sensu stricto*, *H. pametensis*, and *H. pylori* have all been identified in the stomach of dogs or cats with non-*Helicobacter pylori* species predominating.[9,18] Mixed infections with two or more *Helicobacter* spp. appear to be common in dogs and cats. Several studies showed a high prevalence of GHLO in cats and dogs, with up to a 100% infection rate amongst laboratory animals, 50–100% amongst healthy pets, and 41–100% among vomiting pets.[19] Housing conditions and age appear to play an important role, with pets living in shelters or colonies having a higher prevalence. The mode of transmission of *Helicobacter* spp. is still unclear, with both fecal-oral and oral-oral transmission being proposed.

In human patients, there is extensive evidence implicating *H. pylori* in the pathogenesis of chronic superficial gastritis. Eradication of *H. pylori* by use of antimicrobial therapy may cure gastritis in people. Infection with *Helicobacter* spp. also predisposes humans to the development of gastric neoplasia. In pets with naturally acquired *Helicobacter* colonization, however, the pathogenic role of this organism is still highly debated, and loss of tolerance is suspected of leading to disease rather than colonization. Obvious clinical signs of infection are absent in the majority of infected cats and dogs, and few studies have investigated the cellular and immunological consequences of infection. In dogs, mild gastritis with infiltration of the gastric mucosa involving lymphocytes and plasma cells is most commonly identified, but a correlation between the histopathological changes and the occurrence of GHLOs is inconsistently identified in dogs.



In dogs, mild gastritis with infiltration of the gastric mucosa involving lymphocytes and plasma cells is most commonly identified, but a correlation between the histopathological changes and the occurrence of gastric Helicobacter-like organisms is inconsistently identified in dogs.



In some cats with *Helicobacter* colonization, histopathologic findings vary from normal gastric mucosa to mild to moderate gastritis and lymphoid follicular hyperplasia. Gastric inflammation can persist even with the eradication of the organism.[20]

Non-invasive tests such as serology by ELISA or Western blotting are assays developed for detection of *Helicobacter pylori* in people but provide little utility in dogs and cats where non-*H. pylori* species predominate. Amplification of *Helicobacter* DNA from canine fecal samples has recently been described.[21] However, with this technique, the presence of *Helicobacter* DNA is not specific for GHLOs. The definitive diagnosis for the presence of *Helicobacter* spp. in the stomach requires demonstration of the organism on mucosal tissue samples and confirmation of the presence of *Helicobacter* spp. by culture or polymerase chain reaction. A rapid urease test (also called CLO test for *Campylobacter*-like organism test) can be used to increase suspicion of the organism. A mucosal tissue sample is incubated in a broth containing urea and phenol red as a pH indicator. As the urease breaks down urea into ammonia, the pH rises, and a color change occurs. The results can often be obtained within 1–3 hours but may take up to 24 hours, and the test is susceptible to false-positive results secondary to the presence of other urease-producing bacteria such as *E. coli* or *Proteus* spp. Histopathology relies on the visualization of *Helicobacter* organisms in gastric biopsy samples. Special staining such as Warthin-Starry silver, Giemsa, or toluidine blue stain will enhance the visibility of *Helicobacter* spp. Due to the patchy distribution of the *Helicobacter* organisms, several biopsies from the antrum and corpus should be evaluated. Culture for *Helicobacter* spp. is cumbersome and the least sensitive method for diagnosing these organisms; however, a positive culture is highly specific. Polymerase chain reaction (PCR) of DNA extracted from a biopsy specimen permits definitive identification of the *Helicobacter* strain present. Treatment with triple therapy (amoxicillin 20 mg/kg PO q8–12h, metronidazole 20 mg/kg PO q8–12h, omeprazole 0.7 mg/kg PO q12–24h) is reasonable in animals that fail other therapies and have evidence of gastric inflammation in association with *Helicobacter* organisms; however, many animals will have evidence of re-infection or recrudescence after cessation of therapy.

## Infectious gastritis

Parasitic disease is a relatively common cause of gastritis and should be ruled out before performing more invasive and expensive diagnostic tests.

**Physaloptera spp.** are commonly identified nematodes[5] with an indirect life cycle requiring an intermediate host to develop into the infective stage. Suitable intermediate hosts (e.g., cockroaches, field crickets, canal crickets, or flour beetles) ingest the eggs, which have been shed by the definitive hosts (e.g., cats, dogs). After the intermediate hosts are ingested by either paratenic (e.g., frogs, snakes, or mice) or definitive hosts, the adults develop and attach to the gastric or duodenal mucosa. Clinical signs of parasitic gastritis/gastroenteritis can include delayed gastric emptying, vomiting, regurgitation, diarrhea, weight loss, melena, and lethargy.[22] Diagnosis can be difficult as centrifugal fecal flotation, especially in the case of *Physaloptera* spp., can be falsely negative. Identification of worms in the vomit or endoscopic visualization of stomach worms (1–6 cm in length, stout, cream-colored to white, straight or coiled; ▶Fig. 6-6), appears to be most successful in the diagnosis of this parasite.

**Ollulanus tricuspis** is a common gastric nematode of cats with a prevalence of up to 20% that also occurs rarely in dogs. After oral ingestion of third-stage larvae, the complete life cycle occurs within the stomach of the host, where the parasite attaches to the gastric mucosa. Infective larvae are vomited up and survive in the environment for up to

15 days, where they can infect another animal. Common clinical signs are inappetence, intermittent vomiting, and weight loss. Gastric erosions, increased mucus production, mucosal hyperplasia, and infiltration with inflammatory cells can be present. Diagnosis can be achieved by examining vomited material or gastric lavage solution. Parasites are rarely found on the histopathologic evaluation of gastric biopsies. Like for *Physaloptera*, fecal flotation for this parasite is rarely diagnostic. Thus, empirical anthelminthic therapy (as outlined in acute gastritis; ▶Chap. 6.3.1.2) is recommended as a first step therapeutic for any animal presenting with chronic vomiting. Evaluation for the presence of other parasites that can be identified in the stomachs of dogs and cats (e.g., *Gnathostoma* spp., *Spirocerca*) should be considered based on the animal's environment and travel history.

**Pythium insidiosum** is an oomycete that can cause both cutaneous and gastrointestinal signs in dogs. Most commonly, infected dogs are young, large breed dogs that live in tropical, subtropical, or temperate regions. *Pythium* can infect all parts of the gastrointestinal tract, including the esophagus, stomach, and small and large intestine. With gastric infection of *Pythium*, vomiting, with or without signs of delayed gastric emptying, may be an early sole sign of disease; however, in advanced stages, dogs often have additional clinical signs including diarrhea, weight loss, and palpable abdominal masses. Circulating anti-*Pythium insidiosum* antibodies combined with the identification of abdominal masses with abdominal imaging can be used as non-invasive tests to support the diagnosis. Detection of branching hyphae in pyogranulomatous inflammation from gastrointestinal mucosal biopsies that are non-staining on hematoxylin and eosin (H&E) and black to brown staining on Gomori methenamine silver (GMS) is highly suggestive of *Pythium*. Definitive diagnosis requires pan-fungal PCR and sequencing. Dogs with GI pythiosis have a poor prognosis, but findings from a series of five dogs suggested that there may be improved survival for those treated with a combination of surgery and antimicrobial drugs (mefenoxam, itraconazole, and terbinafine).[23]

#### 6.3.1.3.2 Diagnosis

As vomiting is a common sign but is not pathognomonic for gastritis, systemic causes of chronic vomiting should be ruled out by evaluating the **history**, **physical examination**, including fundic and retinal examinations, and a **minimum diagnostic database**, including a CBC, serum chemistry panel, urinalysis, urine sediment exam, and thyroid hormone testing for cats >7 years old, when appropriate. Animals with **pancreatic diseases** (▶Chap. 10.3), such as exocrine pancreatic insufficiency or chronic pancreatitis, or hepatobiliary disease, can also be presented for clinical signs similar to those due to chronic gastritis and therefore tests to evaluate for these diseases (e.g., abdominal ultrasound, pancreatic lipase immunoreactivity, bile culture, and pre- and post-prandial bile acids) should be considered in the diagnostic plan. **Fecal testing** (zinc and sugar fecal flotation, fecal antigen tests) with anthelminthic treatment is a reasonable first-tier approach in animals with mild signs. In dogs and cats with more severe signs, the presence of blood work abnormalities, or those unresponsive to anthelminthic therapy, **abdominal radiographs and ultrasound** are recommended to evaluate thickness and wall layering of the stomach and small intestine, size of abdominal lymph nodes, presence of discrete masses, and the echogenicity and size of the pancreas and surrounding mesentery. Cats with inflammatory bowel disease (IBD) and GI lymphoma tend to have increased small intestinal wall thickness as a result of increased thickness of the muscularis propria. Diffuse thickening of the small intestinal muscularis layer in addition to colic lymph node enlargement may be associated with GI lymphoma.



**Fig. 6-6** Endoscopic picture of the stomach of a dog with a single *Physaloptera* specimen.
(Courtesy of Dr. Michael Willard, Texas, USA.)

**NOTE**
Both dogs and cats with IBD can have an ultrasonographically normal stomach and small intestine.

If no abnormality can be identified on blood work or abdominal imaging, and anthelminthic therapy does not eliminate the symptoms, **additional testing** is recommended based on the history, signalment, clinical signs, and results of the first-tier

diagnostics. This may include but is not limited to evaluation of thoracic radiographs and **infectious disease testing** (e.g., *Histoplasma* EIA, heartworm infection [cats], viral testing such as feline leukemia virus, feline immunodeficiency virus, and feline infectious peritonitis; *Pythium* ELISA). **Enteropathogen panel testing** is not recommended for evaluation of chronic vomiting unless the animal demonstrates signs of systemic illness, consumes a raw food diet or treats, or lives in or has been recently adopted from a high-density housing environment, such as a shelter or breeding colony. Low serum **vitamin $B_{12}$ concentrations** are often observed in dogs and cats with intestinal or pancreatic disease. Hypocobalaminemic animals often do not respond as readily to treatment of the primary disease unless supplemented with this vitamin. Thus, cobalamin deficiency is an important clinical consideration in any patient presenting with signs of chronic gastrointestinal signs. For dogs and cats that do not respond to anthelminthic or dietary intervention as outlined below, intestinal biopsies should be obtained by endoscopy or surgery and submitted for **histopathologic examination** (▶Chap. 1.8.1). Endoscopy is less invasive, allows for visualization of luminal abnormalities and multiple sampling along the GI tract, is often less expensive, and provides information and direct sampling of the mucosal abnormalities. The quality of intestinal biopsies obtained by endoscopy depends on the experience of the endoscopist, quality of the instrumentation, and acquisition and processing of diagnostic biopsies. If there is a concern for alimentary lymphoma or infiltration of the submucosa or muscularis layers is observed, surgical biopsies of the gastrointestinal tract may be preferred. Exploratory surgery also allows for the acquisition of biopsies from the mesenteric lymph nodes, pancreas, and liver, which is recommended to ensure an accurate diagnosis and direct therapy for extra-gastrointestinal diseases. Often, further characterization of gastrointestinal and lymph node tissue by **immunophenotyping**, clonality testing via polymerase chain reaction for antigen receptor rearrangement (**PARR**), or fluorescence in situ hybridization (**FISH**) for detection of entero-adherent bacteria may be necessary. The results of these tests should be interpreted in light of the animal's clinical signs and histologic examination. Immunophenotyping and PARR aid in both the diagnosis of lymphoma as well as in determining the subtype of lymphoma, which may have an impact on prognosis. False-negative PARR results caused by cross lineage rearrangements (e.g., T-cell lymphoma with clonal rearrangement of immunoglobulin heavy chain gene) are possible, as are false-positive results. Therefore, PARR should be considered complementary and not be used as a stand-alone diagnostic test.

#### 6.3.1.3.3 Therapy

Targeted therapy for an underlying etiology, such as excision of a neoplasm or treatment of an infectious disease, is most likely to result in the resolution of gastritis. In cases of idiopathic chronic gastritis where no underlying etiology can be identified, rational treatment options include dietary management or immunosuppressive therapy.

Options for **dietary management** (▶Chap. 3.2) include low-residue, low-fat diets to promote more rapid gastric emptying and intestinal transit time or limited ingredient diets (i.e., single protein and carbohydrate sources), to which the animal has not yet been exposed to, and hydrolyzed diets to minimize a reaction secondary to food intolerance. In most cases, some response should be seen after a two-week strict dietary trial. In young animals, dietary intolerances are a common cause of gastrointestinal signs. Thus, multiple different diet trials should be pursued before declaring dietary management a failure. **Immunosuppressive drug therapy** can be considered for dogs and cats that do not respond to dietary management alone, for which abdominal imaging and infectious disease testing does not reveal an obvious etiology, and where the owner has declined acquisition of gastrointestinal biopsies. Corticosteroids, in addition to their immunosuppressive and anti-inflammatory properties, have regenerative effects on gastric parietal cells. However, they can also cause gastric erosions in dogs at high doses. Therefore, dogs receiving steroids for a prolonged period should be monitored for gastric bleeding. Initially, prednisone or prednisolone is given at a dose of 1–2 mg/kg PO q12h. In larger dogs, the author does not go above a dose of 30 mg per dog PO q12h. This dose is then gradually tapered in 25–30% decrements over a period of several months. Budesonide, a corticosteroid with high hepatic first-past metabolism, can also be considered to reduce systemic side effects. Budesonide (3 mg/m$^2$ q24h) requires compounding and is more expensive than prednisone but is a good option in dogs and cats where systemic glucocorticoid effects are a concern (e.g., diabetic animals). Additional supportive care, as outlined for acute gastritis, can also be considered during the diagnostic evaluation and treatment trial periods.

### 6.3.1.4 Gastric ulceration

Gastrointestinal ulceration causes significant morbidity in dogs. As clinical signs of gastric ulceration can mirror those of gastric bleeding secondary to a coagulation disorder, assessment of platelet count, function, and coagulation is recommended prior to evaluation of a primary cause of gastric ulceration in the dog and cat. The most common

causes of gastric ulceration in dogs and cats are GI neoplasms, pro-ulcerogenic drug administration (NSAIDs, palladia, chemotherapeutics), or liver failure.

**NSAID administration** is reportedly the most common cause of severe gastric ulceration in the dog, representing 1/3 of those requiring packed red blood cell (pRBC) transfusions in one study.[24] NSAID-induced gastric ulceration most commonly occurs in the gastric pyloroantral region or small intestine. NSAIDs are weak acids that can be directly injurious to the gastric and proximal duodenal epithelium and inhibit the synthesis of protective prostaglandins that normally aid in gastrointestinal mucosal blood flow, mucus secretion, and epithelial repair. In the lower small intestine, NSAIDs with a carboxylic acid function group that undergo enterohepatic recirculation can form an acyl glucuronide metabolite with biliary secretion. The downstream effects of this are repeated disruption of intestinal epithelial mitochondrial function and impaired epithelial renewal. The pathophysiology and prevalence of GI ulceration and bleeding in animals with hepatic disease are uncertain. Several mechanisms have been proposed, including the development of portal hypertension, gastric antral vascular ectasia, hypergastrinemia, altered gastric mucosal barrier, coagulopathy, and in the case of intrahepatic portosystemic shunts, concurrent GI disease.

**Rapid evaluation and stabilization** should precede or occur alongside the diagnostic evaluation in dogs and cats with gastric ulceration. The severity of bleeding can be assessed by evaluation of clinical data, including a CBC and serum biochemistry panel, to evaluate the degree of anemia and hypoproteinemia. An abdominal ultrasound may help confirm the presence of ulceration and, in severe cases, perforation; however, a full sonographic view of the stomach is not always possible because of its location and the presence of gas, and therefore, ulcerative lesions can be missed. Contrast radiography may identify a filling defect; however, endoscopy remains the gold standard for the identification of erosive and ulcerative lesions in the stomach.

The **treatment** of gastric ulceration, as well as its prognosis, is dependent on the underlying etiology and disease severity. Surgical removal of the injured mucosa is generally recommended for animals with or at risk for gastric perforation or where a neoplasm is the underlying cause of the ulceration. Proton pump inhibitor (PPI) therapy (▶Tab. 6-2) is recommended while determining the underlying cause of ulceration. For animals with NSAID-induced ulceration, misoprostol, a prostaglandin E1 analog, can be given concurrently with the PPI. The PPI therapy is generally continued q12h for 3–4 weeks in animals with NSAID-induced ulceration. Adjuvant acid suppressant therapy may not promote healing in animals with hepatic failure; thus, monitoring for response to therapy and consideration of alternative approaches (e.g., vasoactive drugs, lysine analogs) is recommended when clinical signs or lab work abnormalities do not improve with gastroprotectant drugs. Prophylactic use of gastroprotectant drugs is generally not recommended (e.g., in healthy dogs receiving NSAIDs) unless the animal has multiple risk factors for GI ulceration or bleeding. Sucralfate may be beneficial in animals with particularly painful lesions.

**KEY FACTS**

- The diagnostic and therapeutic plan for patients with suspected gastritis should be based on the severity of clinical signs and disease duration.
- The cause of chronic gastritis is rarely determined, and therapy is largely approached sequentially, beginning with empirical treatments for parasitic and food-responsive diseases.
- Chronic gastritis is classified based on the cellular infiltrate, the presence of morphologic changes, and lesion severity.
- The treatment of gastric ulceration, as well as its prognosis, is dependent on the underlying etiology and the severity.

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
svg.to/9842-06-03-01

## 6.3.2 Motility disorders

Silke Salavati Schmitz

Gastric digestive motility is a highly coordinated process triggered as a response to ingesta in the stomach. Functionally, the stomach is divided into the proximal "storage" compartment (consisting of the cardia, the fundus, and the first third of the antrum) and the distal "milling and emptying" compartment (consisting of the distal two-thirds of the corpus and the antrum).[1] Dogs have distinctly different contraction patterns during the digestive and inter-digestive phases of motility, which are also different from other species.

During digestion, milling and breaking down of particles commences in a process called **trituration**, which only allows particles of <2 mm in size to pass through the pylorus.[1–3] During inter-digestive motility (i.e., when the stomach is empty apart from larger components that cannot be fur-

ther broken down), so-called **migrating motor complexes** (**MMC**) occur that cycle at regular intervals through different phases and are only interrupted by another meal:

- Phase I (quiescence)
- Phase II (irregular contractions)
- Phase III (regular contractions)[1]

These coordinated "waves" of motility directed in an orad to aborad direction allow a "clean sweep" of the stomach and transport of larger non-digestible particles or foreign objects through the pylorus.

#### 6.3.2.1 Clinical presentation and causes of motility disorders

The most common clinical signs associated with gastric motility disorders are listed in (▶box Clinical signs). History, as well as physical examination, may reveal additional findings associated with the underlying disease (e.g., endocrinopathies) and/or the systemic effects of vomiting or regurgitation (e.g., aspiration pneumonitis/pneumonia) but physical examination can also be normal. In cases of postoperative ileus (POI) or critical illness-related motility disorders (CIRMD) (▶Fig. 6-7), intestinal sounds are usually absent.

**Clinical signs associated with delayed gastric emptying in dogs and cats**

- Vomiting, especially when occurring long after food intake (8–16 h). Projectile vomiting can occur with mechanical or functional pyloric outflow obstruction.
- Regurgitation
- Nausea (hypersalivation, restlessness, lip licking, etc.)
- Hyporexia/anorexia
- Increased burping
- Abdominal distension/bloating
- Abdominal discomfort
- Weight loss
- Polydipsia
- Pica
- Signs associated with aspiration pneumonia (dyspnea, tachypnea, cyanosis, pyrexia)

Traditionally, gastric dysmotility in dogs and cats is considered to be secondary to either a mechanical obstruction, acute functional disease of the stomach, or a number of chronic conditions of the gastrointestinal (GI) tract and associated organs,[2] for example, chronic enteropathy (CE; ▶Chap. 11.2), chronic pancreatitis (▶Chap. 10.3.1) or hepatopathies (▶Chap. 9.5; ▶Fig. 6-7). Certain endocrinopathies (e.g., diabetes mellitus), electrolyte abnormalities and other metabolic or immune-mediated disorders are often cited as causing delayed gastric emptying (GE).[2] However, especially for systemic diseases, this is often based on anecdotal reports or postulated based on extrapolation from human medicine, while a clear demonstration of relevant problems of gastric motility in small animals is mostly lacking.

Relatively subtle delays in GE are often assumed in dogs and cats suffering from the above chronic GI conditions. While they might contribute to some of the main presenting complaints (e.g., vomiting, regurgitation), they are rarely the main consideration in terms of diagnostics, clinical care, treatment, or management. This might be partially due to the fact that diagnostic tools which can realistically be used in routine clinical practice to determine chronically or mildly delayed GE are largely unavailable.

Even though dogs have been used as a model for POI for decades, the prevalence and relevance of this condition in a clinical setting remain to be determined and defined. In most dogs, appetite and thus motility appears to return rapidly after surgery, but subtle delays in GE might be present for longer.[4,5]

Of note, moderate to severe, mostly acute non-obstructive gastric stasis or atony (also sometimes called functional pyloric outflow obstruction) is an increasingly recognized comorbidity in acute disease states, either locally of the GI tract and associated organs (e.g., pancreatitis, hemorrhagic or infectious gastroenteritis) or in the context of systemically or critically ill patients.[3,6] While it seems much more common in critically ill dogs than in cats, gastric stasis is a well-known complication in human patients in intensive care units (ICUs)[7] and can occur regardless of the underlying disease. These so-called CIRMD increase the risk of aspiration pneumonitis/pneumonia, gastric colonization with bacteria, or gastroesophageal reflux (GER).[3] Delayed GE may also prevent effective delivery of enteral nutrition in critically ill patients,[7] especially as early enteral (assisted) feeding is now performed more commonly, and in itself is important to improve outcomes for critically ill patients while reducing hospitalization times and risk for comorbidities.

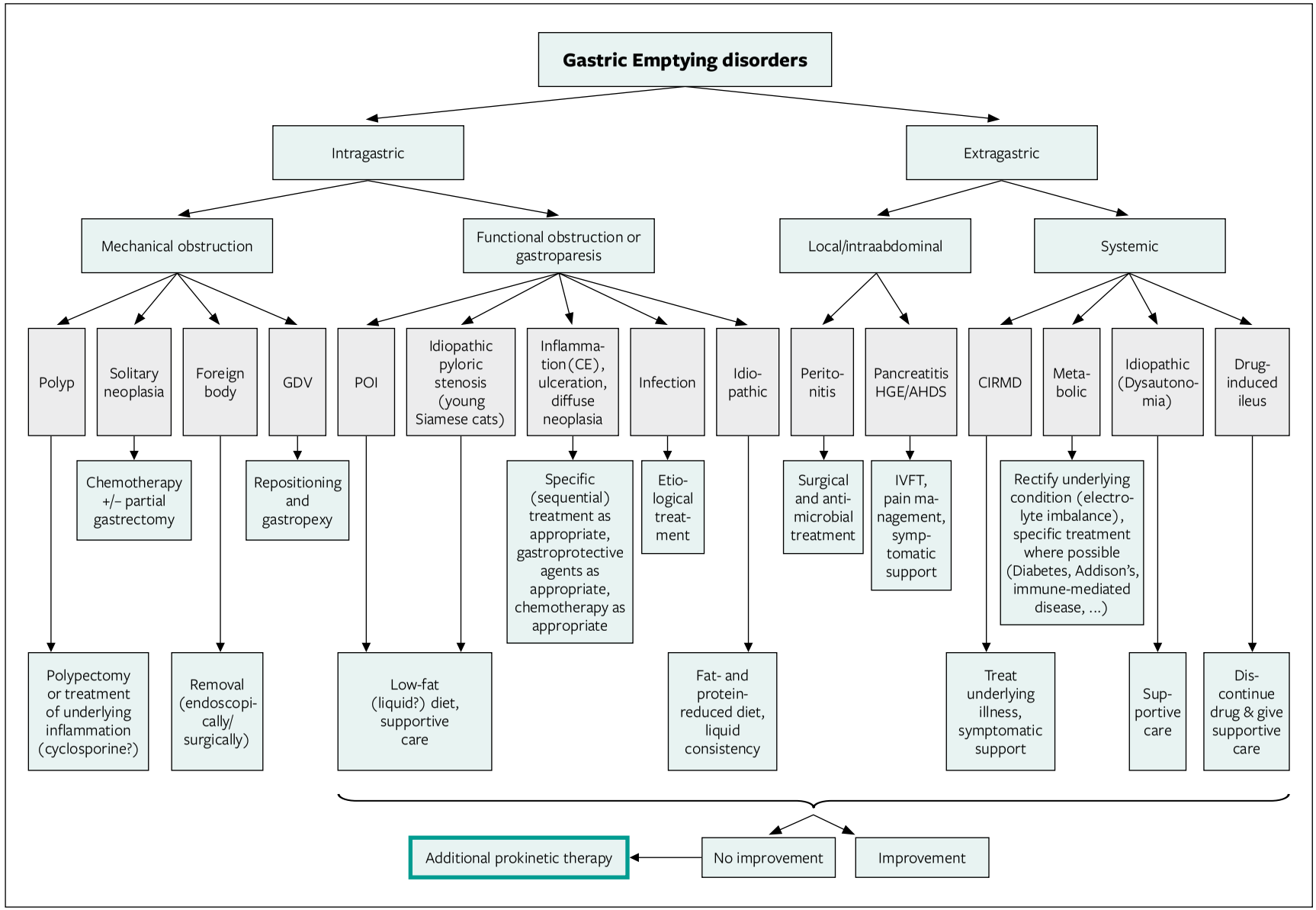



**Fig. 6-7** Differential diagnoses for gastric emptying disorders in small animals divided into intra- and extra-gastric causes and grouped by suspected main mechanism

**AHDS** = acute hemorrhagic diarrhea syndrome, **CE** = chronic enteropathy, **CIRMD** = critical illness related motility disorder, **GDV** = gastric dilatation-volvulus, **HGE** = hemorrhagic gastroenteritis, **IVFT** = intravenous fluid therapy, **POI** = postoperative ileus

(Modified from Schmitz et al. 2013[4])

### CLINICAL PEARLS

- Critical illness-related motility disorders (CIRMD) are increasingly recognized in hospitalized small animal patients undergoing intensive care.
- Large residual gastric volume is often noted on point-of-care ultrasound in these patients.
- Placement of a nasogastric tube and manual emptying of stomach contents is often required in these patients to achieve initial relief of gastric distension and reduce the risk of aspiration pneumonitis/pneumonia from regurgitated gastric content.

Only a minority of critically ill small animal patients with gastroparesis will be presented for clinical signs primarily associated with gastric emptying delay, but they are more likely to present for signs associated with their underlying disease. It is also common for GI signs to not be present initially but to develop during hospitalization. Hence early recognition of gastroparesis and proactive and frequent assessment of gastric filling status, for example, using point-of-care ultrasound, is pivotal for early intervention and mitigation of associated risks.

#### 6.3.2.2 Diagnosis

Even in more pronounced cases of gastric stasis, assessing gastric motility (reliably or quantitatively) is challenging. Diagnostic tests are either not readily available, not practical for routine clinical use, or are not standardized and highly subjective. In addition, even in healthy dogs, GE can have a high degree of intra- and inter-individual variation with regard to speed and pattern of gastric emptying (▶Fig. 6-8). A plethora of internal and external physiological factors, as well as the type, consistency, and composition of ingested food, can influence GE times, making standardization of tests difficult. Abnormal gastric residual volumes in patients in which prolonged fasting for the purpose of GE assessment might not be possible or advisable is a further complication, making the application of most tests in a clinical setting challenging.

▶Fig. 6-9 gives an overview of methods used to assess GE in small animals, which can be divided into diagnostic imaging procedures, blood or breath tracer tests, or tests related to assessments of (epigastric) electrical resistance; the latter is no longer used due to this method's susceptibility to artifacts. Breath and blood tracers would theoretically be amenable for clinical use, but analysis of tracers in biological samples is not routinely available and hence reserved for specialized institutions or research facilities.

The gold standard method to assess GE times is sequential quantification of gastric volume after ingestion of a radiolabeled meal (usually $^{99m}$Technetium) using **scintigraphy**. Not only is this not available in most veterinary settings, but its frequent use is precluded by risks related to handling open sources of radiation and potential external radiation exposure. In addition, quarantining a critically ill animal for several hours during scintigraphy (and afterward, depending on local rules) in a radiation-controlled or -supervised area is simply impractical.

Diagnostic imaging methods like radiographs and ultrasound are most commonly used in a clinical situation, as they are widely available. However, they have inherent dis-

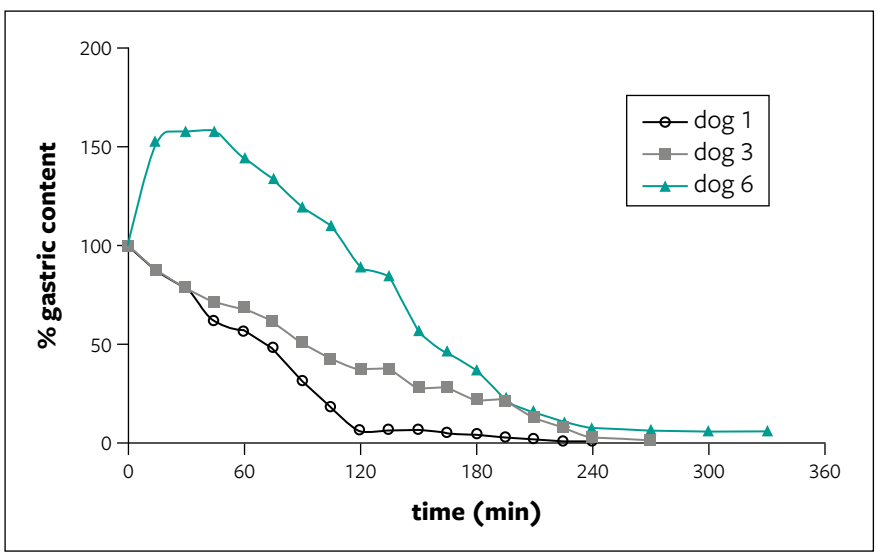



**Fig. 6-8** Gastric emptying of solids as determined by $^{99m}$Technetium scintigraphy in three different dogs showing large inter-individual variation in emptying times

Dog 1 shows a fast linear emptying with a gastric half emptying time ($G_{1/2}$) of approximately 70 min; dog 3 shows a slower linear emptying and $G_{1/2}$ of approximately 100 min, both of them without a lag phase. In contrast, dog 6 shows a lag phase of around 50 min with a $G_{1/2}$ of approximately 150 min.

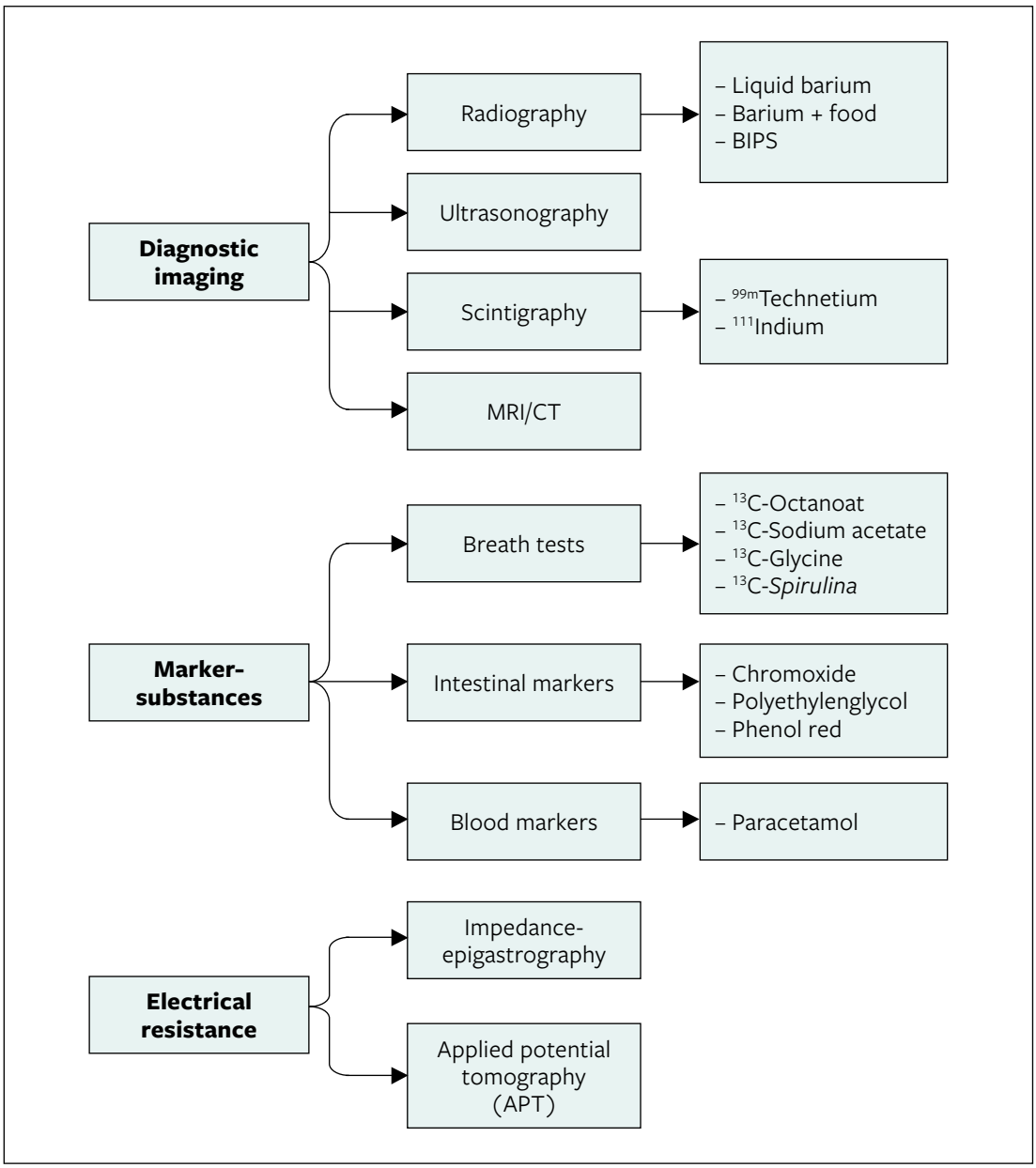



**Fig. 6-9** Different methods to determine gastric emptying times applied to small animals

**BIP** = barium-impregnated polyethylene spheres

(Modified from Schmitz and Neiger 2009[1])

advantages that are not easy to overcome. Additionally, any technique necessitating manual or chemical restraint may provide inaccurate results, as stress and sedatives can interfere with and modulate gastric motility.[8]

As gastric emptying times and patterns of liquid contents are different to emptying of solid contents (▶Fig. 6-10), and liquid barium is most frequently used to assess GI passage using **radiographs**, solid-phase emptying often remains unassessed in small animals. Mixing solid food with contrast not only has patient-related obstacles (animals are often hesitant to voluntarily eat an entire test meal), but also has technical disadvantages (no standardization of the available meal, contrast can separate from food, and even if the contrast and food is blended, it might be representative of semi-solid/liquid-phase gastric emptying). In addition, the method is not very sensitive, and reference values vary widely.[1]

Barium-impregnated polyethylene spheres (BIPS) are similarly not suitable for GE assessment, as their size (3 and

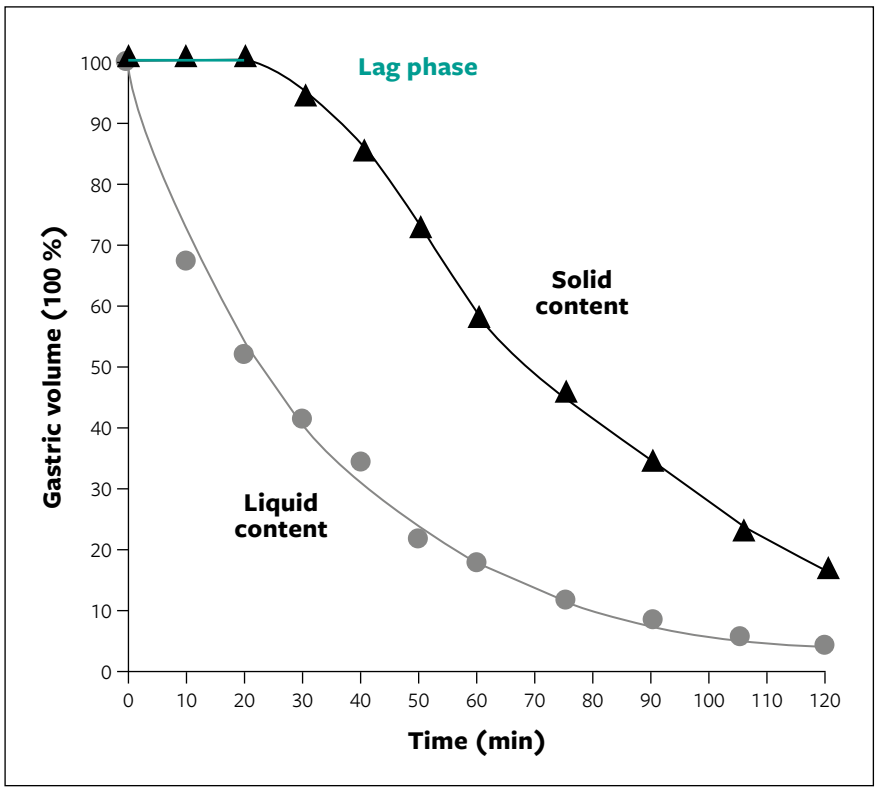



**Fig. 6-10** Schematics of patterns of gastric emptying in small animals

For solids, near-linear emptying is usually preceded by a lag phase representative of trituration. Gastric emptying of liquids does not have a lag phase but commences immediately, following an exponential or sigmoid pattern.

5 mm) will only allow them to empty with inter-digestive motility in dogs. GE times of solids as assessed via scintigraphy compared to BIPS in healthy dogs showed significant differences in lag phase characteristics,[9,10] meaning that if at all, the use of BIPS should be reserved to detect potential (partial) GI obstructions.

**Ultrasound** can be a very valuable tool in assessing gastric filling status and motility, provided that visualization is not impaired by intragastric gas. It is increasingly used not only as a routine diagnostic tool but in an ICU setting as a point-of-care tool to obtain a quick assessment of gastric filling status. A stomach filled with ingesta should contract 4–5 times per minute. This depends, however, on the degree of filling and the time since last meal.[11] Ultrasound has been used in both dogs and cats to quantify GE times.[12,13] It appears that it is more repeatable in cats compared to dogs, possibly due to their more similar sizes and body shapes and their faster GE.[13,14] However, if used to measure GE, the largest obstacle seems to be not knowing the starting volume of the stomach or having to deal with residual volumes of an unknown quantity. In a standardized setting (healthy dogs fed a defined test meal), ultrasound values correlated with those obtained by scintigraphy. However, a skilled operator is required, and operator-dependent variations of measurements have not been assessed.

**CLINICAL PEARLS**

Despite their disadvantages, plain radiography, contrast radiography, and ultrasound remain (even as a point-of-care test for the assessment of gastric filling) the most clinically relevant and available diagnostic tools to assess gastric filling and emptying in small animals.

Wireless motility capsules have also been tested in healthy dogs, and the test results might correlate reasonably well with scintigraphy, but the usefulness of these tests in a clinical setting has not been ascertained.[15]

### 6.3.2.3 Treatment

Treatment of gastric motility disorders should be largely directed at the underlying condition, with supportive management as required. If this does not lead to improved GE, and clinical signs like regurgitation and vomiting persist, while other causes have been thoroughly excluded, prokinetic therapy can be considered. This might be appropriate earlier in the course of disease in animals with acute or critical illnesses being cared for in the ICU, while patients with chronic

conditions often undergo sequential treatment trials, and prokinetics might be added in later.

#### 6.3.2.3.1 Supportive treatment

In acute gastroparesis, supportive treatment should be aimed at **relieving gastric distension** (e.g., via a nasogastric tube), as this reduces the risk of reflux, regurgitation, and thus aspiration pneumonitis/pneumonia. It will also reduce abdominal discomfort and alleviate fluid sequestration, which will help rectify electrolyte disturbances and hypovolemia.[6] Reduced pressure and distension on the gastric wall would likely also help with contractability/motility. Sequestering large volumes of gastric secretions and food in the stomach will also delay nutrition and contribute to malabsorption and increased GI permeability or "leakiness". This, in turn, can lead to extreme dysbiosis and bacterial translocation, which in people is linked to "gut-derived sepsis".[16,17] However, this sequence of events has not been conclusively shown to occur in small animals.

In addition to relieving gastric distension, any drugs that potentially reduce GI motility (e.g., opioids, dopamine, dexmedetomidine) should be stopped, and **early enteral nutritional intervention** should be performed (in the context of critical illness, "early" usually means within 24–48 hours of admission). In a lot of scenarios with very sick animals, feeding via a "constant rate" or "trickle" protocol using a nasogastric tube might be ideal for providing initial nutritional needs.[6] This can be "upgraded" to an esophagostomy tube if longer-term feeding is planned (e.g., in a dog with chronic protein-losing enteropathy). Early feeding is associated with improved blood flow, permeability, and epithelial regeneration of the GI tract in people, as well as with shorter hospitalization times and shorter ventilation times.[18] Unfortunately, in small animal patients, the most beneficial food type, as well as the viscosity of food and the feeding method is unknown; therefore, choices should be driven by the underlying condition. However, in general, low-fat liquid diets are preferred over higher fat or very viscous or solid diets (as they empty from the stomach faster).

Intravenous fluid therapy should be used judiciously in critical patients with severe gastric atony, as excessive volume expansion can lead to gut hypoperfusion, and GI tract wall edema is detrimental to GI motility. Early ambulation, multimodal pain management, and specific prokinetic treatment should be considered as soon as possible in critical patients.[6]

#### 6.3.2.3.2 Prokinetic treatment

Evidence for the use of prokinetic drugs in small animals is sparse (▶Tab. 6-3) and mostly refers to demonstrating effects in healthy animals, while evidence for their use in dogs or cats with delayed GE is even more scarce. Even though a number of findings can be derived from in vivo and in vitro studies in small mammals, and the dog has been used as a disease model for people, very few studies with the dog or cat as beneficiary target species exist. With this in mind, prokinetic drugs should only be administered after etiological and supportive treatment measures have been exhausted and following a risk-benefit assessment for each patient.



**NOTE**

Prokinetic drugs should only be administered after gastrointestinal obstruction has been thoroughly ruled out.

The most controversial drugs are **$D_2$ dopaminergic antagonists**. Even though metoclopramide is most commonly used as a first-line prokinetic in dogs,[2,3,6] there is only weak evidence it actually accelerates solid-phase GE, and in some studies, it actually slows down the emptying of solids. It might accelerate the emptying of liquids,[19] increase lower esophageal sphincter tone, relax the pylorus, and hence improve antro-pyloro-duodenal coordination (APDC).[20] It has also been shown to be effective in treating POI[21] and GER in dogs,[3,22] the latter at high dosages. Domperidone is not considered a prokinetic in dogs, as it has no effect on the LES and may even decrease gastric and duodenal contractions.[20]

Of the available **serotonin ($5\text{-}HT_4$) receptor agonists**, cisapride is the most thoroughly researched. In some countries, it has been taken off the market due to fatal (cardiac) side effects in people. In dogs, it has been shown to improve GE times and APDC in experimental settings,[20,23,24] but its clinical value in dogs with spontaneous gastroparesis is not always as impressive. In some studies using indirect techniques for measuring gastric emptying (e.g., breath tests), it has not shown to have any effect.[25] Alternatives include the more selective $5\text{-}HT_4$ receptor agonists mosapride[26] and prucalopride, but the latter failed to serve as a positive control in one study.[27] These drugs are indirect prokinetics by increasing the availability of acetylcholine within the enteric nervous system (ENS). They are only available as oral formulations in most countries but have anecdotally been effective when administered rectally instead, which can be helpful in patients that do not tolerate oral medications.

**Tab. 6-3** Prokinetic drugs used in dogs and cats

| Prokinetic drug | Type and site of action | Additional mechanism(s) of action | Dose | Comments |
|---|---|---|---|---|
| **Dopaminergic $D_2$-receptor antagonists** | | | | |
| **Metoclopramide** | • Increased LES pressure<br>• Increased tone and amplitude of gastric contractions (pyloric antrum)<br>• Relaxation of pyloric sphincter and duodenum (antro-pyloro-duodenal coordination)<br>• Duodenum (?) | • 5-$HT_3$ antagonism at higher doses (CNS)<br>• 5-$HT_4$ agonism (ENS)<br>• Muscarinergic agonism (ENS) | Dog & cat:<br>• 0.2–0.5 mg/kg IV, IM, SC, PO q8–12h<br>• 1–2 mg/kg (0.04–0.09 mg/kg/h) IV over 24 h as CRI | • Poor prokinetic (and antiemetic) in cats<br>• Administer 30–60 min before feeding<br>• Several potentially serious drug interactions |
| **Domperidone** | Gastrokinetic in humans, but not in dogs or cats | n/a | n/a | n/a |
| **Serotonergic 5-$HT_4$ agonists** | | | | |
| **Cisapride** | • Increases lower esophageal smooth muscle and LES pressure (dogs)<br>• Increases gastric as well as small intestinal and colonic contractions (the latter particularly in cats) | • 5-$HT_3$ antagonism<br>• 5-$HT_2$ antagonism<br>• 5-$HT_1$ agonism<br>• $D_2$-receptor antagonism (weak) | Dog:<br>• 0.1–0.5 mg/kg PO q8–12h (some recommend 30 min before feeding)<br>• Dosages up to 1 mg/kg PO q8h may be required if tolerated.<br><br>Cat:<br>• Initially 2.5 mg/cat PO q12h<br>• Titrate upwards to up to 7.5 mg/cat or 1.5 mg/kg q8h PO if tolerated | • Unavailable (or from compounding pharmacies only)<br>• Effect on gastric emptying times could not be demonstrated in some studies using indirect methods<br>• In high doses (3 mg/kg) decreases gastric motility<br>• Cats with hepatic insufficiency may need dose interval extensions |
| **Mosapride** | Effects mostly on stomach (pyloric antrum) and colon | • n/a<br>• (5-$HT_4$ receptor-specific) | Dog:<br>0.25–2 mg/kg PO q12h<br><br>Cat:<br>5 mg/cat PO q12h | Little information available |
| **Prucalopride** | Pyloric antrum, small intestine (?), colon | • n/a<br>• (5-$HT_4$ receptor-specific) | Dog & cat:<br>0.05–0.5 mg/kg PO q12–24h | • Anecdotally effective when given rectally<br>• Effect on gastric emptying times could not be demonstrated in some studies using indirect methods |

▶▶

**Tab. 6-3** Prokinetic drugs used in dogs and cats (Continuation)

| Prokinetic drug | Type and site of action | Additional mechanism(s) of action | Dose | Comments |
|---|---|---|---|---|
| **Motilin agonists (macrolide antibiotics)** | | | | |
| **Erythromycin** | • Pyloric antrum, small intestine, and colon<br>• Causing MMC type III interdigestive "waves" of motility in dogs<br>• More diffuse activity in cats | n/a | Dog & cat:<br>0.5–1 mg/kg IV or PO q8h | • Inhibitor of cytochrome p450 enzyme CYP3A, leading to a potential for drug interactions<br>• Increased risk of cardiac arrhythmia in people<br>• Tachyphylaxis due to downregulation of motilin receptors has been reported after approximately 1 week of treatment in people |
| **Azithromycin** | Likely similar to erythromycin | n/a | Dog:<br>2 mg/kg IV q8h<br><br>Cat:<br>3.5 mg/kg PO q24h | • Used anecdotally with good success in dogs<br>• As effective as erythromycin in accelerating gastric emptying in cats |
| **Acetylcholinesterase inhibitors** | | | | |
| **Ranitidine** | • May stimulate gastric emptying<br>• LES pressure may be increased | $H_2$-receptor antagonist | Dog & cat:<br>1–2 mg/kg PO, SC, IM or slow IV (max 25 mg/min) q8–12h | • One study found that 1.4–2.3 mg/kg PO q12h was not effective. Therefore, current dose recommendations seem to be too low to be of any effect<br>• Further clinical studies are lacking |
| **Nizatidine** | • May stimulate gastric emptying<br>• Maybe be useful for pseudo-obstruction or constipation | $H_2$-receptor antagonist | Dog & cat:<br>Anecdotal dose (not well established):<br>2.5–5 mg/kg PO q8, 12 or 24h | For prokinetic effects in cats, use with cisapride may be considered |
| **Miscellaneous** | | | | |
| **Bethanechol** | • Primarily used to increase urinary bladder contractility, but has been used as a prokinetic agent and treatment of signs associated with dysautonomia<br>• Might also improve esophageal motility in dogs with megaesophagus | Muscarinergic agonist (cholinergic or parasympathomimetic) | Dog:<br>1.25–25 mg/dog PO q8h (titrate upwards)<br><br>Cat:<br>0.625–5 mg/cat PO or 0.1–0.2 mg/kg PO q8h | • Best given on an empty stomach<br>• Can cause cholinergic side effects/crisis |
| **Mirtazapine** | • Contradictory evidence of an effect on gastric emptying in dogs<br>• No information for cats | • 5-$HT_3$ receptor antagonist<br>• Tetracyclic antidepressant | Dog:<br>0.6–1.3 mg/kg PO q24h<br>The dose should not exceed 30 mg per dog | Can be given with or without food |

**CNS** = central nervous system, **ENS** = enteric nervous system, **CRI** = continuous rate infusion, **IV** = intravenous, **PO** = per os, **SC** = subcutaneous, **IM** = intramuscular, **LES** = lower esophageal sphincter, **MMC** = migrating motor complexes, **n/a** = not applicable, **$H_2$** = histamine, **(?)** indicates that this effect has not been convincingly demonstrated

Erythromycin and azithromycin are **macrolide antibiotics** that mimic the effects of the hormone motilin at low doses, hence inducing strong inter-digestive peristalsis.[2,3,6] They accelerate GE in both healthy dogs and cats, regardless of ingesta particle size. Different esters of erythromycin are available, and it is possible that the kinetics and efficacy will differ depending on the ester used. It is acid-labile and so should be given on an empty stomach.

The **histamine ($H_2$) receptor antagonists** ranitidine and nizatidine have been shown to promote acetylcholine esterase inhibition within the ENS, but they have questionable clinical efficacy, especially in critically ill small animal patients. A recent study in healthy dogs could not detect any significant effect of ranitidine on GI motility parameters.[15]

Mirtazapine, a **5-$HT_3$ receptor antagonist** and tetracyclic antidepressant used as an appetite stimulant, was shown to accelerate GE and colonic transit times without having an effect on small intestinal transit in healthy, fistulated dogs.[28] However, when escalating dosages (0.5 mg/kg to 20 mg/kg) were assessed via $^{13}$C-sodium acetate breath test in healthy non-fistulated beagles, there was no effect on GE compared to placebo.[27]

**Other compounds with potential gastrokinetic effects** include L-arginine and L-glutamate (given as a mixture).[3] Lidocaine was thought to decrease the severity of POI in dogs; however, this could not be supported in healthy dogs.[29] Similarly, maropitant, a neurokinin (NK) 1-receptor antagonist frequently used as an antiemetic in dogs and cats, did not show any prokinetic effect in dogs when assessed using two different methods.[25] Acotiamide is a novel selective acetylcholinesterase inhibitor approved for use as a prokinetic in people in Japan. It enhanced postprandial gastroduodenal activity in healthy dogs when given IV or orally.[30]

Overall, there is no single ideal and reliable prokinetic drug for small animals, and often, several drugs have to be used on a trial basis or combined in an individual patient. Some authors recommend giving the combination of metoclopramide and erythromycin when dealing with CIRMD in ICU patients, as this has been shown to decrease feeding intolerance while accelerating GE and reducing the degree of drug tachyphylaxis in people with this condition.[3] However, managing gastric stasis in acutely and critically ill small animal patients remains a challenge, and it is often hard to determine if improvement of gastric motility is a consequence of effective prokinetic treatment or simply a reflection of improvement due to treatment or resolution of the underlying disease.

#### 6.3.2.3.3 Future prokinetic agents

The lack of consistently effective gastrokinetic drugs in small animals is shared with human medicine, where novel drug development is ongoing.[31] Candidate compounds tested in trials but not yet approved for use in humans include ghrelin antagonists (e.g., relamorelin), which could be interesting due to the availability of capromorelin as a related component licensed for use in dogs and cats, as well as other NK1 antagonists (e.g., tradipitant) and selective 5-$HT_4$ receptor agonists (e.g., felcisetrag). Novel drug targets include cannabinoid type 2 receptor agonists (e.g., olorinab), ileal bile acid transport inhibitors (e.g., elobixibat), or farnesoid X receptor agonists (e.g., obeticholic acid and tropifexor). These agents are also still undergoing evaluation,[31] but might be interesting for use in small animals once evidence is available.

**KEY FACTS**

- Causes of gastric emptying disorders can be found within or outside the gastrointestinal tract, can be obstructive or mechanical in nature, or can be secondary to severe systemic disease.
- Gastric atony or stasis is increasingly recognized in critically ill small animal patients requiring intensive care, contributing substantially to morbidity and motility.
- Rapid, reliable, and clinically applicable diagnostic tests to determine gastric emptying times in dogs and cats are still lacking, and the most reliable tools are only used in a research setting.
- Most conditions resulting in delayed gastric emptying require specific etiologic as well as supportive treatment.
- The addition of prokinetic drugs should be considered in severe, critically ill cases in which obstruction is ruled out, as well as in situations where more specific treatment attempts have failed to improve clinical signs.
- There is no ideal prokinetic drug to accelerate gastric motility in small animals; thus, the pros and cons of their usage and combination have to be considered on a case-by-case basis, and this should be based upon knowledge of their mechanisms of action.

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
svg.to/9842-06-03-02

### 6.3.3 Gastric dilatation-volvulus

Lars F.H. Theyse

Gastric dilatation-volvulus (GDV) is an acute life-threatening disorder mainly affecting large-breed dogs. Although GDV can occur at any age, the risk increases with age, affecting mainly older dogs. In GDV, the stomach rotates and distends, mechanically obstructing the gastroesophageal junction and pyloric outlet. The stomach may contain food and fluid, but the rapid dilatation is mainly due to gas accumulation. With the progression of the gastric distension and torsion, the gastroesophageal junction becomes completely blocked, rendering eructation and emesis impossible. The pyloric outlet is also progressively compressed, blocking the aboral propulsion of gastric content. Progressive dilatation has severe implications for the cardiovascular, respiratory and digestive systems.

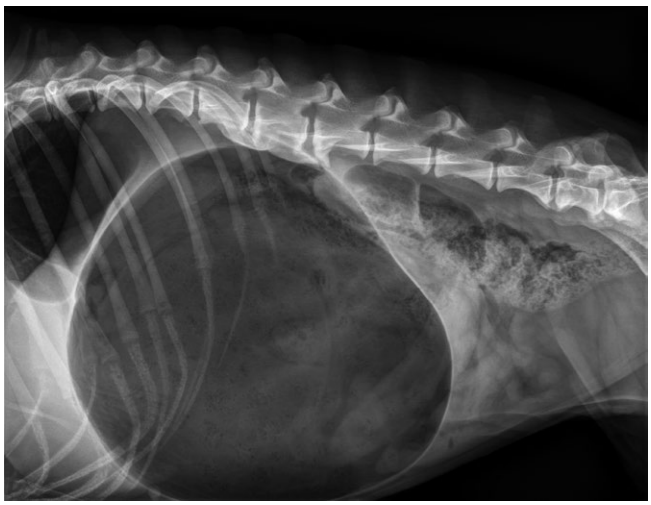


**Fig. 6-11** Radiographic left-to-right (right lateral) view of gastric dilatation-volvulus in a 7-year-old Irish setter dog

The radiograph shows severe distention of the stomach with the typical dorsal fold characterizing the gastric torsion.

#### 6.3.3.1 Etiology

The causes of GDV are not completely understood. In most cases of GDV, the pyloric antrum is dislocated to the left and dorsal of the gastroesophageal junction. This complete torsion means that the pylorus has moved from its initial right ventral abdominal position towards the ventral abdominal midline, crossing the midline to the left and then moving dorsal and left of the gastroesophageal junction.[1] During this process, gastric distension seems to facilitate the progression of torsion. It is clear that abnormal gastric motility plays a role in the development of a torsion. Reported risk factors for GDV include large and giant breed dogs, increasing thoracic depth-to-width ratio, increasing age, decreased food particle size, food composition, fewer meals per day, exercise after meals, stress, and previous splenectomy.[2–6] Many of these risk factors appear contradictory. Nevertheless, several breeds are clearly susceptible to developing GDV, including great danes, Gordon and Irish setters, Saint Bernards, German shepherds, Weimaraners, and others.[7–9] The discussion of whether GDV starts with volvulus or dilatation is irrelevant. In the clinical setting, GDV can only develop when abnormal gastric motility leads to a mutually reinforcing progression of volvulus and dilatation. Gastric torsion without dilatation has not been reported as a clinical problem. In contrast, gastric dilatation can occur in isolation without gastric torsion. Rapid dilatation of the stomach mainly relies on aerophagia. One study reported that gastric gaseous $CO_2$ concentrations exceeded that of normal air, thereby excluding aerophagia as the sole source of tympany. This finding suggests that $CO_2$ diffuses through the stomach wall into the gastric lumen or that intragastric $CO_2$ is produced by fermentation.[10] During torsion, the stomach wraps itself in the greater omentum, causing tension on the splenic artery and vein, left gastroepiploic artery, and vein, and short gastric arteries and veins. In severe cases of GDV, avulsion of the short gastric arteries and veins at the greater gastric curvature, including thrombosis of splenic and gastric veins, can be observed.

#### 6.3.3.2 Clinical presentation

The onset of clinical signs is usually acute or peracute. Clinical signs of GDV are characterized by progressive restlessness, unproductive vomiting and retching, salivation, abdominal distention, gastric tympany, dyspnea, and pain, resulting in progressive signs of shock and stupor. Sudden death may occur from hypovolemic and cardiogenic shock within a few hours of the onset of clinical signs.

#### 6.3.3.3 Diagnosis

During GDV, the stomach becomes progressively distended with gas. Gastric tympany can be confirmed with percussion and auscultation of the dorsal epigastrium. Borborygmi are usually absent. As such, the clinical diagnosis of gastric dilatation is straightforward. Gastric volvulus can be confirmed with a dog in lateral recumbency using a left-to-right (right lateral) abdominal radiographic view. Depending on the severity of gastric torsion and dilatation, the radiographic presentation can vary considerably. During acute GDV, imaging findings are characterized by severe gaseous distention of the stomach with a typical dorsal fold delineating the gastric torsion (▶ Fig. 6-11).

#### 6.3.3.4 Treatment

Emergency treatment of GDV is aimed at **stabilizing** the patient and, in the meantime, **decompressing the stomach**.[11] Fluid resuscitation, using large-bore intravenous catheters, is performed with lactated Ringer's solution or sodium chloride initially at a dose of 90 ml/kg/h with the major aim of rapid expansion of the intravascular volume. Decompression of the stomach is essential to restore venous return through the caudal vena cava. Decompression of the stomach can be achieved using an orogastric tube, gastric trocarisation, or a combination of both.[12] Most dogs tolerate emergency orogastric intubation with the aid of a bite block. Orogastric intubation is most effective in evacuating gas, fluids, and food from the stomach.

After stabilization of the cardiovascular system, **immediate surgical management** of the gastric torsion and prevention of recurrence under general anesthesia is essential. A midline laparotomy is performed. If preoperative orogastric intubation is unsuccessful, passage of the tube can usually be accomplished with manipulation of the tube tip at the oesophageal junction by the surgeon. After decompression of the stomach, the gastric torsion should be reversed by repositioning the pyloric antrum from left to right while moving the gastric body from right to left. With the stomach in its physiological position, the viability of the gastric wall and gastric and splenic vessels should be evaluated. Partial gastrectomy and splenectomy might be indicated in severe cases, but usually **gastropexy** is the next step in surgical management. There are many different gastropexy techniques, but all effectively secure to the stomach wall or abdominal wall.[13–16] The main difference between the techniques is the location of the gastropexy, either attaching the pyloric antrum to the right abdominal wall or performing a midline gastropexy. Prophylactic laparoscopic gastropexy has been advocated in breeds predisposed to GDV.[17] **Cardiac arrhythmias** can develop postoperatively for up to 72 hours and should be monitored and treated accordingly.

#### 6.3.3.5 Prognosis

The prognosis for GDV strongly depends on rapid intervention and therapeutic management of the gastric torsion, subsequent dilatation, and shock cascade. With adequate emergency treatment and surgical intervention, the prognosis is good, with survival rates as high as 90%. Negative prognostic factors are prolonged duration of clinical signs, gastric wall necrosis necessitating partial gastrectomy, vascular compromise of the spleen necessitating splenectomy, preoperative cardiac arrhythmias, and elevated serial plasma lactate concentrations.[18–21] Recurrence rates of volvulus after gastropexy are very low and are independent of the gastropexy technique. A small subset of dogs may present with intermittent gastric dilatation due to aerophagia.

**KEY FACTS**

- Gastric dilatation-volvulus is an acute life-threatening disorder.
- Emergency treatment combined with surgical intervention and gastropexy is critical.
- With timely and appropriate treatment, prognosis is good, with survival rates as high as 90%.

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
svg.to/9842-06-03-03

### 6.3.4 Neoplastic conditions of the stomach

Katie Z. Wright, Ann E. Hohenhaus

#### 6.3.4.1 Introduction

Gastric tumors are rare in dogs, accounting for <1% of all canine malignancies.[1] The most common neoplasia affecting the canine stomach is carcinoma. However, many tumor histologies are reported, including leiomyosarcoma, leiomyoma, gastrointestinal stromal tumor (GIST), mast cell tumor, extramedullary plasmacytoma, histiocytic sarcoma, lymphoma, and benign tumors.[1,9–13]

Affected dogs are usually older, with a median reported age of 7.5–10.2 years.[1] Some case series report an equal male-to-female ratio, but most report a male predominance.[1–8] Breed predispositions for gastric carcinomas include the Staffordshire bull terrier, rough-coated collie, Belgian Tervueren, cairn terrier, and chow chow, suggesting a possible hereditary component in the development of gastric carcinoma.[2,5,6,14–16] Tumors can occur in any anatomic region of the canine stomach.

Solitary gastric neoplasia is considered very rare in cats. Lymphoma (▶Chap. 11.3) is the most common feline tumor, accounting for approximately 30% of all feline cancers.[17–19] The most common anatomic location of feline lymphoma (50–75% of cases) is the gastrointestinal tract.[17–19]

Two studies reported that in 15–18% of all feline gastrointestinal (GI) lymphoma cases, the tumor is confined to the stomach, making lymphoma the most common gastric neoplasia in the cat.[1,17,19–22] Both large-cell lymphoma or a more indolent small-cell lymphoma can affect the feline stomach. Solitary gastric lymphoma tends to be high-grade B-cell lymphoma, whereas GI small-cell lymphoma tends to be low-grade and T-cell phenotype.[20,23,24] Three published case series, collectively including 96 cats with GI tumors, reported a mere three cases of gastric carcinoma.[1,25,26] There is little data available for non-lymphoma gastric neoplasia in cats, but 8.7–10.6 years is reported as an average age.[17,26,27] Sex and breed predilections have yet to be determined, but Siamese cats may be more commonly affected.[26,27]

**Tab. 6-4** Histologic types of canine gastric tumors

| | |
|---|---|
| **Primary epithelial (glandular) tumors** | Adenoma: papillary, tubular, papillotubular |
| | Adenocarcinoma: tubular or acini, papillary, signet-ring, mucinous |
| | Undifferentiated carcinoma/solid |
| **Primary nonepithelial (non-glandular) tumors** | Carcinoid |
| | Fibroma/fibrosarcoma |
| | Hemangioma |
| | Leiomyoma/leiomyosarcoma |
| | Lipoma/liposarcoma |
| | Lymphoma |
| **Secondary tumors** | Metastatic carcinoma |
| | Metastatic sarcoma |
| **Tumor-like lesions** | Polyps (inflammatory or regenerative) |
| | Scirrhous eosinophilic gastritis |
| | Hypertrophic gastritis |
| | Pyloric stenosis |

### 6.3.4.2 Histology

All three major histological types of tumors, carcinoma, sarcoma, and round cell tumors, can affect the canine stomach. Gastric carcinomas represent the majority of reported cancers, accounting for 70–80% of canine gastric tumors.[3] These tumors commonly affect the pyloric antrum and can extend into the body of the stomach via the lesser curvature.[3,17] Tumors of the canine stomach are summarized in ▶Tab. 6-4.

Adenocarcinomas form tubular structures, or acini, and can be further distinguished by the predominant growth pattern (▶Fig. 6-12).[17] Papillary tumors develop finger-like fibrous cores covered with neoplastic cells.[17] Mucinous tumors are diagnosed, with >50% of the cells being mucin-producing.[17] The third type of adenocarcinoma is the signet-ring type. These cells are named for their characteristic feature of having eccentric nuclei with mucin-containing distended cytoplasm (▶Fig. 6-13).[17] Lastly, tumors that lack a glandular structure are often referred to as solid or "undifferentiated."

Infiltration of a tumor into the gastric wall occurs commonly and often causes excessive secondary fibrosis referred to as scirrhous reaction.[17] The scirrhous nature of gastric carcinomas is the result of fibrotic desmoplasia induced by the malignant epithelium.[17] The term "carcinoma in situ" is used when a carcinoma has not infiltrated the muscularis mucosa.[17]

Mesenchymal and round cell tumors occur less commonly in the canine stomach than carcinomas. Leiomyomas are the second most common gastric tumor in the dog.[28] Gastric lymphoma has been reported in dogs but is usually found in patients with multicentric disease, not confined to the stomach.[13,29,30] Carcinoids are tumors derived from the endocrine cells scattered throughout the GI tract and have been reported in dogs and a cat.[1,31,32] While gastric tumors in dogs are most commonly malignant, benign gastric tumors are also reported.[3,17,28,33] Benign tumors are often described as solitary, polypoid lesions, 0.5–1 cm in diameter, found incidentally in the pyloric region at necropsy.[17]

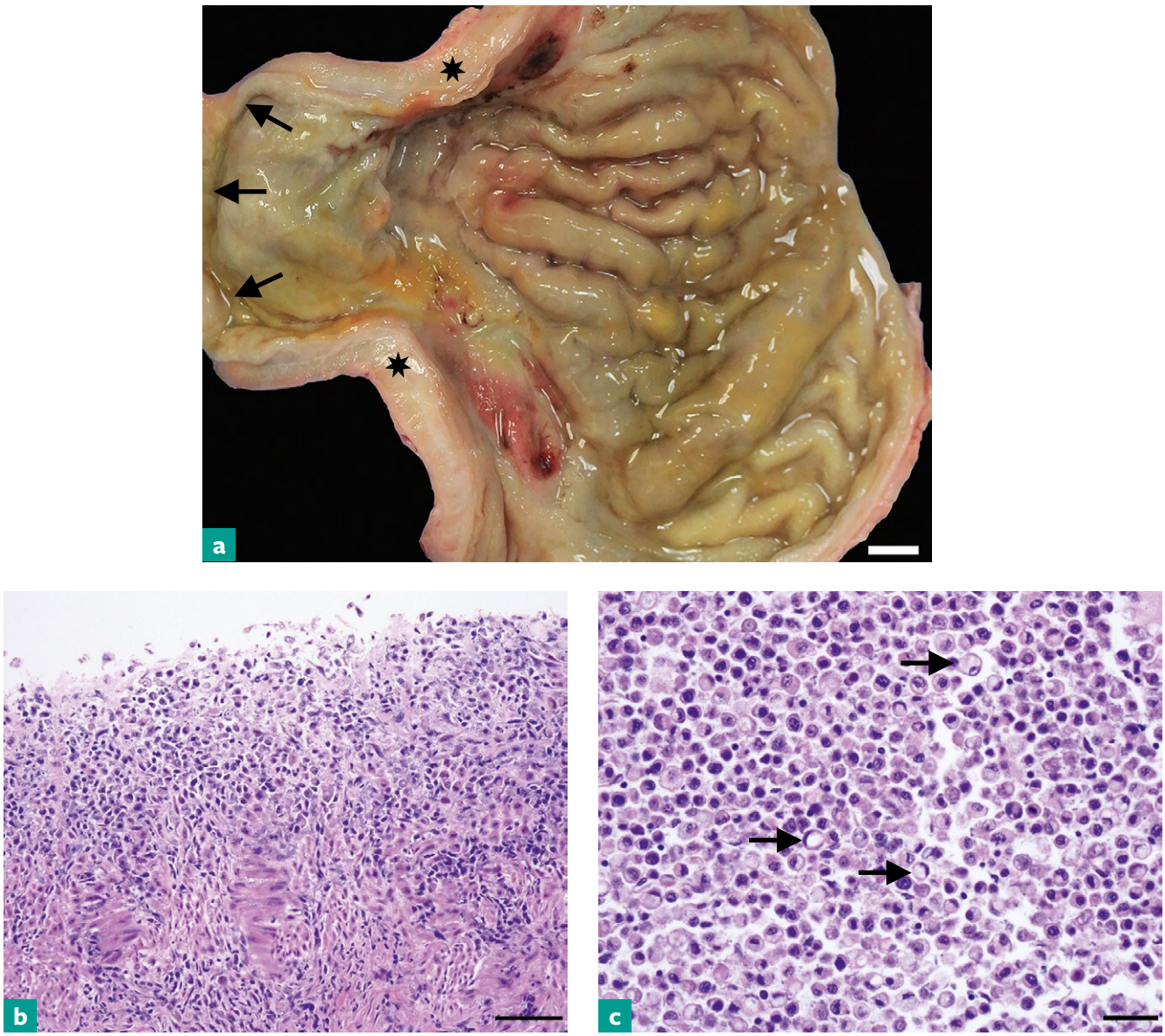



**Fig. 6-12** Canine signet ring adenocarcinoma

Gross image **a** shows a signet ring gastric adenocarcinoma with arrows outlining the tumor margin. Note severe thickening of the gastric wall (**asterisks**); bar: 1 cm.

Microscopic image **b** shows the histology of a signet ring gastric carcinoma infiltrating the superficial mucosa (H&E, 200x, bar: 50 µm).

Microscopic image **c** demonstrates the sheets of carcinoma cells infiltrating into the gastric wall, characterized by abundant amphophilic or clear cytoplasm with an eccentrically located nucleus in the signet ring cells (**arrows**) (H&E, 400x, bar: 20 µm).

(Courtesy of Dr. Taryn Donovan, Department of Pathology, Schwarzman Animal Medical Center, New York, NY.)

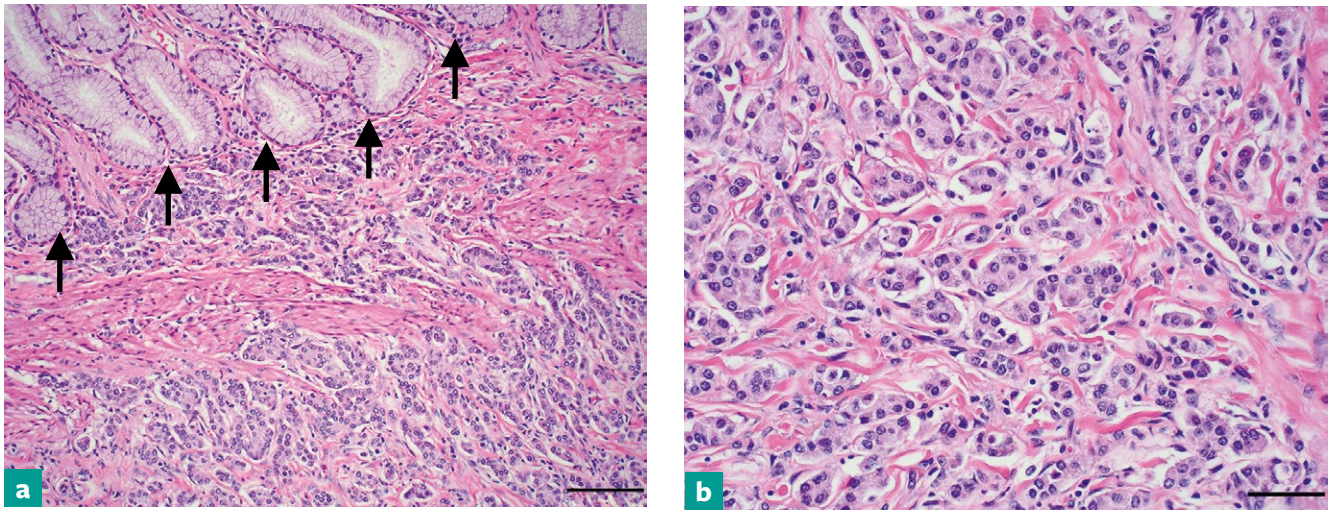



**Fig. 6-13** Canine gastric adenocarcinoma

Microscopic image **a** shows the transition zone between normal gastric glands (top left corner, **arrows**) and infiltration by the neoplastic cells. Neoplastic cells form acinar structures and are surrounded by pink, fibrous stroma (H&E, 40x, bar: 50 µm).

Microscopic image **b** shows a higher magnification view of gastric adenocarcinoma acini (H&E, 40x, bar: 50 µm).

(Courtesy of Dr. Taryn Donovan, Department of Pathology, Schwarzman Animal Medical Center, New York, NY.)



### 6.3.4.3 Clinical signs

The most common clinical signs of gastric neoplasia in dogs include chronic vomiting, anorexia, and weight loss.[1,3,34] These signs can be present for weeks to months prior to presentation (median: 2 months, range: 2 weeks–18 months).[1] Vomiting is often persistent and progressive despite supportive care. Bleeding gastric lesions can occur, leading to partially digested blood or "coffee grounds" appearance to the vomitus.[1] Hematemesis, melena, abdominal pain, and pallor can occur due to chronic bleeding leading to iron deficiency and a secondary microcytic hypochromic nonregenerative anemia.[3,7,8] Malignant ulceration occurs in >50% of dogs with gastric carcinoma. Perforation of a gastric mass occurs more frequently with lymphoma (▶Fig. 6-14) than other malignancies and can cause signs of an acute abdomen with peritonitis.[1,35] Diarrhea can be seen in dogs with gastric lymphoma if intestinal segments are also affected.[1,9,19] Dogs with leiomyomas are often presented for the investigation of anemia, which may be microcytic, or associated with melena.[28]

Clinical signs in cats with gastric tumors are similar to those observed in dogs. Weight loss and vomiting are the most commonly reported clinical signs and are often accompanied by anorexia and lethargy.[18,19,26] Cats with gastric lymphoma often have a history of chronic and vague clinical signs that progress to anorexia, vomiting, weight loss, and/or diarrhea.[1,19] Cats with lymphoma may present acutely with clinical signs of spontaneous gastric perforation.[36]

### 6.3.4.4 Clinical pathology

Results of clinical pathology testing in pets with gastric cancer are often nonspecific. Clinicopathologic abnormalities are commonly due to secondary inflammation, gastric outflow obstruction, malabsorption, or blood loss. Hypoproteinemia secondary to hypoalbuminemia and increased serum liver enzyme activities is common.[2,4] In dogs with tumor-induced gastric outflow obstruction and vomiting, a hypochloremic metabolic alkalosis with paradoxical aciduria may develop.[1,4] Frequently, a complete blood count demonstrates an inflammatory leukogram and nonregenerative microcytic hypochromic anemia.[2–4] Measurement of reticulocyte hemoglobin may be useful in identifying iron deficiency in dogs and cats.[37,38] If gastric bleeding is acute, the anemia will be regenerative, but if hemorrhage is chronic, the anemia will become nonregenerative due to iron deficiency and chronic disease. In dogs with a rare gastric leiomyoma or leiomyosarcoma, paraneoplastic hypoglycemia may be noted.[39]

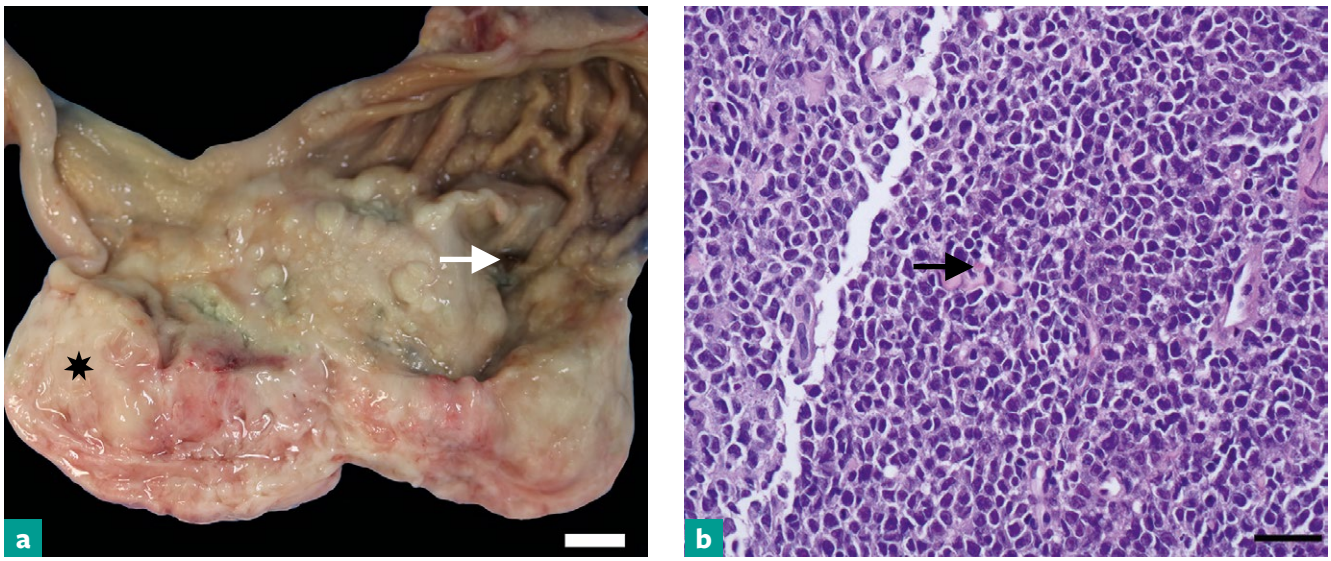



**Fig. 6-14** Feline gastric lymphoma

Gross image **a** shows a gastric lymphoma from a feline patient with secondary perforation (**arrow**). Note severe thickening of the gastric wall (**asterisk**); bar: 1 cm.

Microscopic image **b** shows a feline large-cell gastric lymphoma. Sheets of round cells with small amounts of cytoplasm, round to indented nuclei, and prominent nucleoli. The nuclei of neoplastic cells are at least two times the diameter of an erythrocyte (**arrow**). (H&E, 400x, bar: 20 µm).

(Courtesy of Dr. Taryn Donovan, Department of Pathology, Schwarzman Animal Medical Center, New York, NY.)

### 6.3.4.5 Diagnostic imaging

Diagnostic imaging is an important component of identifying a gastric mass and the possible involvement of surrounding organs. Unfortunately, the diagnostic imaging features of both benign and malignant gastric masses and the various histologies overlap, and neither abdominal radiography nor abdominal ultrasonography can differentiate between specific tumor types.

#### 6.3.4.5.1 Radiography

In some patients with gastric tumors, survey abdominal radiographs may be unremarkable. Abnormal findings can include excessive fluid or gas in the stomach despite fasting.[4] A mass or caudal displacement of the gastric axis on the lateral radiograph can be seen in dogs with gastric tumors.[3] A gastric mass may be identifiable along with possible evidence of metastatic spread to other organs.[1]

#### 6.3.4.5.2 Contrast radiography

Using contrast facilitates radiographic visualization of gastric wall thickening, distortion of the gastric lumen, filling defects, and derangement of rugal folds caused by tumor infiltration. The stomach may also appear rigid and non-distensible, termed "linitis plastica" or leather bottle stomach. Ulcers can also be highlighted by contrast material.[8] Delayed gastric emptying on contrast radiography is commonly identified with gastric tumors.[3,4]

#### 6.3.4.5.3 Ultrasonography

Both benign and malignant gastric tumors are associated with mural thickening, loss of normal wall layering, and decreased or absent motility in the tumor area.[2,4,40,41] The echogenicity of gastric tumors may be hypoechoic, hyperechoic, or mixed regardless of histologic type.[40,41] Carcinomas and lymphoma may appear as sessile masses or diffuse in distribution, while leiomyoma and leiomyosarcoma are typically discreet lesions.[40] An ultrasound finding called pseudolayering appears to correlate with an uneven intramural distribution of tumor cells seen histologically in dogs with gastric carcinoma.[2] Extension of the tumor through the serosal surface of the stomach has been identified in dogs with carcinoma.[40]

The accuracy of the ultrasonographic diagnosis increases with the expertise of the ultrasonographer.[42] The utility of ultrasound in identifying gastric masses decreases when the patient is uncooperative or gas and ingesta obscure the stom-

ach wall.[42] Nonneoplastic gastric disease such as gastritis can appear similar to gastric neoplasia in some cases.[42] Ultrasonography is also useful to identify regional lymphadenopathy, although finding enlarged lymph nodes is not specific for metastatic gastric neoplasia. Ulcer identification is common with ultrasonography allowing for optimized patient care.[40]

#### 6.3.4.5.4 Computed tomography

In humans, computed tomography (CT) is a widely performed technique for diagnosing and staging gastric tumors.[43] The use of a CT scan to identify the extent of GI tract involvement and diameter is described in the dog.[44] However, most of these dogs were not diagnosed with neoplasia.[44] In a report about CT findings in dogs with gastric neoplasia, contrast-enhanced CT was noted to provide useful information for characterizing the tumors based on early vs. late enhancement patterns, site of origin, extent of local invasion, and distant metastasis.[43] As CT accessibility continues to increase, the additional utility of this imaging modality is expected for pets with gastric tumors.



### 6.3.4.6 Biopsy techniques

Although clinical signs, laboratory data, and diagnostic imaging may suggest a gastric tumor, histopathology is essential for a definitive diagnosis. Exploratory laparotomy or laparoscopic surgery can be used to obtain tissue biopsy samples. Multiple samples can easily be obtained and are typically adequate in size to obtain an accurate diagnosis, but the procedure is invasive. Gastroscopy using a fiberoptic or video endoscope allows a tissue sample to be obtained and allows visualization of the gastric lesion prior to surgical resection. Multiple, deep mucosal tissue biopsies are recommended to increase the likelihood of an accurate diagnosis because of the significant inflammatory infiltrate in gastric tumors.[1] Ultrasound-guided percutaneous fine-needle aspiration of gastric masses to obtain cytologic samples is reported. This procedure is accurate for the diagnosis of gastric tumors.[2,4,46]

### 6.3.4.7 Treatment

Except for lymphoma, curative-intent surgery is the recommended treatment for pets with gastric cancer.[1,3,28] Given that gastric tumors are rare and often advanced at the time of diagnosis, reports of treatment are limited to small case series and case reports.[1,3,46] Relief of gastric outflow obstruction by side-to-side gastrojejunostomy (Billroth II) can be achieved.[3] Total gastrectomy or gastroduodenostomy (Billroth I) have been attempted to achieve complete tumor resection.[3,47] The dog undergoing gastroduodenostomy was provided nutrition through a jejeunostomy tube and was also treated with a combination chemotherapy protocol.[3] Photodynamic therapy has been reported for the treatment of a dog with gastric carcinoma.[5]

Chemotherapy is the recommended treatment for pets with gastric lymphoma.[13,19,35,48,49] However, a recent study suggests the combination of surgery and chemotherapy offers a survival advantage in cats.[21]

### 6.3.4.8 Systemic complications of gastric neoplasia

Chronic vomiting, gastric ulceration, and the production of a hypoglycemic factor can result in systemic complications of gastric neoplasia. **Hypochloremic metabolic alkalosis** causing paradoxical aciduria occurs in dogs with gastric carcinoma and severe vomiting.[4] Vomiting leads to loss of hydrogen and chloride ions, alkalosis, and volume depletion. Normally, the renal tubules will resorb sodium ions in exchange for chloride ions to respond to alkalosis and hypovolemia. However, when chloride is depleted, the kidney resorbs sodium and excretes hydrogen ions instead of chloride to maintain electrical neutrality, leading to paradoxical aciduria.

**Iron deficiency anemia** results when gastric tumors cause ulceration and chronic gastrointestinal blood loss. Loss of iron into the feces and inadequate intake of replacement iron due to vomiting and anorexia results in a microcytic, hypochromic, nonregenerative anemia. Pneumoperitoneum and peritonitis result when the tumor causes an ulcer and erodes through the entire gastric wall.[36,50]

**Paraneoplastic hypoglycemia** with a low serum insulin concentration has been described in a dog with gastric leiomyosarcoma.[51] The diagnostic investigation of this patient suggested the synthesis of an uncharacterized hypoglycemic factor by the tumor. Nonislet cell tumors associated with hypoglycemia are typically large and palpable on physical examination.[51]

### 6.3.4.9 Tumor invasion and metastasis

Most histologic types of gastric tumors are highly metastatic. Reported metastatic rates for canine gastric carcinoma are as high as 74% at the time of diagnosis.[3] Gastric carcinoma most commonly metastasizes to the regional lymph nodes. However, it also widely disseminates to any abdominal organ, the central nervous system, the myocardium, mediastinum, long bones, and testicular connective tissue.[3,5,42,52,53] The single case of a gastric carcinoid tumor in a cat was found to have widespread metastasis.[32] Gastric leiomyosarcoma in

dogs was shown to metastasize to the liver and duodenum.[3] Both dogs with gastric sarcoma in that study had metastatic disease at the time of surgery.[3]

Feline gastric lymphoma as the sole manifestation is a relatively uncommon presentation of feline lymphoma. A recent report found 24% of feline gastrointestinal lymphoma cases to involve gastric tumors, but only 15–18% were exclusively in the stomach, with a predominance of large B-cell lymphoblastic lymphoma diagnosed.[19–21,24] In cats diagnosed with small-cell GI lymphoma, approximately 20% have gastric involvement, with only 6% of cases having the tumor confined to the stomach.[54]

#### 6.3.4.10 Prognosis

In general, the survival of dogs with gastric cancer is poor.

One case series reported a median survival of 3 days with a range of 0 days to 10 months.[3] Occasionally, longer survival times are reported in single cases. Survival of 9 months was reported in two dogs undergoing gastrectomy.[46,47] Canine gastrointestinal lymphoma has reported survival rates following chemotherapy at <3 months.[30]

Feline gastric lymphoma treated with chemotherapy has reported survival times of 171 days.[19] Seventy-five percent of cats experienced remission, with an overall first remission duration of 108 days.

Response to treatment was prognostic as in other types of feline lymphoma. Cats achieving complete remission had longer survival times compared to cats with only partial remission.[19] Treatment of cats with a diagnosis of small-cell gastrointestinal lymphoma typically results in prolonged survival.[49]

**KEY FACTS**

- Most gastric tumors are malignant and are highly metastatic.
- Diagnostic imaging contributes to the diagnosis of gastric tumors. However, a biopsy is required to arrive at a histologic diagnosis and determine if the tumor is benign or malignant. Tissue biopsy samples can be obtained via exploratory laparotomy or endoscopy.
- Hypochloremic metabolic alkalosis with paradoxical aciduria, iron deficiency anemia and hypoglycemia are paraneoplastic syndromes associated with gastric tumors.
- Surgery is the only curative-intent option for localized gastric carcinoma. Chemotherapy alone, or following surgery, is the treatment of choice for pets suffering from gastric lymphoma.
- In general, survival is poor in dogs and cats with gastric neoplasia due to the advanced stage of disease at the time of diagnosis. However, long-term survival is possible for individual animals.

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
svg.to/9842-06-03-04

# 7 Small intestine

## 7.1 Anatomy

Craig G. Ruaux

### 7.1.1 Introduction

The intestinal tract is the point of entry of all metabolic energy into the animal. The processes of digestion and absorption undertaken in the intestinal tract need to be carried out over a large surface area. Many of the anatomical features of the intestine act to increase the surface area exposed and available for carrying out the major intestinal functions.

The intestinal tract has numerous functions, all of which are necessary for normal digestion (▶Tab. 7-1).

**Tab. 7-1** The five main digestive functions of the intestinal tract

| |
|---|
| **Motility** |
| The movement of ingesta through the intestinal tract from the stomach to the colon/rectum and eventual expulsion as feces |
| **Secretion** |
| Secretion of fluid, enzymes, and electrolytes into the gastrointestinal lumen |
| **Digestion** |
| Degradation of ingesta occurs in the proximal small intestine, mediated largely by pancreatic digestive enzymes. The small intestinal mucosa also has a role in the further digestion of food material at the brush border |
| **Absorption** |
| Following degradation of ingested foodstuffs, the resulting nutrients need to be assimilated and introduced into the animal's circulation. Fluid and electrolytes secreted during the processes of digestion are reabsorbed during the formation of feces |
| **Barrier function** |
| Prevention of the translocation of intestinal bacteria and digestive enzymes into circulation, as well as the prevention of loss of plasma proteins |

In addition to the digestive functions listed above, the intestinal tract has an important role in normal immune function, antigen processing, and presentation, and a role in the endocrine regulation of digestive enzyme synthesis and release by other digestive organs, such as the pancreas. In this section, the anatomical structure of the intestinal tract is described, particularly with reference to the anatomical features contributing to the large surface area of the SI. The endocrine and immunological features of intestinal function are described in ▶Chap. 7.2.

### 7.1.2 Gross anatomy of the intestinal tract

The intestinal tract is essentially a muscular tube with a varying diameter and mucosal structure in the different sections of the tract. The variations in diameter, mucosal structure, and function relate to the differing physiological role of each area; for instance, the stomach is readily distensible, while the SI is much less distensible.

The intestinal wall is divided into four discrete layers. The four layers are visible on cut sections of the intestine and can be readily distinguished by differences in echogenicity during ultrasound examination of the intestinal tract.

Proceeding from the lumen outwards to the serosa, the four layers of the intestinal tract visible during ultrasound examination are:

- Mucosa (slightly hypoechoic)
- Submucosa (hyperechoic)
- Muscularis (hypoechoic)
- Serosa (brightly hyperechoic)

In addition to the four physical layers described above, a very narrow hyperechoic layer is usually visible at the interface between the mucosa itself and the intestinal lumen.

## 7.1.3 Anatomical features of the small intestine

### 7.1.3.1 Increasing available surface area

Several anatomical features increase the available surface area of the intestinal epithelium (▶Fig. 7-1).

The inward folding of the mucosa into grossly visible folds (**rugae**) increases the available surface area by a factor of approximately 3 over a plain tube of equivalent diameter. The mucosa is arranged into finger-like structures (**villi**), which increase the surface area by an additional factor of approximately 10.

Enterocytes have a microscopic brush-border modification of their luminal cell membrane called **microvilli**. These microvilli increase the available surface area for digestion and absorption of nutrients by a factor of nearly 20 over the surface area of the villous projections.

In combination, the three structural elements of rugae, villi, and microvilli increase the effective surface area of the intestinal mucosa by a factor of approximately 600 compared with a plain tube of the same diameter. The loss of one element, for instance, villous blunting, as occurs with some viral enteropathies (▶Chap. 7.3.1.1) or idiopathic inflammatory bowel disease (IBD; ▶Chap. 11.2), will dramatically alter the function of the SI.

### 7.1.3.2 Microscopic anatomy

The villus is the functional unit of the SI mucosa. Enterocytes arise from the division of stem cells in crypts at the base of the villus. They then migrate and mature along the length of the villus and are finally shed from the villus tip into the lumen. As enterocytes migrate along the villus, their function alters, starting from a mainly secretory function in the crypt and lower villus, maturing to a mostly absorptive function in the upper part of the villus (▶Chap. 7.2.2).

### 7.1.3.3 Spatial variation in intestinal structure

The small intestine has three major anatomical divisions. Proceeding from oral to aboral, these are:

- Duodenum
- Jejunum
- Ileum

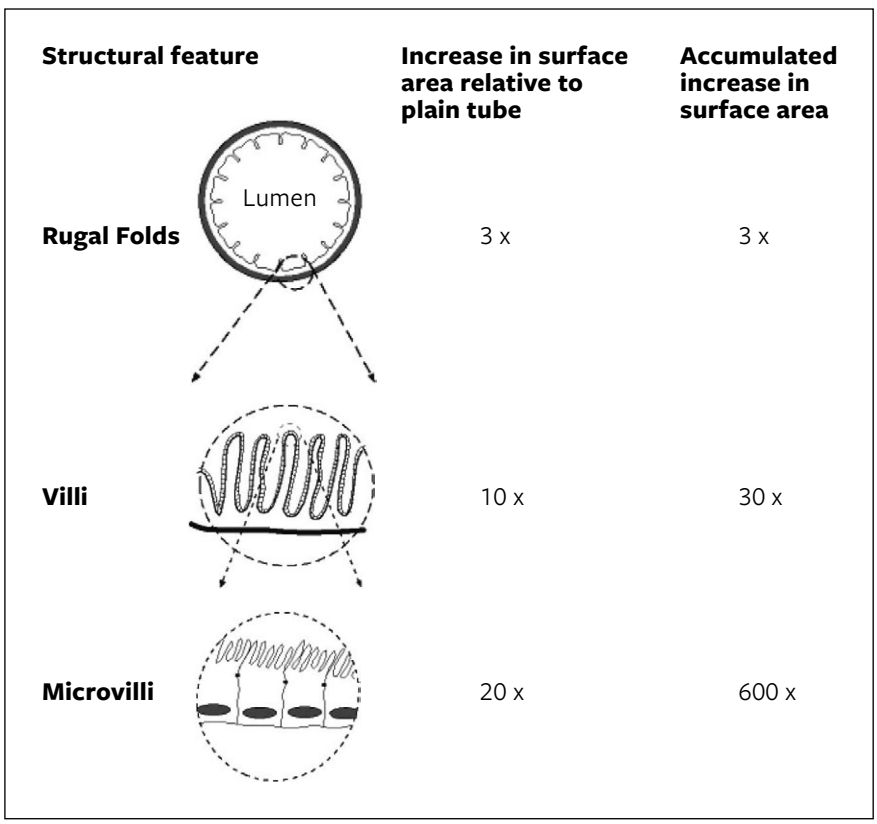



**Fig. 7-1** Macroscopic and microscopic anatomical structures increasing the surface area of the intestine

The specific function of these three regions varies, with the digestion of nutrients primarily occurring in the duodenum. The jejunum has both transport and absorptive functions, and the ileum is almost exclusively absorptive. The size and structure of the villi vary down the length of the SI, with the duodenal villi being short and blunt, while the villi of the jejunum are long and narrow. In the duodenum, the ratio of the villus length to crypt depth is nearly equal, while the jejunal and ileal villi are much longer than the crypt depth. This anatomical difference reflects the greater need for increased surface area for the absorptive processes in the jejunum and ileum.

**KEY FACTS**

- The small intestine in dogs and cats is relatively short and simple, reflecting a predominantly carnivorous diet.
- The small intestine has several anatomical features that increase its effective surface area.
- Small intestinal anatomy varies along its length, reflecting the differing functions of different sections of the small intestine.

## 7.2 Physiology

Craig G. Ruaux

### 7.2.1 Introduction

The normal regulation of the SI is carried out by a highly complex, interconnecting group of physiological mechanisms. Normal functioning of the intestine requires the production and secretion of digestive enzymes, pancreatic juice, bile acids, normal motility of the intestines and associated organs, mixing and compartmentalization of the gut contents, feedback regulation of the stomach and pancreas, and the regulation of food intake. To achieve these various functions, the GI tract produces and responds to a large number of hormonal substances.

The GI tract also possesses a complex enteric nervous system, receiving efferent inputs from the central nervous system (CNS) and providing afferent signals to the CNS.

The GI tract provides an enormous surface area that is in constant contact with dietary and environmental antigens. A complex system of gut-associated lymphoid tissue (GALT) regulates the gastrointestinal mucosal immune responses to potential pathogens and dietary allergens and regulates the expression of immune mechanisms and antibodies on other mucosal surfaces in the body.

The SI contains a complex population of microorganisms that play a role in maintaining the normal structure and function of the intestine (▶Chap. 7.2.5). The SI is also in direct if circuitous, contact with the external environment of the animal and thus represents a major potential point of entry for bacteria, viruses, and allergens.

### 7.2.2 Function of the villus

The villus is the functional unit of the SI mucosa. Enterocytes arise from stem cell division in crypts at the base of the villus, then migrate and mature along the length of the villus and are finally shed from the villus tip into the lumen. As enterocytes migrate along the villus, their function alters, from a mainly secretory function in the crypt and lower villus, maturing to a mostly absorptive function in the upper part of the villus. The normal physiology of gastrointestinal epithelial cell generation and maturation is discussed in detail elsewhere.[1] ▶Fig. 7-2 shows an idealized illustration of a typical villus.

Enterocytes have a microscopic brush-border modification of the luminal cell membrane, the microvilli. These microvilli increase the available surface area for digestion and absorption of nutrients by a factor of nearly twenty over the surface area of the villous projections.

As the function of the enterocytes varies with their location, the pathological effect of diseases affecting the small intestinal mucosa varies depending upon which part of the villus is predominantly affected.

**CLINICAL PEARLS**

Rotaviral and coronaviral diarrheas are typically mild and self-limiting, affecting the older enterocytes and thus reducing the absorptive capacity of the small intestine but sparing the younger enterocytes. This contrasts with the effects of parvovirus (▶Chap. 7.3.1.1), which damages much younger enterocytes than in the rotaviral and coronaviral enteritides. This loss of younger enterocytes compromises mucosal permeability, promotes bacterial translocation and gastrointestinal bleeding, and leads to a loss of absorptive function as the enterocytes are no longer present to mature. Consequently, feline and canine parvoviral enteritides are severe diseases that are associated with high morbidity and mortality.

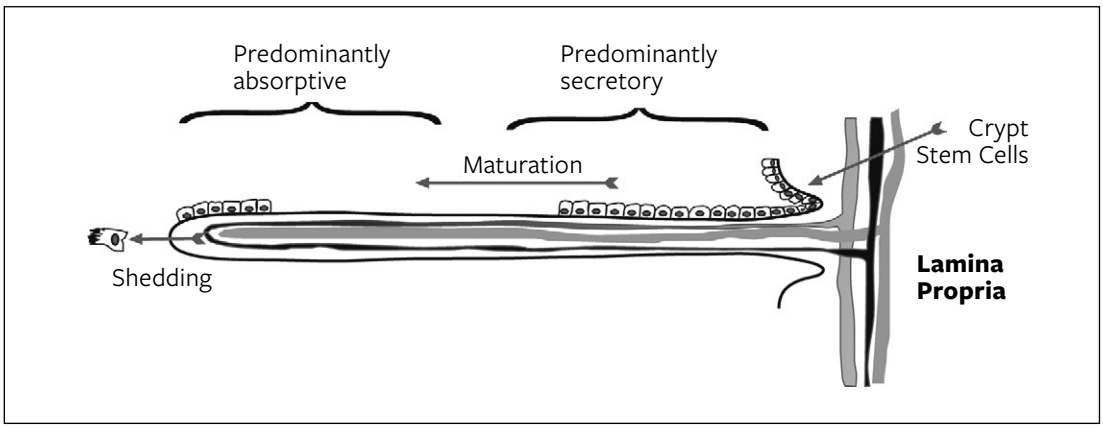



**Fig. 7-2** Diagrammatic representation of the structure and function of the small intestinal villus

Gastrointestinal epithelial cells (enterocytes) arise from stem cells in the mucosal crypts. As they mature, they migrate along the length of the villus. During maturation, the function of the cell changes from predominantly secretory at the base of the villus to predominantly absorptive at the tip of the villus. Enterocytes are shed into the gastrointestinal lumen from the tip of the villus.

The brush border of the enterocytes of the apical villus provides an enormous increase in the surface area of the villus. This large surface area provided by the brush border promotes contact of the partially digested intestinal contents with the brush border enzymes that carry out many of the last steps of digestion. The large surface area also promotes the absorption of nutrients by increasing the number of receptors and carrier molecules available and promoting the passive diffusion of simple compounds, water, and some electrolytes.

Loss of the brush border will reduce the uptake of fluids secreted by the villus crypts and younger enterocytes, leading to an increased fluid content in the intestinal tract. Visualization of the brush border is difficult with routine histopathological examination; thus, subtle alterations in brush border morphology and function may not be detected by routine histopathology.

### 7.2.3 Gastrointestinal hormones

The GI tract is the largest endocrine organ in the body, both in terms of the total mass of hormone-producing cells and the total number of hormonal substances produced.[3,4] The vast majority of gastrointestinal hormones are small peptides. These compounds are liberated from endocrine secretory cells into circulation, manifesting a physiological effect on tissues distant from the cells that produce the hormone. Representative examples of the best-known and most thoroughly characterized gastrointestinal hormones are listed in (▶Tab. 7-2). The GI tract regulates its own motility and secretory processes in response to food input and changes in the luminal environment.

**Secretin**, a 23-amino-acid peptide hormone produced in the mucosa of the duodenum, was the first hormone to be isolated and its function described. This hormone, produced by the "S" cells in the duodenal mucosa in response to acidification of the duodenal lumen, stimulates the pancreas to produce pancreatic juice with a high concentration of bicarbonate, neutralizing the acid in the duodenal lumen. Bicarbonate production and neutralization of the gastric acid is necessary for the optimum function of exocrine pancreatic and duodenal mucosal digestive enzymes, most of which have pH optima near neutrality (pH 7.0).

After observing secretin activity in duodenal extracts, an endocrine activity of gastric antral mucosal extracts was detected on gastric acid secretion. The responsible substance was originally called "gastric secretin" but was subsequently abbreviated to **gastrin**.[3] Gastrin is a 17-amino-acid peptide produced by "G" cells in the antral mucosa in response to the presence of protein and fat in the distal gastric antrum. Gastrin acts upon enterochromaffin-like cells to increase the production of histamine by these cells. Histamine released by enterochromaffin-like cells then stimulates gastric acid production by the chief cells. Entry of food into the SI stimulates the production of **cholecystokinin** (**CCK**). CCK is released from duodenal "I" cells, stimulating gall bladder emptying and the production of digestive enzymes by pancreatic acinar cells.

These three "classical" GI hormones were isolated, and their predominant functions were identified some decades ago. As all three are stimulatory, elucidating their effects on the GI tract and associated organs was relatively simple. Inhibitory hormones, which decrease gastrointestinal

**Tab. 7-2** Examples of endocrine compounds with major effects on the gastrointestinal tract

| Hormone | Source | Function(s) |
|---|---|---|
| **"Classical" gastrointestinal hormones** | | |
| Cholecystokinin | Duodenal mucosa, "I" cells | Stimulates gall-bladder contraction and pancreatic enzyme secretion |
| Gastrin | Gastric antrum, "G" cells | Stimulates gastric acid secretion |
| Secretin | Duodenal mucosa, "S" cells | Stimulates pancreatic bicarbonate secretion |
| **"Modern" gastrointestinal hormones** | | |
| Enteroglucagon | Distal small intestine, "L" cells | Enhances release of insulin in response to hyperglycemia |
| Gastric inhibitory peptide (GIP) | Proximal small intestine | Inhibits gastric motility and acid secretion |
| Ghrelin | Gastric epithelium | Stimulation of growth hormone release, regulation of appetite |
| Motilin | Proximal small intestine | Stimulates migrating motor complexes |
| Pancreatic polypeptide (PP) | Pancreatic acinar cells | Affects pancreatic secretion, complex effects on gastrointestinal motility |
| Somatostatin | Pancreas, enteric nervous system, gastrointestinal epithelium | Inhibits secretion of many other gastrointestinal hormones |

secretion and/or motility, are more difficult to demonstrate in whole-animal studies. The major hormone with inhibitory effects on the GI tract, **somatostatin**, was not isolated and identified until nearly 40 years later.

The SI mucosa is the source of **motilin**, a peptide hormone that stimulates gastrointestinal motility. Motilin is released into circulation during the interdigestive phase. This pulsatile release of motilin stimulates cyclical muscle contractions that sweep the length of the intestine. These cyclical "housekeeping" contractions are called the migrating motor complex.

Sensations of hunger and satiety are important in the regulation of food intake. **Ghrelin**, another peptide hormone produced in the gastric mucosa, is released into circulation when the stomach is empty. Ghrelin acts on the CNS to regulate hunger and satiety, with circulating concentrations increasing during the interdigestive period, then rapidly decreasing after feeding. Ghrelin's name is derived from another important systemic function of this hormone, acting as a growth hormone-releasing hormone (GhRH) in the pituitary. Ghrelin is a potent stimulator of growth hormone release, while somatostatin suppresses growth hormone release. The actions and release patterns of ghrelin and somatostatin, in concert with GhRH from the hypothalamus, lead to a pulsatile release of growth hormone. Thus, the stomach mucosa, and the state of gastrointestinal filling, play an important role in the integrated regulation of body-wide physiology by its production and release of ghrelin, and thus its influence on growth hormone production.

Ghrelin concentrations are lower in obese humans than in lean controls (▶Chap. 11.5). Conversely, in patients with Prader-Willi syndrome, extremely high circulating ghrelin concentrations are observed in association with a voracious appetite and extreme obesity.[5]

Pharmacological manipulation of the ghrelin receptor through a ghrelin receptor agonist, capromorelin, has been shown to increase appetite in dogs.[6] This compound became the first ghrelin receptor antagonist licensed for use in any species.

### 7.2.4 Gut-associated lymphoid tissue and immune system

As the largest area of mucosal tissue exposed to the external environment, it is understandable that the GI tract plays an important role in regulating the immune system (▶Chap. 11.2). The GI tract is a major component of the "common mucosal immune system". Exposure to antigens in the GI tract is associated with increased secretory IgA (sIgA) production at other mucosal sites and IgG systemically. Conversely, exposure to potential gastrointestinal pathogens at other mucosal surfaces will lead to increased production of sIgA in the gastrointestinal mucosa.[7]

**Immune system cells** occur throughout the GI tract. Intra-epithelial lymphocytes are widely distributed in the gastrointestinal mucosa (▶Chap. 1.8.1), where they may mediate antibody-dependant cellular cytotoxicity or act as natural killer cells. Mast cells are also scattered diffusely throughout the mucosa, submucosa, and lamina propria of the intestine. Particularly in the ileum, immune cells of the GI tract may be organized in lymphoid follicles, forming **Peyer's patches**. Specialized mucosal cells in the epithelium over the Peyer's patches endocytose antigens. The antigens are passed to dendritic cells and macrophages, which act as antigen-presenting cells within the lymphoid follicles. Immunocompetent T cells produced within the Peyer's patch can subsequently migrate to other mucosal surfaces, where they produce IgA. After exposure to antigen within the Peyer's patches, some T cells will migrate into the gastrointestinal mucosa, where they become cytotoxic T cells, directed against potential pathogens.

The GI tract is constantly exposed to a vast number of antigens. These may be derived from food proteins, the intestinal microbiota, or the host organism itself. It has been said that the GI tract normally exists in a constant state of inflammation. However, excessive inflammatory cell activation will lead to disease, such as chronic inflammatory enteropathy (CIE ; ▶Chap. 11.2) or colitis (▶Chap. 8.3.1). The normal regulation of the immune system's reactivity to antigenic challenge is carried out by a complex system of cytokines and regulatory cells, which have been reviewed elsewhere.[7]

**Increased gastrointestinal immune system responsiveness** to either endogenous antigens or bacterial proteins has been postulated to be an underlying cause of CIE in many veterinary patients. It is unclear whether the underlying problem is inappropriate reactivity, IgE-mediated allergic disease, suppressed down-regulation of immune cells, or some combination of multiple predisposing causes that lead to the pathological process referred to as CIE (▶Chap. 11.2).

The predominant immunoglobulin subtype produced by the GI tract is **IgA**. Dimeric and polymeric IgA molecules are produced by plasma cells within the lamina propria, then taken up by enterocytes, complexed with a secretory component, and released into the intestinal lumen. Within the lumen, sIgA binds with surface proteins of many potential pathogens, helping prevent their adhesion to the mucosa and subsequent bacterial invasion of the epithelium.

**Secretory IgA deficiency** is the most common immune deficiency of humans, and has also been described in some dog breeds, such as the German shepherd dog.[8,9] While sIgA deficiency in dogs is associated with an increased incidence of intestinal disease by some authors,[7] the actual prevalence of IgA deficiency in both healthy and diseased dogs and the role of sIgA deficiency in veterinary gastroenterology is an area of active research.

### 7.2.5 Intestinal bacteria

The GI tract is home to a vast population of microorganisms, including bacteria, archaea, fungi, protists, and a complex assemblage of viruses. These are collectively referred to as the gastrointestinal microbiome. Particularly in the more distal parts of the intestine, the gastrointestinal microbiome is an important source of some vitamins and has critical roles in the metabolism of many compounds. *Lactobacillus* and *Bifidobacterium* spp., for instance, can ferment complex polysaccharides such as inulin and fructooligosaccharides, generating short-chain fatty acids (SCFA) that are used as an energy source by the enterocytes.

The normal canine intestinal microbiome is highly complex, varying markedly from individual to individual and at differing points within the GI tract.[10] Each individual appears to have a unique bacterial flora present within its GI tract. Based on longitudinal studies in several species, this flora is quite stable in healthy individuals.

Recent years have seen a vast amount of research into the structure and roles of the gastrointestinal microbiome in dogs and cats. Our current understanding of the gastrointestinal microbiome is discussed in much greater detail in ▶Chap. 7.3.4.

**KEY FACTS**

- Physiological regulation of the intestine involves complex interactions between the endocrine, neural, and immune systems specific to the intestine.
- The villus is the functional unit of the small intestine. Diseases affecting the villus are associated with osmotic and/or secretory diarrhea and malabsorption.
- The gastrointestinal microbiota plays an integral part in normal intestinal physiology.

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
svg.to/9842-07-01-02

# 7.3 Small intestinal disease

## 7.3.1 Infectious causes of small intestinal disease

### 7.3.1.1 Viral causes of diarrhea in dogs and cats

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#### 7.3.1.1.1 Etiology and epidemiology

**Parvovirus** is the most common viral cause of diarrhea in dogs, with high morbidity and mortality rates among dogs and cats worldwide. Members of the parvovirus genus infect a wide range of mammalian hosts but do show host specificity. Canine parvovirus (CPV) is multi-host in dog and wildlife interface areas, with attendant implications for transmission ecology and the protection of wild species.[1,2] The virion is a simple, small, non-enveloped, single-stranded DNA virus with a genome size of around 5,000 base pairs. The capsid proteins are the key structures determining host specificity and antigenicity. The host range of canine and feline parvovirus differs and is determined by less than 10 amino acid differences in the capsid.[3] The virus uses the transferrin receptor to gain entry to cells, and polymorphisms in this receptor are responsible for host specificity.[4] There is evidence that viral pathogenicity is related to phylogeny.[5]



Feline parvovirus (FPV) replicates in vitro in feline but not in canine cell cultures.



Canine parvovirus (CPV), on the other hand, replicates in both feline and canine cell cultures. FPV can replicate to a limited extent in dogs but without causing illness. It infects the canine thymus and bone marrow but does not appear in body fluids, leading to an inability to spread amongst dogs.[6]

The first CPV discovered in 1967 was called the minute virus of canines (later called CPV-1).[7] It is clinically insignificant today.[8] CPV-2 was discovered in dogs in 1978 in the United States, and it was responsible for a devastating global pandemic within months.[9] It is now well established worldwide and is probably the single most common infectious disease of dogs with high morbidity and mortality. This virus has subsequently mutated into CPV2a, CPV2b, and lately to CPV2c. This latter virus was first identified in Italy in 2000[10–12] but is now reported worldwide. CPV2a and CPV2b can infect cats and cause a rare clinical illness indistinguishable from panleukopenia.[13,14]

The fecal-oral route is the traditionally understood means of transmission, but fomite transmission is also very efficient. Diseased dogs can shed the virus at very high titers (up to $10^9$ $TCID_{50}$ per gram of feces) in their stools.[15] In the authors' hospital, the caseload has been directly correlated with wind speeds and inversely to humidity.[16] There is also evidence of seasonality in CPV in Canada[17] and feline panleukopenia across North America, which corresponds to a peak in the susceptible kitten population.[18] Certain dog breeds appear more susceptible to infection, including Rottweilers, American pit bull terriers, Doberman pinschers, English springer spaniels, and German shepherd dogs.

In contrast, there is no published evidence of breed susceptibility among cats. Moreover, the odds of developing CPV enteritis were higher in purebreds than in mixed-breed puppies in one study.[19] Because antibodies confer immunity, maternally derived titers mean that neonates are rarely affected. Approximately 90% of maternally derived antibodies are from colostrum and have a half-life of approximately 10 days.[20] Susceptibility increases as maternal immunity wanes at around 12–14 weeks of age. Vaccination is highly effective at protecting from infection. The age at which puppies and kittens are predominantly affected coincides with an abundant supply of susceptible animals, which increases disease incidence. Introducing infected animals into shelter environments may also result in large outbreaks. Other factors that contribute to infection include intestinal parasites, overcrowding, and unsanitary and stressful environmental conditions. Both CPV and FPV are extremely stable in the environment, making indirect transmission important and environmental decontamination difficult. Care should be taken in veterinary clinics where unvaccinated or inadequately vaccinated puppies are likely to come into contact with contaminated surfaces. Dogs admitted to the hospital for treatment should be kept isolated from the rest of the hospital population. Flies can also play an important role in spreading the infection amongst dogs.[21]

**Distemper virus** is an important cause of enteritis in unvaccinated dogs worldwide. The disease is multisystemic and varies in presentation. A detailed discussion of this disease is beyond the scope of this chapter. Distemper-associated diarrhea is indistinguishable from parvovirus-associated diarrhea (▶ Fig. 7-3).

However, it is almost always accompanied by a seropurulent nasal discharge, conjunctivitis, coughing, and pneumonia

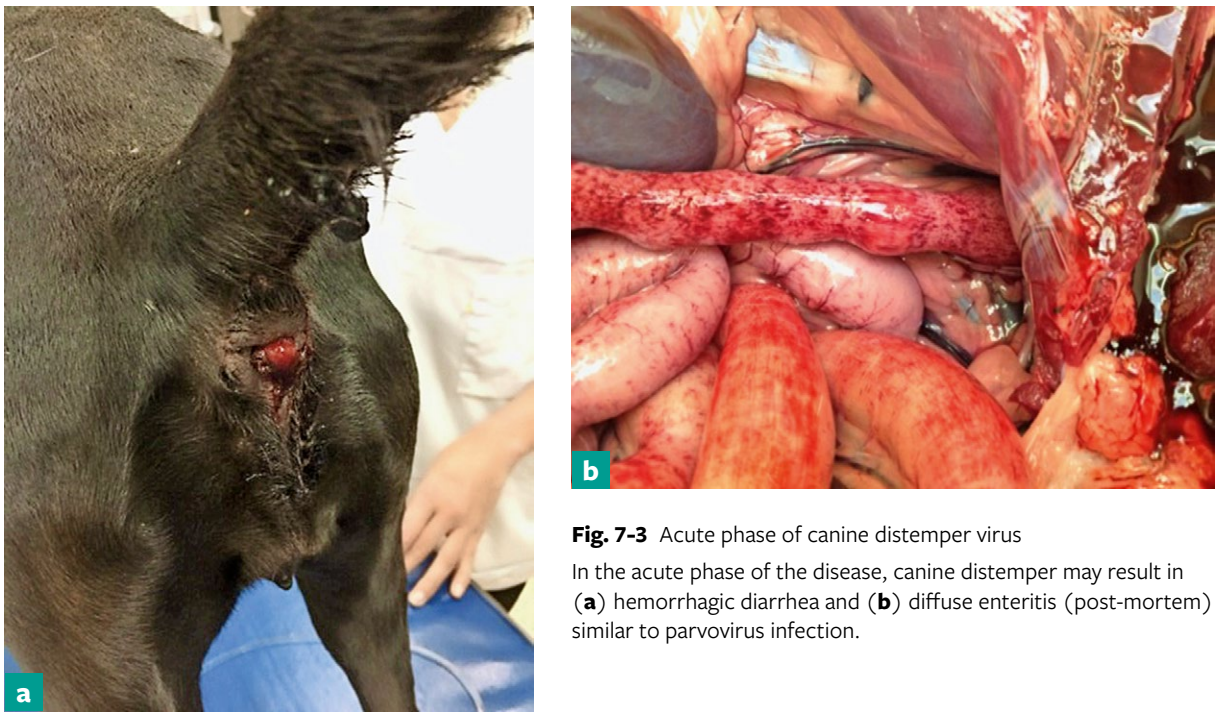


**Fig. 7-3** Acute phase of canine distemper virus
In the acute phase of the disease, canine distemper may result in (**a**) hemorrhagic diarrhea and (**b**) diffuse enteritis (post-mortem) similar to parvovirus infection.

– at least during the acute catarrhal stage (▶Fig. 7-4). Dogs with central nervous system signs of distemper infection do not frequently present with diarrhea. These signs are more typical towards the end of the acute catarrhal stage. Later stages of the disease may be characterized by dental hypoplasia (▶Fig. 7-5a) and naso-digital hyperkeratosis (▶Fig. 7-5b and ▶Fig. 7-5c).

Clinicians should carry a high diagnostic suspicion for these two important viral etiologies because the same dog population (young, unvaccinated, and frequently from disadvantaged backgrounds) is typically affected. All dogs with diarrhea and upper or lower respiratory involvement should be tested for distemper. Admission of a dog with distemper to an isolation facility where parvovirus-infected dogs are cared for can have devastating effects. Distemper is highly contagious, and infection of an already immunosuppressed parvovirus-infected host profoundly worsens prognosis.



**Fig. 7-4** A young chow dog demonstrating the typical early catarrhal signs of upper respiratory clinical signs (**a**) associated with distemper infection and (**b**) a close-up view of the nose with purulent discharge from both nostrils.

**Canine coronavirus** has been reported as a cause of diarrhea in dogs, but its clinical importance is unknown. Co-infections with distemper and parvovirus and coronavirus with parvovirus have been reported to result in more severe clinical signs. There are occasional reports of other diarrhea-causing viral co-infections in dogs, such as rotavirus,[22] kobuvirus,[23] and bufavirus.[24] These are very rare and of minimal clinical significance.

**Feline leukemia virus** (FeLV) and **feline immunodeficiency virus** (FIV) can be associated with gastrointestinal signs, particularly diarrhea, due to secondary bacterial, protozoal, viral, or fungal infections resulting from the immunosuppressive state. Mild, transient, and self-limiting diarrhea can also be caused by an infection with **feline coronavirus** (FeCoV).

This chapter will focus on parvovirus infection because of its importance as a cause of diarrhea in dogs.

#### 7.3.1.1.2 Clinical features

##### Clinical presentation and disease pathogenesis

Parvovirus is unable to induce mitosis in the cells it infects, and thus it relies on the rapidly multiplying cells of the body for its replication. Thus, the virus shows a **tropism** for the **thymus, bone marrow, spleen**, and **crypt cells of the gut epithelium**. Stress factors, in particular parasitic and other factors such as weaning, may predispose dogs to infection by increasing mucosal cell activity.[25] A robust antibody response is protective against parvovirus infection. Consequently, it is almost exclusively a disease of unvaccinated or inadequately vaccinated animals less than a year old that have passed the age of maternally-derived antibody protection. Therefore, vaccination status plays an important role in disease susceptibility.

Following oral infection, the virus disseminates to the regional lymph nodes of the pharynx and the tonsils. In an experimental study in dogs, fecal shedding was present from day 3 after oral infection, peaked on days 3 and 4, and was greatly reduced by day 7.[26] Shedding may occur a day or two before clinical signs are apparent. The incubation period of the disease varies from 4 days (under experimental conditions) to the more typical 1–2 weeks (under natural conditions). Following infection of lymphoid tissues of the upper GI tract (including the tongue), a cell-free viremia ensues. Under experimental conditions, this lasts from day 1–5 post-infection, with serum antibodies developing on day 5 and peaking from day 7 onwards.[26] Thymic and lymphoid tissue infection leads to thymic atrophy, lymphoid depletion, lymphopenia, and immunosuppression. The parvoviral anti-

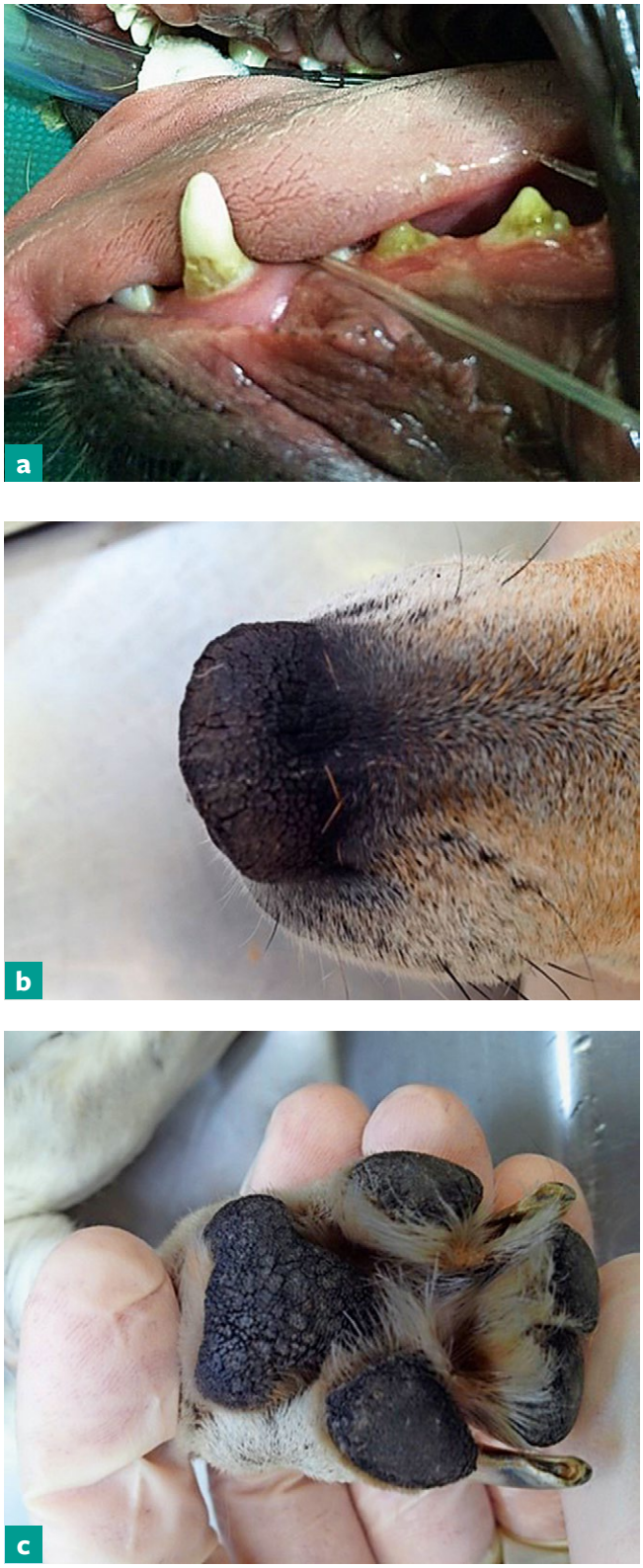



**Fig. 7-5** Dog after survival of acute distemper virus

Dogs with distemper that survive the acute disease may go on to demonstrate (**a**) dental hypoplasia or (**b** and **c**) naso-digital hyperkeratosis.



**Fig. 7-6** A young Basset hound puppy that recovered from parvoviral diarrhea complicated by secondary *Salmonella* bacteremia

The bacteremia resulted in ear-tip skin necrosis, probably due to micro-embolization of the peripheral vasculature.



**Fig. 7-7** An isolation ward used exclusively for the treatment of puppies with parvovirus infection

Strict hygiene and barrier nursing practices are necessary in a facility where a high level of veterinary care is possible.

gen is detectable in the proliferative zone of the intestinal crypt epithelium from day 4. Very little antigen remains in either the lymphoid tissues or gut epithelium from day 7 onwards. Subclinical infection is probably common, especially in older immune-competent animals.

**Bone marrow infection** may cause bone marrow necrosis in dogs and cats.[3] This leads to leukopenia and may contribute to the anemia seen in some cases. In most cases of CPV and FPV, leukopenia is present by the time hemorrhagic diarrhea and vomiting are present. Thrombocytopenia is, however, not a feature of the disease.[27] An increased concentration of granulocyte colony-stimulating factor has been documented in dogs with CPV, which is likely a response to neutropenia.[28] The neutropenia is also partially due to an overwhelming demand in the gut. The immunosuppression associated with CPV makes affected dogs very susceptible to acute secondary infections. The most common of these are bacterial bloodstream infections, most likely resulting from a compromised gut barrier, which can manifest clinically as endotoxic shock. Also, upon recovery, some puppies develop skin necrosis (▶Fig. 7-6), bacterial polyarthritis, or discospondylitis.[29] Due to the immune-suppressed state, barrier nursing practices should be strictly enforced (▶Fig. 7-7), and puppies with other infectious diseases should not be kept within the same ward.

**NOTE**

The most important differential diagnosis for canine parvovirus (CPV)-like clinical signs, is canine distemper virus infection. Every effort must be made to prevent this highly contagious disease from being cared for in a facility that admits CPV-infected puppies or by the same caregivers.

Viral infection of the gut leads to crypt necrosis and villous collapse with **loss of the normal gut barrier function** and serious consequences because elements of the luminal content can no longer be kept out of the bloodstream.[30,31] *Escherichia coli* was recovered from the lungs and liver of 88/98 (90%) CPV-infected puppies in one study.[32] Blood loss into the gut may be significant, resulting in melena, hematochezia, and anemia (which may be masked in dehydrated animals). Ascarid infestations are a common aggravating co-morbidity that may result in additional intestinal blood loss. Concurrent giardiasis and coccidiosis (▶Chap. 7.3.1.3) are less common.

Early in the CPV-2 disease pandemic, when dogs were not vaccinated, and dams transferred no maternal antibodies to their pups, very young (<8 weeks of age) or pups *in-utero* became infected. Their clinical presentation involved the myocardium and was somewhat different from what it is today. Myocardial disease due to CPV is now rare,[33] although



**Fig. 7-8** A young mixed breed puppy suffering from parvovirus infection

**a** Note the perineal soiling with very watery diarrhea.

**b** The stools are often bloody and mucoid.

**c** Placing a nasoesophageal feeding tube early in the disease course greatly helps early enteral feeding, hydration support, and medication administration. In cases of severe gastric paralytic ileus, removing excessive fluid from the stomach (by advancing the tube into the stomach) can provide some added comfort.

it still occurs in isolated unvaccinated populations.[34] However, these findings have recently been questioned as evidence of myocarditis, and myocardial fibrosis in dogs was shown by *in-situ* hybridization to be associated with CPV-2 despite high levels of vaccine uptake, which would be assumed to have provided protection.[35] Enteric clinical signs were not always present with cardiac signs. The latter can vary widely from peracute congestive heart failure to more chronic failure that becomes evident months after infection. However, it would appear that CPV is not a common trigger for myocardial disease in dogs anymore.[36] Incidentally, FPV was identified by polymerase chain reaction (PCR) in 10/31 cats (32%) with cardiomyopathy but none of the 17 controls in one study, suggesting a possible role of viral infection in the pathogenesis of feline cardiomyopathy.[37]

The ultimate cause of death in acute CPV and FPV infection is **septicemia, endotoxemia, and shock**. Endotoxin and the subsequent inflammatory cascade initiated by endotoxin are related to disease severity and outcome.[38,39] One study showed that 22% of the IV catheter tips used for fluid therapy were infected, and most of the organisms cultured were Gram-negative gut-associated bacteria.[40] Hypoglycemia is also a common finding. This is likely due to the young age of most affected dogs, concomitant anorexia, and the hypermetabolic state associated with endotoxic shock. Seizures in puppies with CPV infection most likely result from neuroglycopenia.

### Physical examination findings

The earliest clinical signs include fever, depression, and a loss of appetite. This is followed by diarrhea and vomiting. The diarrhea is initially characteristic of small bowel disease. It may quickly become mucoid, melenic, and then frankly hemorrhagic and take on the character of a mixed small and large bowel type diarrhea (▶Fig. 7-8). These puppies have a very characteristic fetid odor. Vomiting usually increases in frequency and can become very severe and frequent with little more than foam produced. Hematemesis may be present, and ascarids may also be observed in the vomitus.

Anorexia, vomiting, and diarrhea cause devastating fluid and electrolyte losses, leading to dehydration and electrolyte deficiencies. The dehydration would be classified as isotonic or hypotonic (due to hypertonic fluid loss) and results in dry mucous membranes, increased skin turgor, increased capillary refill time, tachycardia, hypotension, collapse, and reduced urine production.

#### 7.3.1.1.3 Diagnosis

The diagnosis of parvoviral disease is not problematic and is usually based on combining a cluster of findings that include the presentation of the typical signalment (young and un- or inadequately vaccinated), classic chief complaints of depression, anorexia, vomiting, and diarrhea (which may be hemorrhagic), and the typical clinical findings of pyrexia, dehydration, fluid-filled and gassy abdominal palpation and leukopenia on a peripheral blood smear. In some cases, no further diagnostic tests are performed, and a legitimate presumptive diagnosis is made. The next diagnostic step typically involves using a fecal parvovirus antigen ELISA to confirm the clinical suspicion. These tests are widely used and will detect CPV-2a, b, and c, but they have some limitations regarding sensitivity.[41] However, specificity is less of a problem with these tests. On rare occasions, false positives may occur due to the shedding of vaccine virus for 4–8 days following vaccination (although up to 28 days was shown in one study)[42] with a modified live CPV vaccine. The vaccine strain has even been shown to be transmitted amongst dogs,[43] and a similar problem is reported following FPV vaccines.[44]



**NOTE**

It must be remembered that fecal viral shedding is transient, and fecal antibodies may bind the virus, making it unavailable in the assay.

Serology is seldom used. Semi-quantitative ELISAs for anti-CPV-2 antibodies can be used to determine the need for vaccination rather than diagnosis. Fecal electron microscopy, although useful, is seldom used because it is impractical and of limited availability. PCR is well-described and used in parts of the world where it is available commercially. Fecal flotation and wet-mount examination to detect verminosis and giardiasis, respectively, should be routine in all cases of suspected CPV.

#### 7.3.1.1.4 Clinical pathology findings

The **leukopenia** associated with CPV enteritis may be very severe. A transient lymphopenia is the most consistent finding. However, leukopenia may not be present, especially during the early stages of the disease or in less affected puppies. These hematological changes can be attributed to the destruction of hematopoietic progenitor cells in the bone marrow and other lymphoproliferative organs, including the thymus, lymph nodes, and spleen.[45,46] Despite the severe changes seen in the blood precursor cell lines, it appears that early pluripotent cells are spared.[45] One study reported that a lack of leukopenia and lymphopenia 24 hours post-admission has a positive predictive value for survival. An increasing lymphocyte count after admission was also seen in puppies that recovered.[46]

Anemia is not an uncommon hematological finding in CPV enteritis. However, it is unlikely to result from the suppression of erythropoiesis as circulating red blood cells have a long half-life relative to the short period the virus affects the bone marrow.[47] Anemia is more likely due to a combination of intestinal hemorrhage and rehydration fluid therapy.[48] A state of increased oxidative stress and altered antioxidant status to counteract cellular damage has been reported in these puppies, contributing to the anemia.[49,50]

Abnormalities of hemostasis were documented in a small study of nine dogs with parvoviral infection. The study showed a high prevalence of clinical thrombosis or phlebitis and laboratory evidence of decreased antithrombin activity, prolonged activated partial thromboplastin time, increased maximum amplitude in the thromboelastogram, and increased fibrinogen concentrations. This cohort thus demonstrated hypercoagulability without overt signs of disseminated intravascular coagulopathy (DIC).[27] Clinically obvious petechiation or hemorrhage from sites other than the gut are not features of CPV infections. Using thromboelastography, a recent study reported that the hypercoagulable state observed in puppies with CPV was exacerbated after fluid resuscitation and persisted for hours after large-volume crystalloid fluid administration. This finding may be due to crystalloid fluid therapy, disease progression, dilution of antithrombin in the blood, or a combination of these factors.[51] Recent work reported on possible damage to the endothelial glycocalyx and showed serum concentrations of endothelial cell-specific molecule-1 (ESM-1) at the time of admission to be higher in dogs with CPV enteritis, specifically dogs that died.[52]

**Electrolyte imbalances**, including severe hypokalemia, hyponatremia, and hypochloremia, are the most notable serum biochemistry abnormalities in CPV enteritis and result from anorexia, vomiting, and diarrhea.[48,53] Decreased total blood calcium concentrations may be a result of hypoalbuminemia.[48] Other serum biochemistry abnormalities include increased urea nitrogen (BUN), creatinine, and inorganic phosphate, all resulting from dehydration (prerenal azotemia). Liver enzyme activities, such as alkaline phosphatase (ALP) and alanine transaminase (ALT) activity, may be increased due to hepatic hypoxia secondary to severe hypovolemia or the absorption of toxic substances from the compromised gut barrier.[48] The response of the adrenal

and thyroid glands to critical illness is essential for survival. High serum cortisol and low serum thyroxine concentrations post-admission were indicators of a poor prognosis.[52]

The acid-base disturbances are complex and heavily influenced by chloride, free water, and albumin. Severely affected animals tend to show hypochloremic alkalosis, whereas mildly affected puppies have hyperchloremic acidosis. The strong ion model proposed by Steward provides better insights into pathological mechanisms than the traditional Henderson-Hasselbalch model.[54]

**Hypoproteinemia** is predominantly a result of intestinal hemorrhage and rehydration fluid therapy. However, studies have also shown an increase in acute-phase proteins secondary to systemic inflammation and tissue damage present with the disease. Acute-phase protein generation occurs at the expense of albumin synthesis in critical illness.[55] C-reactive protein (CRP), a major acute-phase protein in dogs, is increased in dogs with CPV. Also, higher serum CRP concentrations at 12 and 24 hours, compared with admission concentration, are associated with shorter survival times in these puppies than those with lower CRP concentrations. Also, dogs that survive with higher CRP concentrations at 12, 24, and 36 hours after admission have longer hospitalization periods.[56]

Increased canine pancreas-specific lipase (measured as Spec cPL) was observed in 49% of dogs with CPV in one study, but only a small number of cases showed ultrasonographic or histopathologic changes consistent with acute pancreatitis. Spec cPL increases had no impact on disease outcome or length of hospital stay, suggesting that acute pancreatitis (▶ Chap. 10.3.1) in CPV enteritis, if present at all, is mainly subclinical and does not influence the disease outcome.[57]

### Diagnostic imaging

The most common reason for imaging these animals is to rule out intestinal foreign body obstruction (▶ Chap. 7.3.6.1) or intussusception (▶ Chap. 7.3.6.2). Abdominal radiographs usually demonstrate findings typical of paralytic ileus. Poor radiographic detail is not uncommon in young puppies as they usually lack contrast-enhancing abdominal fat. Ultrasonographic changes associated with CPV infection of puppies include fluid-filled, atonic small and large intestines, duodenal and jejunal mucosal layer thinning (sometimes with disrupted wall layering). The mucosal and submucosal surface of the duodenum often appears corrugated. The mucosa of the duodenum and jejunum often shows hyperechoic speckling and thinning. The degree of ultrasonographic changes is proportional to the severity of the disease, but none of the findings are pathognomonic of the disease.[58]

#### 7.3.1.1.5 Pathology

Viral replication depends on the cellular activity only during nucleoprotein synthesis. Thus, the pathology induced by the virus is greatest in tissues with a high mitotic index. These include enteric epithelium, hematopoietic, and lymphoid tissues. Large basophilic nuclear inclusions may be found in infected cells. However, these inclusions are typically not seen in tissues arising from cases presented for postmortem examination because they are most abundant before extensive lysis and exfoliation of infected cells. Macroscopic findings are typical of severe enteritis that mainly affects the small intestine. The jejunum is most consistently affected, with lesions in the duodenum and ileum being more variable. The gut serosa is typically discolored and shows hemorrhage. Gut contents are usually scant and hemorrhagic, and the mucosa may be ulcerated and demonstrate hemorrhage. The stomach can be filled with bloody fluid and/or mucous. Mesenteric lymph nodes are typically edematous. Severe hypoalbuminemia may result in anasarca and free peritoneal fluid. The carcass may demonstrate anemia, with the bone marrow showing signs of necrosis. Histologically, the major findings are small intestinal crypt necrosis and generalized lymphoid atrophy or necrosis (▶ Chap. 1.8.1). Intestinal crypts are usually distended with necrotic material and mucous. Villi are usually shortened and can be fused, and there may be evidence of hemorrhage and fibrinous inflammation. Myocardial fibrosis is sometimes seen.

#### 7.3.1.1.6 Treatment

The level of care strongly affects patient outcomes. A monoclonal antibody to treat parvovirus infection in dogs has recently become available, but clinical experience with it is in its infancy. Inpatient care is expensive, which may be a reason for owners to elect euthanasia.[59,60] Although inpatient care is superior to outpatient care, the outcome of dogs treated with a simple outpatient protocol may not be different from those treated as inpatients.[61] Large numbers of infected dogs have convincingly been shown to be successfully treated in a welfare setting with practical, easily applied treatment options.[59] Outpatient care is based on daily subcutaneous or intraperitoneal (IP) fluid therapy (KCl can be added to the IP fluid as needed), subcutaneous antibiotic (amoxicillin/clavulanate or cefovecin), maropitant injection (occasionally metoclopramide for home administration may be added), fenbendazole orally (for 5 days), an oral rehydration mixture for home administration, and a high energy liquid diet to be dosed by the owner at home (▶ Fig. 7-9a, ▶ Fig. 7-9b). Daily veterinary revisits are scheduled until recovery. In severely

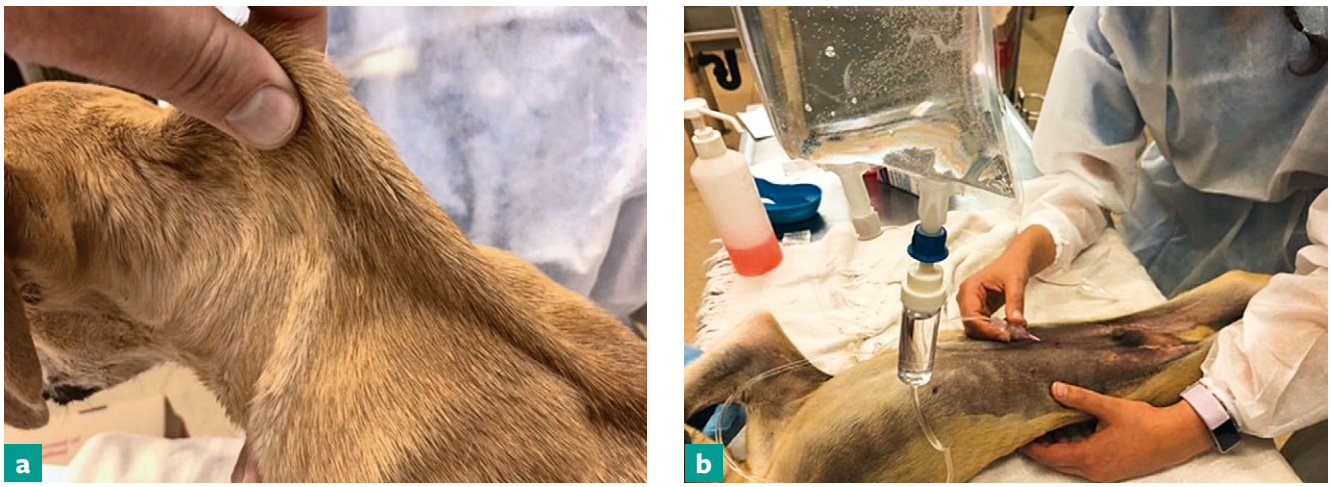



**Fig. 7-9** Treatment of a severely dehydrated puppy

**a** Note the skin tenting of this severely dehydrated puppy.

**b** The dog is treated with intraperitoneal (IP) fluids, parenteral antibiotics, and antiemetics before being discharged to the owners' care. The puppy will need to return daily for IP fluid administration until able to maintain hydration orally.

affected dogs (i.e., in hypovolemic or endotoxic shock) or in cases where owners can afford more advanced treatment, cases are admitted to a facility that can provide isolation and barrier nursing.

Aggressive treatment with crystalloid fluids, synthetic and natural colloids, correction of hypoglycemia and any electrolyte disturbances, and treatment with a combination of antimicrobials, antiemetics, analgesics, enteral nutritional support, and anthelminthics usually form the basis of the **treatment plan**. Although a coagulopathy in CPV has been described both before and after crystalloid fluid administration, it was clinically insignificant.[62] There is a concern that hetastarch may cause a bleeding tendency in dogs through dilution of clotting factors, but these changes are not clinically significant.[63] Considering these two findings and the fact that the authors have used hetastarch in critically ill, hypovolemic, hypotensive, and hypoalbuminemic puppies routinely with clinical benefit, it is felt that synthetic colloid support can be clinically useful.[62,63] **Fluid therapy** to treat dehydration, re-establish effective circulating blood volume, and correct electrolyte and acid-base disturbances is the mainstay of managing more severely affected puppies.[64] Fluid therapy in these patients can be complex, and careful attention should be paid to physical examination findings in addition to electrolyte and acid-base status.[65] The preferred administration route is intravenous (IV), but intraosseous administration, although rarely used, may be used in patients that need immediate fluid support when IV access is impossible. All IV catheters should be replaced q72h. The initial fluid of choice is a balanced electrolyte solution isotonic to blood (i.e., lactated Ringer's solution). The initial rate of fluid administration will depend on the condition of the patient. IV fluid boluses (10 ml/kg, repeated if necessary) may be necessary for patients in hypovolemic shock. Fluid deficits should be replaced as soon as possible (within 1–6 hours of presentation, provided the patient has no cardiovascular risk).[64] Once perfusion is restored, the IV fluid rate is reduced to a maintenance rate plus estimated ongoing losses. Hypokalemia is common, and KCl should be added to the IV fluid until potassium concentrations have normalized. Continuous rate infusion of metoclopramide in an IV line separate from the IV fluid line is recommended. Hypoglycemia is also common (especially in smaller dogs), and in severe cases, a 25% dextrose bolus should be given to correct this. Following a dextrose bolus, the IV fluid can be supplemented with glucose (to a 2.5–5% solution) to maintain normoglycemia until appetite returns.

Hypoalbuminemia is common as a result of protein-losing enteropathy (▶Chap. 7.3.8.2.2). Colloid oncotic pressure may require support with a synthetic **colloid** (e.g., hetastarch) if albumin is reduced below 2g/dL (20g/L) or with an obvious third-space fluid loss. The role of **blood products** in the treatment of CPV is controversial. Patients suffering from anemia secondary to hemorrhagic diarrhea or concurrent endoparasitism should be transfused with packed red blood cells or whole blood. Fresh frozen plasma (FFP) transfusion is recommended in treating CPV enteritis for its ability to provide oncotic components (albumin), immunoglobulins, and serum protease inhibitors, which may help to neutralize circulating virus and control the systemic

inflammatory response (SIRS) associated with this disease.[66] FFP infusion is a poor means of supporting colloid oncotic pressure because very large volumes need to be infused to improve this measure.[67] A recent study evaluated the effects of IV hyperimmune plasma and found that markers of shock were improved. However, it was insufficiently powered to evaluate the effect on hospital stay or patient mortality.[68]

Evidence supports the use of **early enteral nutrition**. A recent study showed that puppies receiving early enteral nutrition via a nasoesophageal feeding tube had earlier clinical improvement, significant weight gain, and improved gut barrier function (limiting bacterial or endotoxin translocation) than puppies that received nil per os (NPO) until vomiting ceased. In some cases of severe paralytic ileus, obvious gastric distension can be relieved through suctioning gas and excess stomach contents if the tube is advanced into the stomach. The authors have seen a benefit in this, although caution is advised as excessive suctioning can exacerbate fluid, electrolyte, and caloric deficiencies. Once vomiting has ceased, an oral deworming program should be initiated.

**Antiemetics** are indicated in the management of CPV enteritis. The most commonly used antiemetic drugs for this disease are metoclopramide, prochlorperazine, ondansetron, cisapride, and maropitant. In cases of intractable vomiting, combination therapy and continuous IV infusions of these drugs may be more effective than monotherapies and/or medication boluses. A retrospective study showed that antiemetics did not completely control vomiting in many cases, and puppies that received antiemetics generally required longer hospitalization. In some cases, although vomiting stops, antiemetics may need to be continued to control nausea and encourage the return of an appetite. Although this study demonstrated an association between antiemetic use and prolonged hospitalization, a cause-and-effect conclusion cannot be drawn.[69] Antacids (proton pump inhibitors such as omeprazole, 1 mg/kg PO q12h) are also indicated in cases where hematemesis is present. These drugs may prevent or help reflux esophagitis. Gastroprotectants (such as sucralfate) may also be helpful.

Treatment with IV, broad-spectrum, bactericidal **antibiotics** is warranted in puppies with CPV enteritis due to the disruption of the intestinal barrier and severe leukopenia. A β-lactam antibiotic (ampicillin, 20 mg/kg IV q8h) or β-lactamase resistant penicillin (amoxicillin-clavulanate, 20 mg/kg IV q8h[70]) with or without an aminoglycoside (amikacin, 20 mg/kg IV, IM or SC q24h once the dog has been rehydrated; used for a maximum of 5 days) will provide effective coverage. Metronidazole (15–20 mg/kg PO q12h for up to 10 days) or (preferably) fenbendazole (50 mg/kg PO q24h for 5 days) is indicated in cases where motile protozoa are found on fecal wet mount preparation. Despite the lack of canine interferon products, several studies have shown recombinant interferons to ameliorate severe enteritis caused by CPV and significantly reduce mortality.[71–73] A recent study concluded that recombinant canine granulocyte-colony stimulating factor (G-CSF) increased white cell counts, but its effect on outcome remains unclear.[74] Analgesia is an important component of case management in almost all cases because the enteric pain can be severe. The most commonly used drugs include buprenorphine, fentanyl, and – in some cases – a lidocaine-ketamine combination CRI. Several other adjunctive agents have been investigated, including recombinant human G-CSF (rhG-CSF) and recombinant bactericidal/permeability-increasing protein (rBPI21), but neither of these has demonstrated any benefit.[75,76] Oseltamivir, an antiviral drug that inhibits neuraminidase (NA), was recently investigated and found to be of minimal benefit.[77] Enteric dysbiosis is a feature of CPV,[78] and a recent study evaluating fecal microbiota transplantation (FMT; ▶ Chap. 7.3.4.5) showed that it resulted in a faster resolution of diarrhea.[79]

**Daily monitoring** of the patient to allow treatment adjustments and assessment of progression is crucial. Clinical data (including a physical examination) to specifically assess hydration, frequency of vomiting and defecation, abdominal palpation (to palpate for intussusception), and assessment of pain levels are standard care. The following laboratory data should be monitored at least daily (and in some cases even more frequently): hematocrit, total serum solids (or total serum protein and albumin), serum electrolytes ($Na^+$, $K^+$, $Cl^-$), and blood glucose concentration.

#### 7.3.1.1.7 Prognosis

The outcome of parvoviral infection varies greatly, with a survival rate of around 10% in untreated puppies to more than 90% with intensive treatment. This is often a function of what owners can afford.[60,80,81] Despite this, outpatient-based treatments and welfare/shelter-based treatment protocols have shown encouraging survival data at significantly reduced costs.[59,61] The earlier in the disease course the animal presents for veterinary care, and the sooner aggressive treatment is initiated, the better the outcome. Various hematological variables have been associated with prognosis, including leukopenia, lymphopenia, monocytopenia, and neutropenia.[19,46] The presence of SIRS (systemic inflammatory response syndrome) at the time of admission was also a negative indicator.[19] Other factors that were correlated with worse outcomes include season of presentation,[81] purebred nature,[17,80,82] low body weight,[83] vomiting, hypercoagulability,[27] hypercortisolemia,[52,84] hypothyroxinemia,[52,84,85] hypoalbuminemia,

increased serum CRP,[56] increased tumor necrosis factor concentrations, hypocholesterolemia,[86] and hypocitrullinemia.[83] Recently, a more flexible method of modeling yielded very sensitive and specific predictions of disease outcomes and identified a combination of antithrombin concentrations, serum aspartate aminotransferase and lipase activities, and monocyte and lymphocyte counts as the combination of clinical parameters with the highest predictive value.[87] It was also shown that dogs that survive parvoviral infection have a significantly increased risk of developing chronic gastroenteric disease.[88]

#### 7.3.1.1.8 Prevention

The cornerstone of CPV and FPV protection is **vaccination**. Live attenuated and inactivated vaccines are widely available and part of the core vaccination program for dogs and cats. Immunity is antibody-dependent and sterile, and immunity following the clinical disease is probably life-long. It is unsafe to vaccinate pregnant animals with the live vaccine because the fetuses may be negatively affected. Inactivated vaccines are not as fast at providing protection, translating to a much longer period of susceptibility early in life. By far, the most common cause of vaccine failure remains vaccine neutralization by maternally-derived antibodies. Traditional vaccination programs start at 4–6 weeks, are boosted a month later, and again a month after this (with the last and most effective vaccination occurring at 14–16 weeks of age).[89] Where problems exist in breeding establishments, very early vaccination programs may reduce the window of vulnerability. It has been shown that a high-titer modified live virus (MLV) vaccine can protect puppies vaccinated as early as 4 weeks old.[90] The frequency of boosting throughout life is contentious, but it is generally accepted that a booster should be given at a year of age and then every 3 years thereafter.[91,92] Some concern has been raised about the ability of available CPV-2 strain vaccines to protect against CPV-2c.[93] However, challenge studies using dogs vaccinated with CPV-2 have demonstrated good protection against CPV-2c.[94,95]

The highly contagious and resistant nature of the virus makes barrier nursing of infected animals and very stringent disinfection protocols (e.g., 0.75% hypochlorite) crucial to preventing contagion.[96] Because natural environments cannot be disinfected, only vaccinated animals should be allowed onto potentially contaminated surfaces.

### KEY FACTS

- Parvovirus is the most common viral cause of diarrhea in dogs, with high morbidity and mortality rates among dogs and cats.
- Distemper virus, canine coronavirus, feline immunodeficiency virus (FIV), feline leukemia virus (FeLV), and feline coronavirus (FeCoV) infections are also associated with gastrointestinal signs.
- Canine parvovirus (CPV) shows a tropism for the thymus, bone marrow, spleen, and crypt cells of the gut epithelium and can cause loss of the normal gut barrier function.
- Diagnosis is based on combining a cluster of findings of the typical signalment (young and un- or inadequately vaccinated), classic chief complaints of depression, anorexia, vomiting, and diarrhea, and the typical clinical findings of pyrexia, dehydration, fluid-filled and gassy abdominal palpation, and leukopenia on a peripheral blood smear. The next diagnostic step typically involves using a fecal parvovirus antigen ELISA to confirm the clinical suspicion.
- Aggressive treatment with crystalloid fluids, synthetic and natural colloids, correction of hypoglycemia and any electrolyte disturbances, a combination of antimicrobials, antiemetics, analgesics, enteral nutritional support, and anthelminthics usually form the basis of the treatment plan with a survival rate of about 10% in untreated puppies to more than 90% with intensive treatment.
- The cornerstone of parvovirus protection is vaccination and strict hygiene, including disinfection.

### References

The complete list of references for this chapter can be downloaded from vetline.de:
svg.to/9842-07-03-01-01

### 7.3.1.2 Bacterial infections

Els Acke

The gastrointestinal tract contains a resident microbiota essential in maintaining normal digestive and immune function. A range of enteropathogens can colonize the small (SI) and large intestine (LI) in dogs and cats without causing clinical signs. However, these organisms may become significant pathogens depending on several internal and external factors influencing regulatory mechanisms and the individual microbiota composition. Subclinical infection, carrier state, and the organisms acting as primary or secondary pathogens with the development of mild to severe acute or chronic clinical signs and extra-intestinal disease are possible outcomes of infection. *Clostridia*, *Salmonella*, *Campylobacter*, *Escherichia coli*, and *Yersinia* species (spp.) have been described with similar prevalences in diarrheic compared with non-diarrheic animals, complicating the interpretation of diagnostic test results.[1,2] Infection occurs via a contaminated environment by the fecal-oral route, water, and fomites. Also, raw meat-based diets (RMBD) have gained popularity, adding a source of infection with increased fecal shedding, enteritis, and even fatal septicemia documented.

Clinical bacterial enteritis is relatively rare in dogs and cats, and clinical signs and minimum database findings are non-pathognomonic. Complete blood count and clinical chemistry results may reveal either no changes or non-specific abnormalities seen with severe acute gastroenteritis (e.g., neutrophilia, electrolyte disturbances, and evidence of intestinal blood or protein loss as described in ▶Chap. 7.3.1.1.4). Severe cases may progress to extra-intestinal disease and sepsis (e.g., neutropenia, hypoglycemia, and coagulopathy) if disseminated intravascular coagulopathy (DIC) develops. A complete diagnostic evaluation, including diagnostic imaging, is essential to exclude more common differentials. The significance of demonstrated organisms, toxins, and toxin genes should be carefully questioned when fecal diagnostic panels are performed. Antimicrobial therapy should not be considered before a final diagnosis is confirmed, with further diagnostic workup as indicated on an individual case basis. This includes testing for other infectious causes of enteritis (co-infections are common) and other underlying or concurrent disorders. Bacterial culture of fecal samples is especially advised in dogs and cats with signs of acute diarrhea, where the response to supportive therapy is poor, and there is a history of multiple animals affected or possible zoonosis, RMBD feeding, or signs of SIRS or sepsis develop.

**CLINICAL PEARLS**

Clinical signs are usually self-limiting with supportive therapy and dietary modification in cases with mild to moderate enteritis. Antimicrobial therapy should be based on susceptibility testing where possible and be reserved for severely affected animals (e.g., fever, left shift), immunocompromised patients, or those with extra-intestinal infections or granulomatous colitis (▶Chap. 8.3.1.2).

Cross-species transmission of commensal and pathogenic bacteria between pets and their owners is a growing concern. Especially in clinical cases posing a risk to their environment (infants, young children, pregnant women, elderly, immunocompromised people in the household), adequate hygiene measures are essential.[1,2]

#### 7.3.1.2.1 *Clostridioides* (*Clostridium*) *difficile*

*Clostridioides* (reclassified former *Clostridium*) *difficile* (*C. difficile*) is an anaerobic Gram-positive spore-forming bacillus colonizing the intestinal tract of humans and animals. The organism is ubiquitous in the environment, with spores highly resistant to different conditions and most disinfectants.

##### Epidemiology and clinical presentation

*C. difficile* is of major importance in humans as a cause of nosocomial and antimicrobial-associated enteritis, pseudomembranous colitis, toxic megacolon, and colonic perforation. *C. difficile v*irulence is mainly related to the production of exotoxins A and B, encoded by genes *tcd*A and *tcd*B. Some strains also express the binary toxin CDT. *C. difficile* also plays a role in enteritis in food animals, horses, and pets. Dogs can be subclinical carriers, have self-limiting SI, LI, diffuse enteritis, or severe hemorrhagic diarrhea.[1,3] An association between toxigenic *C. difficile* infection (CDI) and clinical signs was confirmed in several reports, including a hospital-acquired outbreak in dogs and cats. Nevertheless, the organism is more likely a secondary pathogen and can be an opportunist, or detection may be an incidental finding. *C. difficile* was isolated from up to 58% and 21% of healthy dogs and cats, respectively, with higher rates in young animals and veterinary hospitals. Identified risk factors for *C. difficile* colonization in dogs include antimicrobial administration, visiting human hospitals, contact with children, living with an immunocompromised owner, and antimicrobial admin-

istration to the owner.[1] Feline intestinal pneumatosis linked to CDI with multifocal necrotizing hemorrhagic enterotyphlocolitis is also reported.[4]

### Diagnosis and treatment

Diagnosis via identification of *Clostridia* (anaerobic fecal culture, antigen ELISA, or for best specificity and sensitivity, real-time PCR) combined with fecal toxin A and B detection by PCR is recommended.[1] Treatment should be supportive. In cases receiving prior antimicrobial therapy, this should be discontinued if possible, as microbiome alterations (▶ Chap. 7.3.4) may have resulted in clinical signs. Metronidazole (10–15 mg/kg PO q12h) is generally the antimicrobial of choice for dogs and cats with CDI if indicated,[1] but antimicrobial resistance to this drug has been documented in up to 21% of *C. difficile* isolates from dogs. Fecal microbiota transplantation (FMT) is an effective treatment of human CDI and has also been described in small animal medicine, especially as a treatment option for dogs with acute or chronic enteritis associated with abnormal dysbiosis index.

### Zoonotic potential

The zoonotic potential of *C. difficile* is suggested to be minor. However, subclinical carriage is common and identical ribotypes and toxigenic strains that cause human CDI are detected in pets. Thus, pets should be considered a potential source of community-acquired human CDI.

#### 7.3.1.2.2 *Clostridium perfringens*

*Clostridium perfringens* is an anaerobic Gram-positive spore-forming bacillus present ubiquitously in the soil and the intestinal tract of vertebrates. There are seven toxinotypes (A–G) based on the possession of major toxin genes (*α, β, ε, ι, cpe*, and *netB*), expressing several toxins linked with pathogenicity (e.g., *C. perfringens* enterotoxin; CPE).[1,5]

### Epidemiology and clinical presentation

All *C. perfringens* strains possess the α toxin gene (*cpα*) linked to food poisoning and diarrhea in humans and acute or chronic SI and LI disease in dogs. Clinical signs in dogs vary from mild, self-limiting to potentially fatal hemorrhagic diarrhea. *C. perfringens* is detected in fecal samples by culture in up to 84% of healthy dogs and 91% of diarrheic dogs and is considered a commensal organism.[5,6] The zoonotic potential of *C. perfringens* requires further research. The association of toxin production and the presence of toxin-encoding genes with clinical signs of enteritis in dogs has been further investigated. Such an association was detected for the *cpe* gene; CPE confirmed by ELISA and quantitative real-time PCR for the *cpα* gene appears to be a useful marker for *C. perfringens*-associated diarrhea.[7,8] Studies in cats are lacking, but the prevalence is lower than in dogs, and the association of clinical signs with toxin production remains unclear. Shelter cats commonly had *cpα* gene detected by real-time fecal PCR (50% and 42% in diarrheic and healthy cats, respectively). Also, 49% of cats with gastrointestinal signs in multi-cat households tested positive.[9] One case of feline intestinal pneumatosis likely linked to *C. perfringens* and *E. coli* infections has been reported.[10] Proliferation and sporulation of *C. perfringens* with increased toxin production following changes in the intestinal environment can induce clinical signs, but further investigations on the role of *Clostridia* and their toxin production in intestinal dysbiosis are needed. The term "acute hemorrhagic diarrhea syndrome" (AHDS), previously known as "hemorrhagic gastroenteritis" (HGE), was proposed in 2014 for dogs with acute onset bloody diarrhea and vomiting where other differentials were ruled out (▶ Chap. 7.3.3). *C. perfringens* was identified in SI biopsies, and investigations of *C. perfringens* toxin production revealed novel pore-forming toxin *netE* and *netF* genes via fecal real-time PCR in a significant number of AHDS cases.[11]

### Diagnosis and treatment

There is currently no gold standard in the diagnosis of *Clostridia*-related diarrhea in dogs and cats, and confirmation of *C. perfringens* combined with toxin gene and/or toxin detection is recommended.[1] Fecal enterotoxin immunoassays are commercially available but lack specificity and sensitivity and should be combined with molecular methods to detect a range of toxin genes. Because these genes can be present in feces from healthy dogs and dogs with diarrhea from other causes, ruling out other disorders and quantification via real-time PCR is necessary.

Treatment of *C. perfringens*-associated enteritis is generally supportive, and probiotic administration may result in a faster recovery of the normal intestinal microbiome. Antimicrobial therapy is reserved for severe cases (e.g., in AHDS with signs of sepsis). *C. perfringens* strains are generally susceptible to metronidazole, tylosin, erythromycin, and ampicillin. These are the antimicrobials of choice, but resistance has also been described.

#### 7.3.1.2.3 *Campylobacter* spp.

*Campylobacter* spp. are Gram-negative rods belonging to the order Campylobacterales that can occur singularly, in pairs or chains as long spirals. In many host animals, they are considered commensal organisms colonizing the intestinal tract. Campylobacteriosis is the leading cause of bacterial enteritis in humans in the developed world, with especially *C. jejuni* and *C. coli* established as pathogens. In dogs, the *Campylobacter* species most frequently isolated from fecal samples in order of importance are *C. upsaliensis*, *C. jejuni,* and *C. helveticus;* and in cats, *C. helveticus*, *C. upsalienis,* and *C. jejuni*. Reported prevalences of *Campylobacter* spp., confirmed by bacterial culture, range from 0–87% for dogs and 0–75% for cats depending on the animal's age and species, housing, concomitant disease, season, geographic region, and the study design. Immature dogs and cats and intensively housed animals have a higher prevalence.[2]

*Campylobacter* spp. have been detected in up to 28% of commercial RMBD for pets.[12]

Several virulence factors were identified, and pathogenicity involves motility, adhesion, invasion, and toxin production. In addition, they possess multidrug resistance and stress response genes. Although several studies failed to detect a significantly increased prevalence of *Campylobacter* spp. in animals with signs of diarrhea, other studies have confirmed an association with clinical signs, and clinical cases of enterocolitis are described with disease outbreaks due to *Campylobacter* spp. infection in colony dogs.[2] Also, a more extensive species range and higher concentration of *Campylobacter* spp. (by quantitative PCR) were detected in dogs with diarrhea compared with those without clinical signs.[13] Many animals shed *Campylobacter* spp. intermittently or transiently, as illustrated in longitudinal studies, and the collection of multiple samples increases the recovery rate.

##### Clinical presentation

In most dogs and cats, *Campylobacter* infection is subclinical. However, young animals and those with predisposing factors (e.g., co-infections, concurrent disease) are more prone to developing clinical signs. Mild to watery diarrhea (sometimes with blood, mucus, and tenesmus), lethargy, dehydration, anorexia, and (less frequently) fever, vomiting, and abdominal pain are reported in dogs and cats. Extra-intestinal *C. jejuni* infections are also described, for example, in dogs with cholangiohepatitis or cholecystitis.[1,2] *Campylobacter* spp. may be involved in chronic enteric disease with significantly higher numbers of *C. coli* demonstrated in endoscopic biopsies from cats with neutrophilic than those with lymphoplasmacytic enteritis (chronic inflammatory enteropathy, CIE; ▶Chap. 11.2) applying fluorescence in situ hybridizations (FISH).[14]

##### Diagnosis and treatment

Isolation rates for specific *Campylobacter* spp. are highly dependent on the techniques used, and there is no common method allowing the isolation of all *Campylobacter* spp. Most *Campylobacter* species grow under microaerobic conditions at 37°C on specialized agar, but many "emerging species" gaining clinical importance and detected in companion animals (e.g., *C. concisus*, *C. rectus*) require other conditions, such as a hydrogen-enriched or anaerobic environment. As for Clostridial disease, internationally accepted breakpoints for susceptibility testing of veterinary *Campylobacter* spp. are lacking. Direct PCR may improve diagnostic sensitivity depending on the range of species tested. Traditionally, fluoroquinolones were used as an empirical treatment in humans. However, with increasing antimicrobial resistance rates, especially with indiscriminate antimicrobial use in the food animal industry, macrolides have become the preferred therapeutic option. Treatment in pets, where indicated, is recommended with erythromycin 10–15 mg/kg PO q8h, enrofloxacin 5 mg/kg PO, SC, or IV, or with azithromycin 5–10 mg/kg PO q24h.[1,2]

##### Zoonotic potential

*Campylobacter* spp. are zoonotic, with poultry as the most important reservoir for infection in humans, and consumption of contaminated food is a common infection route. Contact with farm or pet animals can be a source of infection, and especially contact with young and diarrheic pets is a significant risk factor for *C. jejuni* and *C. coli* infection in humans, with children and infants most prone to developing clinical signs.

#### 7.3.1.2.4 *Salmonella* spp.

The genus *Salmonella* belongs to the order Enterobacterales and contains two species: *Salmonella enterica* with six subspecies and *Salmonella bongori*. *S. enterica subsp. enterica* is responsible for the majority of infections in mammals. *S. enterica* organisms are ubiquitous facultative anaerobic Gram-negative rods with an extensive range of different serotypes, further divided into bioserotypes based on three major antigenic determinants (O, K, and H).

### Epidemiology and clinical presentation

*Salmonella* organisms have been associated with intestinal or systemic disease in several animal species but can also cause subclinical infections and be present in healthy carrier animals. Juvenile dogs and cats, animals housed in shelters, stray dogs, working dogs, and dogs fed RMBD have an increased prevalence, and co-infections (e.g., with canine parvovirus) are also reported. *Salmonella* prevalence in healthy pets is generally low, ranging from 0–3.6% in dogs,[1,15] 0–4% in cats,[16] and 0–3.8% and 0–8.6% in diarrheic dogs and cats, respectively.[1,15] Dry diets, pet treats, and especially RMBD have shown to be a possible source of *Salmonella* spp. with isolation rates of up to 80% in homemade bones and raw food (BARF) diets,[17] and 21% in commercially available RMBD.[18] In RMBD fed Greyhounds at an open breeding facility with an outbreak of salmonellosis, 93% of fecal samples and 66% of environmental samples tested positive for *S. enterica*.

Clinical signs included fever, vomiting, lethargy, inappetence, diarrhea, dysentery, and arthritis, and several puppies died.[19] Clinical salmonellosis was also described in three closed colony cats where signs included lethargy, anorexia, vomiting, and hemorrhagic diarrhea.[20] The pathogenicity of different *Salmonella* serotypes varies, and signs of gastroenteritis are caused by mucosal invasion resulting in an inflammatory response. The organisms can persist in enterocytes and lymph nodes, with reactivation and shedding. Most cases with *Salmonella* spp. infection will be either subclinical or develop acute self-limiting signs, including malaise, anorexia, fever, vomiting, abdominal pain, and watery to mucoid diarrhea, sometimes with blood. Chronic enteritis has also been described, and recovered animals can shed *Salmonella* spp. for weeks.[20,21] Depending on the strain and host-related factors, enteritis or systemic infections may result. Clinically significant endotoxemia or bacteremia with extra-intestinal infection can develop regardless of enteritis, especially in juvenile or immunocompromised animals (e.g., to the biliary tract, spleen, kidneys, heart, uterus, joints, and lungs).[21,22]

### Diagnosis and treatment

The diagnosis of salmonellosis is based on confirmation by culture or PCR in conjunction with clinical signs and exclusion of other disorders. Bacterial isolation is recommended on fresh fecal samples or swabs or other appropriate material with extra-intestinal infections and requires selective enrichment followed by culture onto specialized agar. Treatment of mild to moderate cases of acute enteritis, without systemic signs, is supportive. Antimicrobial therapy is controversial and, if needed, must be based on antimicrobial susceptibility testing. Antimicrobials with good cell penetration are preferred (e.g., trimethoprim-sulfonamides, enrofloxacin).[1] *Salmonella* organisms can acquire transferable, plasmid-mediated resistance, reported especially to ampicillin, chloramphenicol, tetracycline, streptomycin, and sulfonamides, with multidrug resistance in a considerable number of isolates.[20,21] Due to prolonged intermittent shedding after clinical recovery, follow-up by collecting multiple samples is advised with PCR considered most sensitive.

### Zoonotic potential

Salmonellosis is one of the most frequently reported foodborne diseases in humans worldwide, with many food animals being subclinical carriers of *Salmonella* organisms. Contact with pets, pet foods, and treats was confirmed as a cause of human salmonellosis.

#### 7.3.1.2.5 *Escherichia coli*

*E. coli* organisms are facultative anaerobic Gram-negative, pleomorphic rods and natural inhabitants of the intestinal tract of mammals. They belong to the order Enterobacterales, with a serologic classification scheme based on their surface antigens O, H, and K. Some serotypes are linked to an increased virulence (e.g., O157:H7 causing hemolytic uremic syndrome in humans). Most *E. coli* strains are part of the intestinal microbiome of clinically healthy animals and can act as opportunistic pathogens causing intestinal and extra-intestinal disease when virulence factors are present and local or systemic immunity is impaired. Pathogenic *E. coli* are categorized into pathotypes depending on specific virulence factors and virulence mechanisms.[1,3] Several pathotypes are described in healthy dogs and cats and animals with acute or chronic intestinal disease: enteropathogenic *E. coli* (EPEC), enterotoxigenic *E. coli* (ETEC), Shiga-toxin-producing *E. coli* (STEC, includes verocytotoxin-producing *E. coli* [VTEC]), necrotoxigenic *E. coli* (NTEC), enteroinvasive *E. coli* (EIEC), enteroaggregative *E. coli* (EAEC), and adherent-invasive *E. coli* (AIEC).[1,23] Granulomatous colitis, also known as histiocytic ulcerative colitis and associated with AIEC, was initially described in boxer dogs,[24] later also in other breeds, and recently in a cat (▶Chap. 8.3.1.2).

Reported prevalences of *E. coli* in healthy and diarrheic dogs and cats vary widely. Shelter kittens with diarrhea can have larger EPEC burdens, and positive kittens have more severe disease and increased mortality.[25] In dogs, EPEC and VTEC are detected significantly more commonly in cases with acute (35% EPEC, 25% VTEC) or chronic diarrhea (32%

EPEC, 28% VTEC), regardless of age and compared with healthy kenneled and pet dogs. With chronic diarrhea, *E. coli* was suspected as a secondary pathogen, a co-infection, or an incidental finding.[23] Investigation of commercially available frozen RMBD showed 23% of diets to contain EHEC O157:H7 and 80% extended-spectrum β-lactamases producing (ESBL) *E. coli*.[26]

### Diagnosis and treatment

Diagnosis of *E. coli* enteritis requires bacterial culture using fecal samples or rectal swabs and selective media (e.g., MacConkey agar). Pathogenic *E. coli* strains can only be confirmed via specific bioassays and on a molecular level (available through specialized laboratories).[3] As with other enteropathogens, antibiotic treatment is usually not required. Treatment is supportive, as clinical infections should be self-limiting. Where indicated, antimicrobial susceptibility testing should be performed, and resistance to chloramphenicol, tetracyclines, ampicillin, and sulfonamides is common.[3] In AIEC granulomatous colitis patients, long-term remission can be accomplished in most cases with 6–8 weeks treatment of enrofloxacin (▶Chap. 8.3.1.2.4).[27]

### Zoonotic potential

Within-household sharing of *E. coli* strains has been confirmed via DNA fingerprinting analysis of *E. coli* isolates from dogs and humans.[28] EHEC reported in a child with hemorrhagic diarrhea and vomiting, being identical to EHEC from fecal samples of the domestic cat without clinical signs, highlights the possible zoonotic role and the importance of hygiene measures in households.[29]

## 7.3.1.2.6 Other enteropathogens

### *Yersinia enterocolitica*

*Yersinia enterocolitica* is a motile Gram-negative facultative anaerobe that usually causes subclinical infections in dogs and cats. However, enteritis and extra-intestinal infections (myocardium, liver) have also been described. Ingestion of contaminated pork products was suggested as a source of infection via RMBD. Clinical signs are self-limiting in most cases, and fecal culture with antimicrobial sensitivity testing is advised where needed. The organism is an important human foodborne pathogen, with contaminated pork as the primary source. Contact with pets may be a risk factor for human infection, and dogs and cats shed bioserotypes considered pathogenic to humans.[30]

### *Clostridium piliforme*

Tyzzer's disease, caused by *C. piliforme*, is rare in dogs and cats. It typically causes hepatitis, enterocolitis, and myocarditis following ingestion of sporulated forms from wild rodent or rabbit feces. Affected patients are young or immunosuppressed with an acute and often fatal clinical course. Diagnosis requires special staining and PCR on histopathology and/or fecal samples.[31]

### *Anaerobiospirillum* spp.

*Anaerobiospirillum* spp., anaerobic Gram-negative spiral-shaped rods, have been described in cats with acute gastrointestinal signs, severe ileocolitis, and systemic progression. The organisms can be isolated from the feces of healthy dogs and cats, but due to unique culture requirements, the prevalence may be underestimated. In humans, *Anaerobiospirillum* spp. infection can cause diarrhea and septicemia.[3]

**KEY FACTS**

- Diagnosis of bacterial enteritis should not rely on fecal testing alone. Exclusion of other infectious and non-infectious causes of gastrointestinal disease using a systematic workup is advised.
- Bacterial enteritis requiring antimicrobial therapy is uncommon in dogs and cats. Indications for antibiotic therapy include severe clinical disease, immunocompromise, extra-intestinal infections, and *Escherichia coli*-associated granulomatous colitis. Duration of treatment depends on clinical response, and subclinically infected animals should not receive antimicrobials.
- Patients with bacterial enteritis should be closely monitored for signs of systemic inflammatory response syndrome or sepsis, with appropriate therapy changes if required.
- Most bacterial enteropathogens have confirmed zoonotic potential. Veterinarians must discuss hygiene measures and increased infectious risk associated with handling immature animals, shelter and diarrheic animals, or those with raw meat-based diet feeding.

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
svg.to/9842-07-03-01-02

### 7.3.1.3 Parasitic diseases

Aurelién Grellet

#### 7.3.1.3.1 Introduction

Dogs and cats are frequently infected with helminth and/or protozoan endoparasites.



The most common parasites found in dogs are *Toxocara canis*, *Giardia* sp., *Cystoisospora ohioensis* complex, and *Cystoisospora canis*.



In cats, the main endoparasites are *Giardia* sp., *Tritrichomonas blagburni* (formerly named *T. foetus*), *Toxocara cati*, *Cystoisospora felis*, and *Cystoisospora rivolta*.

Other less commonly observed parasites include hookworms, tapeworms, and strongyloides.

#### 7.3.1.3.2 Prevalence

Prevalences of these parasites vary among studies and are influenced by geography, the detection methods, whether the animal is symptomatic or not, deworming protocols, the age of the animals, and housing conditions. Dogs living in breeding kennels are more frequently infected with intestinal parasites (*Toxocara canis*, *Giardia* spp., *Cystoisospora* spp.) than household dogs.[1] For example, the prevalence of *Giardia* spp. in canine breeding kennels or shelters is twice as high as in pet dogs.[1] The prevalence of intestinal parasites further increases with the increasing size of the kennel. The prevalence of *Giardia*, for example, is 3.5 times higher in kennels producing more than 30 puppies per year than in kennels producing less than 30 puppies per year (63% vs. 18%).[2] This higher prevalence can be explained by several factors either having an effect alone or in combination: the life cycle of parasites, contagiousness, and stability in the environment; the presence of particularly sensitive (immunologically immature or immunocompromised) animals, the density of animals, and hygiene protocols.

The life cycle of some parasites is strictly related to the reproduction cycle of dogs. For example, dog fetuses can be infected in utero by *T. canis* somatic larvae from day 42 of gestation, which is the most important mode of transmission in dogs. Factors inducing the reactivation of somatic larvae and intra-uterine infection are still unknown, but changes in the hormonal status of pregnant bitches are suspected of playing a role. Activated somatic *Toxocara* larvae can also be transmitted to neonates via colostrum and milk. In addition, some parasites are particularly resistant in the environment. *Giardia* spp. can survive several months outside the host in wet and cold conditions, whereas this parasite is susceptible to desiccation under dry, hot conditions. Environmental resistance can be higher in other intestinal parasites, such as *T. canis*, where eggs survive under optimal conditions for at least one year. The dog's age also influences the risk of infection, which is higher in very young puppies. A retrospective study including 3,590 fecal samples demonstrated most *Cystoisospora* infections (78%) to be found within the first 4 months of life, whereas dogs older than one year rarely (1%) shed oocysts.[3] Variable prevalence rates are also described for *Cryptosporidium* spp., ranging from 0–39% (median 5%) in different feline populations and between 0–45% (median 7%) in different dog populations.

#### 7.3.1.3.3 Clinical presentation

Several different gastrointestinal parasites, including *Giardia* spp., *T. canis*, *Cryptosporidium* spp., and *Cystoisospora* spp., can induce clinical signs of gastrointestinal disease in dogs and cats (i.e., diarrhea, vomiting). However, their pathogenicity depends on the age and immunity of puppies/kittens and co-infection by other enteropathogens. For example, coccidiosis can cause varying degrees of enteric disorders; *Cystoisospora ohioensis* may produce digestive disturbances in very young animals (<7 days of age) but does not affect puppies at weaning, while *C. canis* mainly induces clinical signs in puppies at weaning and, more particularly, after stress.[4]

#### 7.3.1.3.4 Diagnosis

A study evaluating 316 puppies revealed that 40% of these dogs excrete at least two different gastrointestinal parasites,[2] emphasizing the need to evaluate dogs for possible excretion of the main parasites and not focus on a single pathogen. In the same study, a strong association of canine parvovirus (▶Chap. 7.3.1.1) presence on weaning diarrhea was observed. Thus, a transdisciplinary approach linking parasitology and virology is mandatory for the optimal management of patients with diarrhea.

The color of the animal's stool may help identify the pathogen(s) causing diarrhea. For example, giardiasis will cause partial atrophy of the intestinal villi and reduce brush border disaccharidase activity, leading to reduced nutrient absorption and steatorrhea. The feces may appear yellow



**Fig. 7-10** Soft yellow feces from a puppy with giardiasis



**Fig. 7-11** Soft feces, containing mucous and blood, from a puppy with coccidiosis

(▶Fig. 7-10), and coprophagia may be observed as the increased lipid content makes the feces more palatable. An unformed stool containing mucous and blood may indicate coccidiosis (▶Fig. 7-11), or parasites can also be visible within diarrheic feces (▶Fig. 7-12). However, these findings do not permit a definitive diagnosis, and additional tests are usually necessary. Several options, including microscopic examination, ELISA, and PCR analysis, can be useful and should be employed according to clinical suspicion. Several diagnostic tests are available for the diagnosis of *Giardia* spp. infections in dogs and cats. These diagnostic tests include the direct examination of fecal smears for motile trophozoites (low-sensitivity test); concentration techniques including centrifugal flotation with zinc sulfate (ZSFC), sodium acetate/acetic acid/formaldehyde (SAF), or merthiolate/iodine/formaldehyde (MIF) for detecting cysts (moderate to high sensitivity); fecal immunoassays such as ELISA or IFA for group-specific antigens (moderate to high sensitivity); and fecal PCR (highly sensitive). Successful detection of *Giardia* spp. using fecal flotation is operator-dependent. The retrieval of cysts significantly increases from 70% to more than 90% if two or more fecal samples collected at 2–3 day intervals are examined. Should a litter or group of puppies be affected, collective testing on pooled fecal samples can be performed, limiting false-negative results due to the pre-patent period and intermittent parasitic excretion. The SNAP Giardia Test Kit® (Idexx Laboratories, Westbrook, USA) has comparable accuracy to fecal immunoassays and can help with in-clinic screening of dogs showing compatible clinical signs. However, such tests only allow the identification of one infectious agent at a time.

The diagnostic test of choice for coccidia in dogs and cats is fecal flotation with Sheather's sugar solution. In coprophagic dogs, attention must be paid to the possibility of coccidia oocysts being present from other animals. Diagnosis of a helminthic infection is based on demonstrating ova during fecal flotation. *Cryptosporidium* spp. oocysts are small (approximately 4–6 mm in diameter) and often difficult to detect in fecal preparations. When examining only single fecal samples, commercial enzyme immunoassays are frequently more sensitive. With the availability of two consecutive fecal samples for examination, a modified Ziehl-Neelsen acid-fast stain is as sensitive as an immunoassay. PCR-based tests developed to detect *Cryptosporidium* spp. in feces from cats are more sensitive than the available immunoassays.



**Fig. 7-12** Soft feces from a puppy containing a *Toxocara canis* parasite

#### 7.3.1.3.5 Treatment

*T. canis* presents a zoonotic risk, and it is considered that almost 100% of dogs have been in contact with this parasite. Thus, a systematic deworming program must be implemented against this parasite.



To prevent transmission of *Toxocara canis* to fetuses during gestation, the European Specialist Counsel Companion Animal Parasites (ESCCAP) recommends treating pregnant female dogs with macrocyclic lactones on the 40th and 55th day of pregnancy or fenbendazole daily (q24h) from the 40th day of pregnancy until the 14th day postpartum.

Puppies need to be treated starting at 2 weeks of age, then every 2 weeks until 2 months, with fenbendazole/febantel, pyrantel, flubendazole, or nitroscanate.



Transplacental transmission does not occur in cats during gestation. Kittens need to be treated starting at 3 weeks of age, then every 2 weeks until 2 months, with fenbendazole/febantel, pyrantel, flubendazole, or nitroscanate.

Lactating bitches and queens must be treated at the same time as their puppies/kittens to prevent transmission by milk or feces (▶Tab. 7-3).

Although *Cystoisospora* coccidiosis may be self-limiting, anticoccidial therapy can speed up the resolution of clinical signs and may lessen environmental contamination. Several anticoccidial drugs (furazolidone, amprolium, diclazuril, ponazuril, toltrazuril, sulfadimethoxine, and trimethoprim-sulfonamide) can be used to treat *Cystoisospora* infections in dogs and cats. In clinical coccidiosis cases due to *C. canis* or *C. ohioensis*-complex, emodepside plus toltrazuril suspension is effective (reducing oocyst excretion and the number of days with diarrhea).[6] The number of oocysts excreted is also reduced markedly by administering emodepside plus toltrazuril suspension to cats during the prepatent period.

In catteries, breeding kennels, and shelters, these treatments need to be aligned with global hygiene management (▶Clinical pearls).

**Tab. 7-3** Treatment options for main endoparasite infections
This table shows commonly used antiparasitic agents to treat helminth, Giardia, and coccidian infections in dogs and cats.

| Agent | Commonly used dosage |
|---|---|
| **Ascarids and hookworms** | |
| Fenbendazole | 50 mg/kg PO q24h for 3 consecutive days |
| Pyrantel pamoate | 5–10 mg/kg PO once; consider repeating after 2–4 weeks |
| Febantel | 10–20 mg/kg PO q24h for 3 days |
| Moxidectin (to prevent reactivation of dormant *Toxocara canis* larvae and their transmission to puppies) | 1 mg/kg PO administered on days 40 and 55 of pregnancy |
| Milbemycin oxime | 0.5–1 mg/kg PO once |
| **Taenia, echinococcus, and dipylidium** | |
| Praziquantel | 5–10 mg/kg PO or SC; repeat 3 weeks later |
| ***Giardia* spp.** | |
| Metronidazole | 25–30 mg/kg PO q12h for 5–8 days (D) |
| Metronidazole benzoate | 10–15 mg/kg PO q12h for 7 days (C) |
| Fenbendazole | 50 mg/kg PO q24h for 3 days (D) |
| **Coccidia** | |
| Toltrazuril plus emodepside | 9 mg/0.45 mg/kg once |

**PO** = per os; **SC** = subcutaneous; **D** = applies for dogs; **C** = applies for cats

**CLINICAL PEARLS**

**Management of parasite contamination in kennels and catteries**

Breeding kennels and catteries are specific environments with a high density of animals, particularly animals of young age. In these environments, parasite prevention and control measures are very important. These measures are divided into two main categories:

1. Preventing the introduction of parasites
2. Limiting parasite transmission.

**Quarantine** plays an important role in preventing the introduction of some endoparasites. All new dogs need to be housed in a specific quarantine ward, separated from other dogs, prior to being introduced in the kennel. During this period, dogs should be dewormed and groomed (9% of owned dogs carry eggs of *Toxocara canis* on their fur or hair).[5]

Decreasing the risk of parasitic transmissions requires the excretion, persistence in the environment, and exposition to parasites to be limited. Parasite excretion can be reduced by **anthelminthic treatment** adapted to the parasites observed in the kennel. Environmental conditions also affect the survival of parasites. Surface porosity, environmental temperature, and the presence of organic matter are important determinants of parasite survivability. This emphasizes the importance of using adequate surfaces in kennels, which should be highly resistant and of low porosity. To limit the persistence of parasites in kennels, good cleaning and disinfection procedures are mandatory. **Cleaning and disinfection** are to be distinguished; cleaning involves removing visible organic matter with soap or detergent, whereas disinfection is the application of chemicals or other procedures to kill the remaining microbes. The disinfectant should be selected based on the detected parasite. For example, sodium hypochlorite is highly effective against infective *T. canis* eggs, but it enhances the excystation of *Cystoisospora* spp. oocysts. Limiting the exposition to parasites, kennels are required to separate wards or sectors based on the vulnerability of the animals as determined by their physiological status.

An optimum solution is to separate the following areas within the kennel: maternity ward, adult dogs, quarantine ward, and medical ward. Specific cleaning equipment should be available in each sector.

The design should allow movement through the facility to proceed from areas housing animals most susceptible to disease and/or healthiest animals to those likely to be a source of infectious disease (puppies, adult dogs, dogs in quarantine, medical ward).

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
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### 7.3.1.4 Canine schistosomiasis

Johanna Heseltine

#### 7.3.1.4.1 Etiology and clinical presentation

Canine schistosomiasis is caused by infection with the trematode *Heterobilharzia americana*. *H americana* is endemic to the Gulf coast and south Atlantic region of the United States, but canine infections have been reported more widely (Texas, Louisiana, Florida, North Carolina, South Carolina, Georgia, Oklahoma, Alabama, Virginia, Mississippi, Kansas, and Indiana).[1–4] Raccoons and nutria are definitive hosts, but infections also occur in other mammals. Eggs are shed in host feces. When exposed to freshwater, a ciliated miracidium hatches and infects the intermediate host, a lymnaeid snail. Cercariae form within sporocysts in the snail and then emerge in freshwater, where they can penetrate the skin of a dog in the water. Cercariae then migrate through the dog's lungs to the liver, where they mature into adults. Adults travel via portal veins to the mesenteric veins, where they reproduce and lay eggs. Proteolytic enzymes produced by the eggs allow penetration of the mesenteric vein and intestinal mucosa, with entry into the intestinal lumen.[2] Patent infection occurs approximately 68 days post-infection.[2] Young, large breed dogs with outdoor access have an increased incidence of infection.[5] Eggs are deposited in the small and large intestines and can migrate to other organs, including the liver, pancreas, lymph nodes, spleen, and kidneys, where they elicit granulomatous inflammation. The broad tissue distribution and variable degrees of inflammation and fibrosis result in variable clinical presentations. Clinical signs can be acute or chronic. Large intestinal diarrhea, small intestinal diarrhea, or a protein-losing enteropathy (▶Chap. 7.3.8.2) may develop. Weight loss, lethargy, vomiting, hyporexia, abdominal discomfort, and fever may occur. Hypercalcemia is seen in up to 50% of dogs, which may result in polyuria and polydipsia




**Fig. 7-13** Radiographic image showing mineralization of the intestinal wall from a dog infected with *H. americana*

(Courtesy of Texas A&M Radiology Department, College Station, TX.)

(PU/PD).[3] Some infected dogs are asymptomatic.[2,4,5] *H. americana* infection in humans results in cercarial dermatitis ("swimmer's itch").[5]

#### 7.3.1.4.2 Diagnosis

Diagnosis of schistosomiasis requires fecal PCR testing, fecal saline sedimentation, or histopathology of affected tissues. No studies have compared the performance of these tests. Fecal PCR is commercially available (Gastrointestinal Laboratory, Texas A&M University, College Station, TX) and can detect >1–2 eggs/gram of feces.[6] Eggs may be found on fecal saline sedimentation or a direct fecal smear, whereas routine fecal flotation is usually negative. Shedding eggs into feces is intermittent, and testing several samples obtained on consecutive days or using a combination of tests may improve the diagnostic yield.[8] Granulomatous inflammation and fibrosis, sometimes containing eggs, can be found on biopsies of the liver, intestines, or other organs.[4] Less commonly, adult parasites are found in tissues.[8] Confirmation by PCR detection of parasite DNA in formalin-fixed, paraffin-embedded tissues has been described.[7] There is also a case report of eggs identified on cytology obtained via a hepatic fine needle aspirate.[8]

Abnormalities on other diagnostic tests may prompt testing for *H. americana*. Laboratory findings include anemia, eosinophilia, hypoalbuminemia, hyperglobulinemia, increased liver enzymes, hypercalcemia, and secondary renal azotemia. Glomerulonephritis has been reported secondary to *H. americana* infection.[4,9] Abdominal radiographs may be normal, but occasionally show linear mineralizations of the gastric or intestinal wall (▶Fig. 7-13), splenomegaly, or lack of serosal detail. Abdominal ultrasound may show thickening of the intestinal wall, sometimes with linear areas of mineralization in the submucosa or muscularis layers (▶Fig. 7-14).[1] The liver may appear coarse, heterogeneous, mottled, hyperechoic, or hypoechoic.[1,7,8] Granulomas and mineralized eggs may appear hyperechoic pinpoint foci in the liver, pancreas, and intestines.[7,8] Ascites secondary to severe liver disease and portal hypertension has been reported.[1,5] Abdominal lymphadenopathy, splenomegaly, and hyperechoic kidneys may also be seen. During endoscopy (▶Chap. 1.5), the intestinal mucosa may appear thickened and irregular.[1,5] The most common intraoperative or necropsy-derived gross findings are granulomas on the serosa of the intestines and liver.[4]

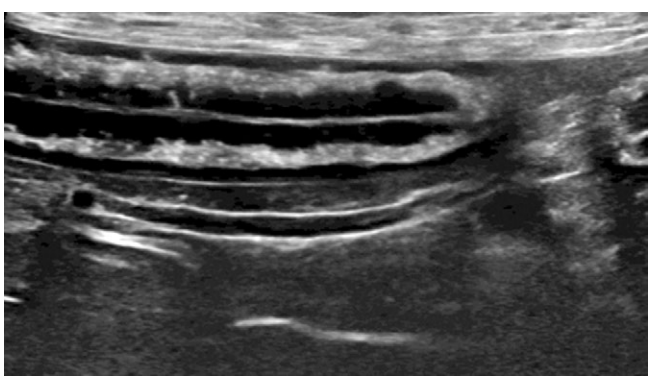


**Fig. 7-14** Ultrasonographic image showing thickening of the submucosal layer of the small intestinal wall with pinpoint hyperechogenicities from a dog with *H. americana* infection

(Courtesy of Texas A&M Radiology Department, College Station, TX.)

#### 7.3.1.4.3 Treatment and prognosis

Successful off-label treatment is reported with praziquantel 25 mg/kg PO q8h for 2–3 days, fenbendazole 40 mg/kg PO q24h for 10 days, or a combination of both drugs.[5] No clinical trials have compared the efficacy of these treatments. Comorbidities such as acute kidney injury should also be managed, although calcium may not normalize until an anthelminthic drug is given.[5] A protocol combining low-dose praziquantel (5 mg/kg PO q8h for 2 days) and fenbendazole (24 mg/kg PO q24h for 7 days) can effectively treat asymptomatic schistosomiasis in dogs.[10]

With treatment, the prognosis is good for acute cases but guarded for chronic cases and depends on the severity of the resulting granulomatous reaction and fibrosis. Treatment is not always successful and may need to be repeated in some cases.[1] Re-testing 2 weeks post-treatment is recommended. However, this may be too early in some cases, as residual eggs can still be shed.[4] Some dogs have had positive tests years apart, and it is unclear if this represents treatment failure or reinfection. Because dogs can be re-infected, the environment should be changed, if possible. Testing of other dogs sharing the same environment is recommended.[1,4] Testing may also be warranted during annual examinations for dogs from endemic regions, especially those exposed to freshwater sources that could be contaminated with *H. americana*.[4]

**References**

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### 7.3.1.5 Fungal and algae infections

Margaux Marclay

#### 7.3.1.5.1 Pythiosis

*Pythium insidiosum* is an aquatic oomycete that causes severe gastrointestinal (GI) or cutaneous lesions in dogs and less commonly in cats. Large breed young to middle-aged outdoor male dogs are predisposed.[1–5] Repeated exposure to freshwater lakes, swamps, and ponds that may contain *P. insidiosum* zoospores increase the likelihood of contracting the disease, but even animals without this history may become infected.[6] Pythiosis is most common in tropical and subtropical regions such as the southeastern United States, Southeast Asia, Central and South America, and eastern Australia.

**Clinical presentation**

Gastrointestinal pythiosis typically causes chronic weight loss associated with clinical signs of GI disease corresponding to the affected sites. Signs of systemic illness, such as lethargy are typically absent, and physical examination often reveals poor body condition in an alert patient. A palpable abdominal mass or thickened colonic mucosa are common findings. Pythiosis causes marked eosinophilic pyogranulomatous inflammation leading to severe segmental, transmural thickening of the GI wall. Mesenteric lymph nodes are often enlarged and reactive but are usually not infected. Acute hemoabdomen and sudden death is an uncommon complication that may result from an invasion of the mesenteric vasculature. Diagnosis of GI pythiosis is suspected based on patient history, clinical signs, and the presence of an abdominal mass. Eosinophilia is often detected.[4,6]

**Diagnosis**

Abdominal ultrasound can confirm the presence of typical lesions and assess their extent and location to determine whether surgical resection is possible. Segmental loss of the normal GI wall layering associated with moderate to severe wall thickening is typically seen.[7] Cytological examination (▶ Chap. 1.7) of ultrasound-guided fine-needle aspirates of GI lesions or rectal scrapings may show eosinophilic pyogranulomatous inflammation and occasionally *P. insidiosum* hyphae. Histopathology is better assessed on surgical than endoscopic biopsies, as the hyphae are usually found in the deep layers of the intestinal wall. Hyphae are broad (2–9 µm in diameter with a mean diameter/width of 5 µm), rarely septate, have non-parallel walls, and stain well with Gomori's methenamine silver. Culture can be successful if appropriate tissue samples are obtained at the time of biopsy. A technique for the extraction, amplification, and sequencing, of fungal and oomycete DNA from formalin-fixed paraffin-embedded tissues is also routinely available.[8] Assessment of anti-*P. insidiosum* antibodies has often been used to support the diagnosis of pythiosis, but false-positive results may occur.[9]

**Treatment**

Complete surgical resection is the treatment of choice, if possible. Otherwise, medical therapy with a combination of itraconazole, terbinafine, and an anti-inflammatory dose of prednisone is recommended.[10]

### 7.3.1.5.2 Histoplasmosis

*Histoplasma caspulatum* is a dimorphic soil-borne fungus reported to cause respiratory, gastrointestinal, or disseminated disease in dogs and cats. Histoplasmosis affects dogs and cats of all ages, but young to middle-aged animals are predisposed.[11,12] Recurrent outdoor activity and contact with nitrogen-rich organic material (e.g., moist soil containing bat guano) is a risk factor.[13] Cats are more predisposed to histoplasmosis than dogs. *H. capsulatum* is found worldwide in temperate and subtropical areas, especially in Missouri, Mississippi, Tennessee, and the Ohio River valleys. Infection occurs with exposure to microconidia by inhalation or ingestion. The disease may remain localized to the respiratory or GI tract, where fungal organisms are phagocytized by macrophages and replicate within these cells.[14] The disease can also disseminate, particularly to the lungs, GI tract, lymph nodes, spleen, liver, eyes, and bone marrow.

#### Clinical presentation

Clinical signs depend on the organ system that is primarily affected, but systemic signs of illness such as lethargy, anorexia, and weight loss, are common. In cats, GI signs other than anorexia are uncommon compared with dogs, in which GI signs are the most common complaint and are associated with small and large bowel diarrhea.[15,16] Physical examination findings reflect the organs involved in the disease process. This may include a poor body condition, peripheral lymphadenopathy, fever, icterus, hepatomegaly, splenomegaly, and respiratory, ocular, and dermal lesions.

#### Diagnosis

Diagnosis is most reliably based on cytology or histological identification of yeasts and pyogranulomatous inflammation. Tissue samples can be obtained from lymph node aspirates, rectal scrapings, or aspirates/biopsies from other organs. The yeasts have round bodies with a basophilic center and clear thin outer rim, measure 2–4 µm in diameter, and are often found within phagocytic cells. An ELISA assay for *H. capsulatum* antigen can be used on serum or urine as a diagnostic test and to assess the response to treatment.[17]

#### Treatment

Treatment relies on the use of itraconazole for at least 6 months and 2 months past the resolution of clinical signs. In animals with severe clinical signs, the addition of amphotericin B can be considered. Prognosis varies from guarded to good and depends on the severity of the clinical signs.

### 7.3.1.5.3 Protothecosis

*Prototheca* spp. are achlorophyllous algae reported to cause cutaneous or systemic disease in dogs and rarely in cats. Young-adult, medium to large-breed dogs, females, and particularly boxers are predisposed.[18] *Prototheca* spp. are found worldwide but especially in warm and humid climates. The pathogenesis is not fully understood, and the infection appears to follow ingestion or cutaneous inoculation of the organism. Algae reproduce asexually by endosporulation to form a sporangium containing multiple sporangiospores.[19] The infection can remain localized to the skin and cause nodular and ulcerative lesions. Systemic invasion may also occur, with the gastrointestinal, ocular, and neurologic systems being commonly affected. Clinical signs of colitis are often noticed several months before other clinical signs occur. Ocular and neurologic involvement develop with disease progression and closer to the time of death or euthanasia.[18]

Diagnosis requires cytology or histopathology. The organisms are usually present in large numbers in affected tissues and may be identified in urine, lymph nodes, rectal scrapings, cerebrospinal fluid (CSF), vitreous, or aqueous humor aspirates. Protothecal organisms are spheroid, ovoid, or elliptical and are delimited by a thick refractile capsule. Depending on the species, their sizes vary from 5–25 µm.[20] Complete surgical excision can be curative for cutaneous involvement, but the prognosis of systemic protothecosis is poor. A combination of itraconazole and amphotericin B was reported to be successful in some cases.[18]

#### References

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## 7.3.2 Dietary indiscretion (garbage can intoxication)

Melanie Werner, Stefan Unterer

Acute gastrointestinal signs in dogs (vomiting and diarrhea) are a common sequela to the ingestion of garbage, table scraps, or other unsuitable food products. Most of the time, clinical signs are self-limiting or only require supportive treatment (e.g., intravenous fluid therapy, antiemetic therapy). Dietary indiscretion is less common in cats. Depending on the kind and amount of unsuitable food consumed, additional signs after such dietary indiscretion may include: neurological (e.g., due to mycotoxins or theobromine ingestion), metabolic (e.g., due to xylitol), hematological (e.g., due to onions, garlic) or urological (e.g., due to grapes or raisins) abnormalities. Adverse food reactions, typically caused by food intoxications or food intolerance mechanisms, stand in contrast to immunological food reactions (food sensitivity), which are true hypersensitivity reactions (▶Chap. 11.1).

Dietary indiscretion-associated food toxicity/intoxication is often related to microbial contamination. Systemic illness due to food poisoning (i.e., *Salmonella* species, *Escherichia coli*, and *Campylobacter* species, toxins of *Clostridium botulinum*, *Staphylococcus aureus*, and *Bacillus cereus*), as is common in humans, is regarded as sporadic in immune-competent, healthy dogs and cats (▶Chap. 7.3.1.2).[1] Nutrient excess, plant-derived toxins, intolerance of specific food components, toxins involved in the food manufacturing process, and microbial spoilage can also occur.



Dogs may be more susceptible to mycotoxins than other species.[2]

Care must be taken when there is a history of ingestions of foods known to be specifically toxic for dogs and/or cats (i.e., onions, garlic, chocolate, nuts, grapes, raisins, macadamia nuts, xylitol). Treatment depends on the type of ingested toxin. More information can be found in specialized veterinary toxicology literature.

Food intolerance can also be caused by metabolic disorders (i.e., deficiency of lactase in adult dogs and cats),[3] idiosyncratic reactions (i.e., to food additives), or intake of inappropriately large amounts of macronutrients. One study documented the association between the intake of an unusual food and pancreatitis in dogs.[4]

**KEY FACTS**

- Clinical signs due to dietary indiscretion are usually self-limiting.
- Even if the unsuitable food products are often microbially contaminated, an infection and systemic illness caused by enteropathogenic bacteria rarely occur in otherwise healthy animals, and antibiotic treatment is usually not necessary.

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
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## 7.3.3 Acute hemorrhagic diarrhea syndrome

Kathrin Busch, Stefan Unterer

### 7.3.3.1 Introduction

Acute hemorrhagic diarrhea syndrome (AHDS), also known as hemorrhagic gastroenteritis, is characterized by an acute onset of hemorrhagic diarrhea commonly preceded by vomiting and is usually associated with hemoconcentration and a rapid clinical improvement with symptomatic treatment.

### 7.3.3.2 Pathogenesis

Despite an extensive diagnostic workup, about half of the acute hemorrhagic diarrhea (AHD) cases in dogs have no underlying cause identified. This idiopathic form of AHD, combined with evidence of hemoconcentration, was defined as an independent syndrome (AHDS), but *Clostridium perfringens* type A was recently identified as a causative infectious agent. Although Koch's molecular postulates have not been proven, there is strong evidence that a combination of several clostridial toxins can cause AHDS. These Gram-positive, anaerobic, toxin-producing bacteria have been detected on the necrotic mucosal surfaces of endoscopically-obtained intestinal biopsies from ten dogs with AHDS.[1,2] Support for an associated pathology is finding a novel, pore-forming toxin (NetF) with cytotoxic effects on various cell lines in a *C. perfringens* type A strain isolated from a dog with AHDS.[3] Also, the prevalence of netF encoding *C. perfringens* strains is significantly higher in dogs with AHDS than in healthy controls.[4]

#### 7.3.3.3 Signalment, history, and clinical presentation

Most affected dogs are small to medium-sized (median 10 kg) and young to middle-aged (median 5 years).[5] Yorkshire terriers, miniature pinschers, miniature poodles, miniature schnauzers, and Maltese are overrepresented. Many of these dogs have a history of chronic gastrointestinal signs without a specific triggering factor identified. AHDS usually has a peracute onset with vomiting (with or without hematemesis) as the first clinical sign, followed by hemorrhagic diarrhea. The enormous fluid loss rapidly leads to lethargy and frequently hypovolemia, clinically reflected by pale mucous membranes, delayed capillary refill time, tachycardia, and weak pulses.

Dogs often present normo- or hypothermic due to hypovolemic shock. Pyrexia is an unusual finding and should raise a suspicion for bacteremia due to bacterial translocation. Even with severe dehydration, the skin turgor might be normal due to the peracute onset of the disease and, therefore, should not be used as a sole indicator of dehydration. Severe abdominal pain is also not a typical clinical finding, and if present other causes of AHD, such as acute pancreatitis (▶Chap. 10.3.1), should be considered.

#### 7.3.3.4 Diagnosis

Unfortunately, there is no specific test to diagnose AHDS. Therefore, the diagnosis is based on the characteristic clinical presentation, normal to increased PCV (packed cell volume), and a rapid clinical improvement with symptomatic treatment combined with excluding other known causes of AHD. These include gastrointestinal disorders such as mucosal irritation and/or ulceration caused by drugs or toxins, infectious enteritides (e.g., due to canine parvovirus, *Salmonella* spp., *Campylobacter* spp.), or partial intestinal obstruction, but also extra-gastrointestinal disorders including hypoadrenocorticism, acute pancreatitis, acute hepatic or renal failure, and heatstroke.

A CBC (complete blood count) is the first step in differentiating hemorrhagic diarrhea from gastrointestinal bleeding. In AHDS, hemoconcentration with a PCV up to >70% in extreme cases (median PCV 53%, range 33–76%) is a typical finding, and a stress leukogram can be observed.[5] If the PCV is below or at the lower reference limit, gastrointestinal bleeding should be considered. The serum biochemistry profile may reveal mildly increased liver enzymes and (surprisingly) rarely an increased BUN concentration due to dehydration. Although total protein and albumin concentrations are mostly within the reference intervals at presentation, these parameters may drop rapidly and markedly during the clinical course. Thus, albumin and PCV should always be rechecked after successful rehydration. Blood gas analysis might show metabolic acidosis and increased blood lactate levels. Atypical laboratory findings in dogs with AHD, suggesting another cause of this clinical presentation, are summarized in (▶Tab. 7-4).

Although endoparasites usually cause less severe clinical signs (▶Chap. 7.3.1.3.3), a fecal flotation and antigen ELISA test for *Giardia* spp. should be performed. Canine parvovirus infection should be considered a differential diagnosis in any young, unvaccinated, neutropenic dog and a fecal parvovirus-antigen ELISA and/or parvovirus-PCR performed (▶Chap. 7.3.1.1.3).

A routine diagnostic test to confirm *C. perfringens* overgrowth and the presence of associated toxins as the inciting cause of AHDS is currently not available. *C. perfringens* is frequently isolated from the feces of healthy dogs,[6] and clostridial toxins are difficult to detect (▶Chap. 7.3.1.2.2). A positive PCR result for netF-encoding *C. perfringens* strains may suggest AHDS (48% prevalence). However, these strains can also be detected in healthy dogs (prevalence up to 12%).[4]

Abdominal imaging does not reveal characteristic changes but is indicated, especially in cases with an atypical clinical presentation, to further evaluate the dog for pancreatitis, focal intestinal lesions (e.g., foreign bodies, intussusception, neoplasia), and mesenteric volvulus. Abdominal ultrasound in dogs with AHDS frequently reveals fluid-filled and sometimes paralytic intestinal loops. Due to acute necrosis, inflammation, and edema, the intestinal wall can appear prominent with an indistinct layering in some cases.

#### 7.3.3.5 Treatment

Patients with AHDS should be hospitalized because deterioration without fluid therapy is usually rapid and closely monitored with adjustments in the treatment plan.

**CLINICAL PEARLS**

Adequate intravenous fluid therapy with balanced electrolyte solutions is the most important therapeutic intervention. Rapid volume replacement is often necessary by giving a shock bolus as fast as 20–30 ml/kg over 10–20 min (repeated up to 3 times if necessary) followed by a constant rate IV infusion.

**Tab. 7-4** Atypical laboratory and/or clinical findings in dogs with acute hemorrhagic diarrhea syndrome (AHDS)

| Atypical laboratory/ clinical findings in AHDS | Differential diagnoses | Further diagnostic tests recommended |
|---|---|---|
| Anemia | • Systemic coagulopathy<br>• GI lesion (e.g., erosions, ulcerations, neoplasia) | • Platelet count (manual) and function testing<br>• Coagulation profile<br>• Selected serum parameters (e.g., bile acids, creatinine)<br>• Abdominal imaging<br>• GI endoscopy |
| Neutropenia | CPV infection | Fecal antigen-ELISA and/or PCR for CPV |
| Neutrophilia, left shift, pyrexia | • Primary bacterial enteropathogen<br>• Bacterial translocation | • Blood culture<br>• Culture of aspirated abdominal fluid/lymph node<br>• Fecal culture |
| ALT/ALP activity >3× upper reference limit | Primary hepatopathy | Pre- and postprandial serum bile acids<br>• If increased: further diagnostic workup for liver disease<br>• If normal: recheck liver enzymes |
| Azotemia + urine specific gravity <1.030 | • Renal dysfunction<br>• Hypoadrenocorticism | • Diagnostic workup for renal pathology<br>• ACTH stimulation test (cortisol, ± aldosterone) |
| Serum baseline cortisol concentration ≤2 µg/dL (≤55 nmol/L) | Hypoadrenocorticism | ACTH stimulation test (cortisol, ± aldosterone) |

**ACTH** = adrenocorticotropic hormone; **ALP** = alkaline phosphatase; **ALT** = alanine aminotransferase; **CPV** = canine parvovirus; **GI** = gastrointestinal

Symptomatic treatment with antiemetics (e.g., maropitant 1 mg/kg q24h IV or SC) and analgesics (e.g., metamizole 30–50 mg/kg q8h IV or PO) usually improve patient comfort and should be administered at the clinician's discretion. Nonsteroidal anti-inflammatory drugs (NSAIDs) are contraindicated with AHDS because of their propensity to cause further gastrointestinal injury. During IV fluid and symptomatic treatment, vital parameters should be checked every 30–60 minutes until the heart rate reaches <120/min in small breed dogs or <100/min in large breed dogs, capillary refill time normalizes to <2 sec, and the dog is alert and has started to urinate when walked outside.

Patients with severe hypoalbuminemia (<2.0 g/dL or <20 g/L) may require colloids, plasma, or albumin solutions. Early enteral nutrition with a highly digestible, low-fat diet, supplemented with glutamine and dietary fibers, is important as it promotes enterocyte proliferation and improves intestinal barrier function. Routine administration of antibiotics is not indicated in uncomplicated cases because it is not associated with a faster clinical recovery or lower mortality rate [7,8] and potentially contributes to intestinal dysbiosis, bacterial toxin release, and selection of antibiotic-resistant bacteria. Antibiotics should be restricted to immunosuppressed and/or neutropenic patients and cases with evidence of systemic inflammation/septicemia (e.g., pyrexia, inflammatory leukogram, hypoglycemia, hyperbilirubinemia). Prophylactic antibiotic coverage with amoxicillin/clavulanic acid (20–30 mg/kg q6h IV) may be considered in severely affected dogs that cannot be closely monitored. Administration of probiotics does not shorten the clinical recovery time. However, high-dose multi-strain formulations might help accelerate the normalization of the intestinal microbiome and displace toxigenic *C. perfringens* strains.[9]

#### 7.3.3.6 Possible complications and prognosis

Because of the severe damage to the intestinal wall, bacterial translocation resulting in bacteremia and disseminated intravascular coagulopathy (DIC) is a possible but infrequent complication of AHDS. The overall prognosis of AHDS is good, with a mortality rate of less than 10% with adequate treatment, but it can be high if untreated. AHDS is often a single clinical event with a low recurrence rate (10–15%), but about 30% of these dogs will develop chronic diarrhea later in life.[10]

**KEY FACTS**

- Acute hemorrhagic diarrhea syndrome (AHDS) is characterized by an acute onset of hemorrhagic diarrhea commonly preceded by vomiting and is usually associated with hemoconcentration and a rapid clinical improvement with symptomatic treatment. *Clostridium perfringens* type A was recently identified as a causative infectious agent.
- The enormous fluid loss rapidly leads to lethargy and frequently hypovolemia, clinically reflected by pale mucous membranes, delayed capillary refill time, tachycardia, and weak pulses.
- Patients with AHDS should be hospitalized because adequate intravenous fluid therapy with balanced electrolyte solutions is the most important therapeutic intervention.

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
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## 7.3.4 Alterations in the intestinal microbiota (dysbiosis)

Jan S. Suchodolski

### 7.3.4.1 Importance and function of intestinal microbiota

The gastrointestinal tract harbors a complex ecosystem consisting of various microbes, including viruses, bacteria, fungi, and protozoa. This microbial collection is termed microbiota when referring to the taxonomy (i.e., "who is there") and as the microbiome when referring to their gene content and function (i.e., "what are they doing").[1] A normal microbiota modulates the immune system, aids in the control of enteropathogens, and provides nutritional benefits. Bacteria are by far the most abundant group of microorganisms in the intestines, comprising >95% of all microorganisms.[1] They convert dietary and host molecules into bacterial-derived metabolites (postbiotics) that have effects on the host. Because of this, the intestinal microbiome is considered a metabolic organ. For example, dietary carbohydrates are converted by bacteria into short-chain fatty acids (SCFA). These are anti-inflammatory, provide energy for the host, regulate intestinal motility, and serve as growth factors for epithelial cells. Indole compounds, byproducts of microbial degradation of the dietary amino acid tryptophan, are immuno modulatory and strengthen the intestinal barrier.

**NOTE**

Bile acids (BA) appear to be one of the most important regulators of the intestinal microbiota.[2,3]

The primary BAs, cholic and chenodeoxycholic acid, are released into the small intestine after a meal. Up to 95% of these BAs are reabsorbed in the ileum and undergo enterohepatic circulation. The remaining BAs reach the large intestine (LI), where they undergo microbial conversion to secondary BAs. In dogs and cats, the beneficial bacterium *Clostridium hiranonis* is the main converter of BAs, and in healthy animals, the fecal BA pool consists mostly of the secondary unconjugated BAs lithocholic and deoxycholic acid.[4] The proper ratio of primary to secondary BAs is important for health, as BAs act as signaling molecules for receptors located across multiple organ systems and thereby exhibit anti-inflammatory effects.[5]

### 7.3.4.2 Pathophysiology

The intestinal microbiota is in contact with the intestinal epithelium, mucus layer, the immune system, and the luminal environment. Changes in these will affect the microbiota composition, and dysbiosis is often an early marker of an abnormal gut environment in disease. The altered microbiota can contribute to clinical signs in some patients.

The microbiota is, to varying degrees, influenced by diet, antibiotics, intestinal inflammation, structural changes, as well as other factors.[6] There are several physiological mechanisms that regulate bacterial colonization in the SI and LI, including secretion of gastric acid and antibacterial factors (i.e., pancreatic and biliary secretions) and intestinal motility. Failure of one or more of these control mechanisms can lead to alterations in the small and/or large intestinal microbiota and may result in clinical signs associated with dysbiosis (▶Tab. 7-5).

For example, acid suppressant therapy with the proton pump inhibitor omeprazole leads to increased lactic acid bacteria in the stomach and duodenum[7] and to an increased fecal dysbiosis index (mainly due to an increase in *Streptococcus* spp).[8] These changes are transient and revert within 10–14 days after the end of therapy.

**Tab. 7-5** Conditions associated with intestinal dysbiosis

| |
|---|
| **Intestinal inflammation and mucosal damage** |
| Chronic enteropathies<br>• Food-responsive enteropathy<br>• Antibiotic-responsive enteropathy<br>• Chronic inflammatory enteropathy (CIE) or idiopathic inflammatory bowel disease (IBD) |
| **Antibiotic-induced** |
| Broad-spectrum antibiotics (e.g., metronidazole, tylosin, clindamycin) |
| **Small intestinal stasis** |
| • Anatomic abnormalities<br>– Congenital blind loops (not yet identified in dogs or cats)<br>– Small bowel diverticula, strictures, or adhesions<br>– Surgical resection of the ileocolic valve<br>– Surgical blind loops (experimentally created by end-to-side anastomosis)<br>• Partial obstructions of the small intestine<br>– Neoplasia<br>– Foreign bodies<br>– Chronic intussusception<br>• Motility disorders<br>– Hypothyroidism<br>– Diabetic autonomic neuropathy<br>– Scleroderma<br>• Abnormal migrating motor complexes |
| **Decreased gastric acid output** |
| • Atrophic gastritis<br>• Administration of acid-suppressing drugs (proton pump inhibitors, $H_2$-blockers) |
| **Exocrine pancreatic insufficiency** |
| Decreased output of pancreatic antimicrobial factors; remnant nutrients in the intestinal lumen |
| **Miscellaneous** |
| Decreased mucosal immunity |

Chronic enteropathies (CE) are often accompanied by inflammatory changes and damage to the mucus layer and mucosal architecture. This results in altered oxygen levels at the mucosal surface and often leads to increases in aerobic bacteria (e.g., *E. coli*), with a concurrent decrease of the normal anaerobic microbiota. The intestinal microbiota can also contribute to clinical signs when there is an abnormal or increased amount of food or drug substrate in the intestinal lumen. The loss of mucosal architecture can lead to decreased numbers of transporters in the small intestine (e.g., transporters for carbohydrates, amino acids, fatty acids, and bile acids), resulting in malabsorption.[4,9] Other causes can be due to feeding diets with poor digestibility or due to lack of digestive enzymes in patients with exocrine pancreatic insufficiency (EPI; ▶Chap. 10.3.2).[10] The pancreatic juice also contains antimicrobial substances that suppress excessive bacterial growth in the proximal small intestine. Dogs with experimentally induced EPI show significantly increased bacterial counts in the small intestine.[11] Similarly, dogs with spontaneous EPI also show an increased fecal dysbiosis index.[12] Competition between bacteria and host cells for nutrients (e.g., cobalamin) may lead to malnutrition. Increased fat metabolism within the GI tract may lead to the production of hydroxylated fatty acids, which can contribute to diarrhea.

The ileocolic valve serves as a natural barrier between the SI and LI in dogs.[13] This barrier, together with intestinal motility, is believed to prevent retrograde migration of bacteria from the highly populated LI into the less populated small intestine.

While some breeds (e.g., German shepherd dogs and Chinese shar-peis) have anecdotally been reported to be at an increased risk for developing small intestinal dysbiosis, no genetic basis has yet been identified.

### 7.3.4.3 Clinical presentation

The clinical signs of an abnormal intestinal microbiota may include chronic intermittent small and/or large bowel diarrhea. Affected dogs are usually active but show a variable appetite, ranging from poor to excessive (i.e., polyphagia). Weight loss or poor growth is frequently observed. Owners often report borborygmus and/or flatulence. In some cases, mild to moderate steatorrhea may be observed due to chronic fat malabsorption. Dogs often show clinical signs related to the underlying cause of the dysbiosis.

### 7.3.4.4 Diagnosis

Intestinal dysbiosis is usually secondary to an altered environment due to underlying intestinal disease and/or environmental factors. Therefore, intestinal dysbiosis should be evaluated in the context of medication history and clinical presentation of the patient.

Bacterial changes can occur either localized in the small or LI, but can often be observed in both, as has been reported in dogs receiving omeprazole,[7,8] dogs with EPI,[12] and dogs with CE.[14,15] However, in some patients, an increased number of bacteria in the small intestine may cause disease. Dogs and cats with small intestinal dysbiosis may show an increased serum folate concentration and/or a decreased serum cobalamin concentration (▶Chap. 7.3.4.4.2).

#### 7.3.4.4.1 Fecal Dysbiosis Index

The fecal Dysbiosis Index (DI) is currently the only validated test for the assessment of intestinal dysbiosis (https://tx.ag/DysbiosisGI). The DI reports the abundance of the total fecal bacterial load as well as seven bacterial taxa that are commonly altered in dogs with CE or after broad-spectrum antibiotic use (e.g., tylosin, metronidazole).[16,17] Reference intervals are available for these bacterial groups. The algorithm combines these data into a single number that expresses the extent of the intestinal dysbiosis (▶Fig. 7-15).

The DI also predicts the ability of the intestinal microbiota to convert primary to secondary BAs by reporting the abundance of the BA-converting bacterium *Clostridium hiranonis*.[2] Normal amounts of secondary BAs are antimicrobial and suppress potential enteropathogens, such as *C. difficile*, *C. perfringens*, and *E. coli*.[18] Therefore, a decreased abundance of *C. hiranonis* and decreased conversion of primary to secondary BA strongly correlate with fecal dysbiosis.

The DI should be interpreted together with the abundance of individual bacterial taxa, and especially *C. hiranonis*, as a decrease in the latter is a major contributor to an abnormal microbiome (▶Fig. 7-15). A DI >2 indicates a major shift in the intestinal microbiota and an intestinal dysbiosis with high specificity, while a DI of 0–2 indicates a moderate shift in the fecal microbiota. Some dogs with CE have a DI <0, but the abundances of some bacterial taxa are outside their respective reference intervals, suggesting a minor form of dysbiosis.

An increased DI, together with a decreased abundance of *C. hiranonis*, is commonly seen in dogs with EPI or CE. Up to 60% of dogs with chronic enteropathy have a decreased abundance of *C. hiranonis* and therefore decreased secondary BA concentrations.[19]

Omeprazole leads to transient increases in the DI but with a normal abundance of *C. hiranonis*. The DI normalizes within 1–2 weeks after discontinuation of therapy. Broad-spectrum antibiotics (e.g., metronidazole and tylosin) induce severe fecal dysbiosis. The microbiota typically normalizes within 2–4 weeks after the end of administration in most dogs. However, some dogs may have persistent dysbiosis with a lack of *C. hiranonis* for several months.[17,20]

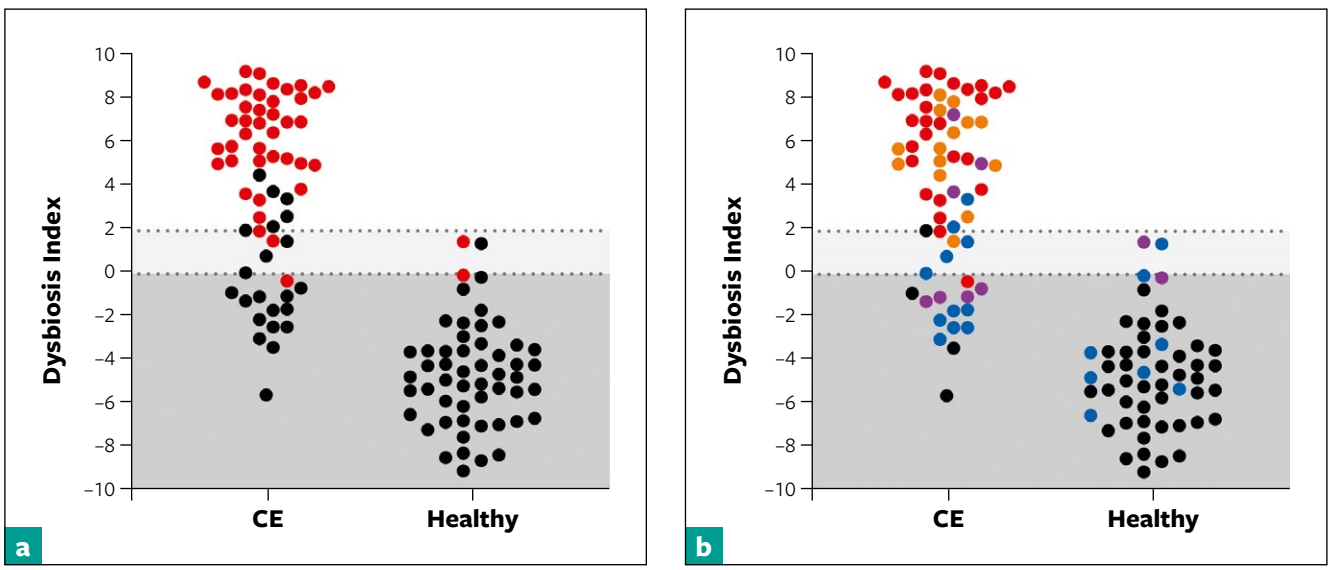



**Fig. 7-15** The Dysbiosis Index (**DI**) in healthy dogs and dogs with chronic enteropathy (**CE**)

The DI combines the abundance of seven bacterial taxa as well as the abundance of total bacteria into one single number. A DI >2 indicates a major shift in the intestinal microbiota and an intestinal dysbiosis with high specificity, while a DI of 0–2 indicates a mild to moderate shift in the fecal microbiota. Some dogs with CE have a DI <0, but the abundance of some bacterial taxa is outside their respective reference intervals, which suggests a minor form of dysbiosis.

**a** The abundance of *Clostridium hiranonis* has a substantial effect on the microbiome. Samples in **red** have a decreased abundance of *C. hiranonis* and therefore reduced conversion of primary to secondary intestinal bile acids, which is associated with an abnormal shift in the microbiome.

**b** A higher DI is generally characterized by less diversity and the abundance of more bacterial taxa outside their reference intervals (colors indicate the number of bacterial taxa outside the reference interval: **black 0**, **blue 1**, **purple 2**, **orange 3**, **red >3**). However, some dogs have all taxa within reference intervals, but due to abnormal shifts within the reference intervals, the DI is increased (**black dots**).

#### 7.3.4.4.2 Serum cobalamin and folate concentrations

The assessment of serum cobalamin and folate concentrations is another useful aid in diagnosing small intestinal dysbiosis. Serum cobalamin may be decreased, and serum folate may be increased in dogs with small intestinal dysbiosis. If both are altered, this is considered highly suggestive of small intestinal dysbiosis. However, both have a rather poor sensitivity and specificity for the diagnosis of small intestinal dysbiosis.[21] The reported sensitivity of a decreased serum cobalamin concentration for a diagnosis of small intestinal dysbiosis (termed small intestinal bacterial overgrowth in the older literature) ranges from 25–55%, and that for an increased serum folate concentration ranges from 50%–66%.[21]

Alterations of the small intestinal microbiota may lead to an increased competition for dietary cobalamin, resulting in decreased absorption of this vitamin. Some bacteria compete for cobalamin since they can utilize cobalamin-intrinsic factor complexes, while other bacteria can only bind free cobalamin, which is present in lower concentrations in the intestinal lumen.

Bacteria present in the distal SI and LI produce large quantities of folic acid. However, as folate carriers responsible for folate uptake are located exclusively in the proximal small intestine, folate produced in distal sections of the intestine will not be absorbed but will instead be excreted in the feces. If folate-producing bacteria migrate upwards into the proximal small intestine, folate of bacterial origin can be absorbed by the host, resulting in increased serum folate concentrations.

However, cobalamin and folate uptake from the small intestine is highly complex and can be affected by several mechanisms other than small intestinal dysbiosis (▶Chap. 1.3.2). For example, a diet high in folate may lead to a falsely increased serum folate concentration, while inflammation of the ileum may damage cobalamin receptors and thus may lead to cobalamin malabsorption. Dogs with EPI have a decreased secretion of antibacterial substances with subsequent small intestinal dysbiosis.[22] As a consequence, dogs with EPI often have increased serum folate concentrations. Thus, in dogs with abnormal serum concentrations of cobalamin and/or folate, serum trypsin-like immunoreactivity (TLI) should be evaluated to rule out EPI as a secondary cause of small intestinal dysbiosis.

#### 7.3.4.4.3 Quantitative bacterial culture

Standard bacterial culture of small intestinal fluid, tissue, and/or feces is not useful to assess changes in the intestinal microbiota, as the majority of intestinal bacteria are strict anaerobes, requiring special growth media. Therefore, only a small fraction of the intestinal microbiota can be cultured. In a recent study, different fecal aliquots from healthy dogs and dogs with chronic diarrhea were submitted to three different veterinary reference laboratories for the evaluation of dysbiosis.[23] There was no agreement in the reported culture results between laboratories, and dysbiosis was more frequently reported in healthy dogs than in dogs with chronic diarrhea. Bacterial culture should only be used to test for specific pathogens such as *Salmonella*.

### 7.3.4.5 Treatment

#### 7.3.4.5.1 General guidelines

Because dysbiosis is often a component of intestinal disease, therapy addressing the underlying disease process is required for long-term resolution. Underlying factors predisposing dogs to dysbiosis (▶Tab. 7-5) should be corrected if they can be identified. For example, in most dogs with EPI, the microbiota returns to normal within a few weeks or months after initiation of pancreatic enzyme replacement therapy (▶Chap. 10.3.2). However, some patients may require additional antibiotic therapy.[12,24] In patients with CE, there are no markers that predict which treatment is best for an individual patient, and often a stepwise treatment trial is employed.[25]

Therapies include dietary modulation, prebiotics, probiotics, synbiotics, antimicrobials, or fecal microbiota transplantation (FMT). Each of these approaches uses a different mechanism to alter the intestinal microbiota, and treatments may need to be combined in chronic cases.[6]

**CLINICAL PEARLS**

While the altered bacterial population in the gastrointestinal tract of the patient is not optimal, the resident bacterial populations are stable and able to resist acute changes, such as those caused by temporary changes in the diet or a short course of antibiotics. Such interventions may be associated with a transient alteration in the intestinal microbiota and some degree of clinical improvement, but dysbiosis is likely to return after the withdrawal of short-term therapy. Therefore, long-term therapy is required in most cases to effectively modulate the intestinal microbiota.

#### 7.3.4.5.2 Dietary management

Various studies have shown that up to 70% of dogs with CE are food-responsive, and many of these dogs have intestinal dysbiosis.[25,26] Furthermore, remission of clinical signs was associated with normalization of the intestinal microbiome as well as bile acid metabolism in dogs receiving either a hydrolyzed[18] or novel protein diet.[27]

These diets are typically hypoallergenic and highly digestible, reducing undigested nutrients in the GI lumen, thereby reducing the nutrients available for uncontrolled proliferation of the intestinal microbiota. In most cases of food-responsive enteropathy, the dietary change alone is sufficient to achieve clinical remission, leading to gradual improvement of the dysbiosis over several months.[27] Based on the clinical response to dietary modulation, it appears prudent that dietary management should be continued long-term in patients with intestinal dysbiosis.

Other diets contain high amounts of prebiotics aimed at promoting the growth of beneficial bacteria in the gut and limiting the growth of more harmful species. These diets can be useful for treating large bowel diarrhea, but limited data is available how these diets affect the intestinal microbiota in patients with intestinal dysbiosis.[28] Some data would suggest that to be able to modulate intestinal microbiota, greater than 2% of the diet has to be provided in the form of a prebiotic.

#### 7.3.4.5.3 Antibiotics

Broad-spectrum antibiotics, such as tylosin or metronidazole, are often used for the treatment of intestinal dysbiosis. However, they are currently not recommended as the first line of treatment, as multiple studies have shown that the **majority of dogs with CE respond to dietary modulation**, and only approximately 10–16% of CE dogs are antibiotic-responsive.[26,29] Furthermore, while antibiotics can lead to initial improvement of clinical signs, they often relapse after treatment.[29]

The exact mechanism of how antibiotics improve clinical signs is not completely understood. They reduce the total bacterial load in the intestinal lumen, but if the underlying disease process is not resolved, bacteria will often regrow after therapy is discontinued, leading to a relapse of clinical signs. Furthermore, tylosin and metronidazole induce major shifts in the microbiota of the LI, which can last for months in some dogs.[16,20] Therefore, it has been proposed that antibiotics should be considered in animals after they have failed dietary and anti-inflammatory trials or in patients with signs of systemic inflammation.[30] Other clinicians prefer an antibiotic trial after a dietary trial but before using an anti-inflammatory/immunosuppressive trial.

A subset of dogs with CE that respond to no other treatment than antibiotics often requires long-term antibiotic administration. Often antibiotics can be tapered to the lowest effective dose. However, decreasing the dose to subtherapeutic levels may increase bacterial resistance. Some patients may require several days to weeks of therapy before responding.

Tylosin is a macrolide antibiotic that inhibits bacterial protein synthesis by binding to the 50S ribosomal subunit. It is speculated that tylosin also may exhibit immunomodulatory effects, but a mode of action has not yet been identified. Tylosin is very well tolerated. Several dosages of tylosin have been reported in the literature, underlining its broad therapeutic safety. Tylosin can be purchased as a powder for use in poultry and can be mixed directly into the food. Due to its broad dynamic and safety range, the dosage can be roughly estimated. For small patients, however, compounding the powder may be necessary. The most commonly used doses range between 15–25 mg/kg PO q12h. The initial treatment period should last at least 6 weeks unless adding tylosin into the treatment protocol does not lead to any improvement, in which case tylosin can be discontinued after 2 weeks. Some patients may have a recurrence after treatment is discontinued. Such patients should be further evaluated for any underlying cause of dysbiosis, but if one cannot be identified, long-term therapy can be initiated. After clinical signs have improved, a reduction to the lowest dose or frequency of administration needed to control clinical signs may be attempted.

#### 7.3.4.5.4 Probiotics

Empirical administration of probiotics may be considered as an ancillary treatment in dogs with CE. Probiotics are defined as live microorganisms, which when administered in adequate amounts, confer a health benefit to the host. The effects of probiotics are strain-specific. Therefore, every probiotic strain potentially has a different mechanism of action. In the USA, probiotics are not regulated and; therefore, there is currently no governing agency overseeing the label claims of probiotic products. Several studies have reported that the majority of commercially available probiotic products marketed for human or veterinary use lack proper product quality.[31] Therefore, many specialists currently recommend that only probiotic formulations from reputable manufacturers should be used, especially those formulations that have demonstrated a benefit in clinical studies.

Only a few commercially available formulations have been evaluated in clinical studies.

A high potency multi-strain probiotic (Visbiome Vet®, ExeGi Pharma, Rockville, MD, USA) used as an adjunct to prednisone therapy showed increased expression of tight junction proteins, suggesting improvement in intestinal barrier function in dogs with CE.[32] The same formulation also led to more rapid normalization of intestinal microbiota composition in dogs with acute hemorrhagic diarrhea syndrome.[33]

A yeast probiotic, *Saccharomyces boulardii*, led to an improved clinical activity index when used as an adjunct to standard therapy in dogs with CE.[37]

A formulation contacting *Enterococcus faecium* SF68 (Fortiflora®, Nestle Purina Petcare, St. Louis, MO, USA) lowered the percentage of shelter cats having diarrhea lasting longer than 2 days significantly.[34] A formulation containing multiple probiotic strains combined with a prebiotic (Proviable DC™, Nutramax Laboratories, Lancaster, South Carolina, USA) improved fecal scores in cats with chronic diarrhea,[35] and decreased the frequency of hyporexia and vomiting in healthy cats receiving the antibiotic clindamycin.[36]

Probiotics are generally considered safe for use in dogs and cats. Some animals may initially experience flatulence and/or a deterioration in stool quality for the first few days, especially when receiving high-dose multi-strain probiotics. In such cases, dose adjustment by reduction of the amount for the first few days is generally sufficient to stop these clinical signs. After that, the amount of the probiotic can be increased to the full dose.

#### 7.3.4.5.5 Fecal microbiota transplantation

Fecal microbiota transplantation (FMT) can help restore the normal microbiota and improve clinical signs. In small animal patients, FMT is an emerging mode of therapy, and only a few case series have been reported. The success appears to depend on the underlying cause of the dysbiosis. FMT has been shown to improve fecal scores (▶Chap. 1.1) in patients with acute diarrhea[17] and when used as an adjunct to treatment to standard antimicrobial therapy in puppies with parvovirus infection,[38] and in case reports of young dogs with chronic diarrhea due to confirmed *C. difficile* infection.[38,39]

In dogs with CE, dysbiosis is often a secondary condition due to intestinal inflammation and structural damage. Recurrence of dysbiosis and clinical signs will occur as long as the underlying pathology is still present. Therefore, FMT has a variable success rate in patients with CE. Anecdotal reports suggest that many dogs with CE will have improvement in fecal scores within 2–3 days, but often a few weeks later, diarrhea will relapse. Therefore in these patients, dietary and anti-inflammatory treatment of the underlying disease process is required (see above), and FMT can be considered as an adjunct treatment for patients with suboptimal response to standard therapy.[39]

#### 7.3.4.5.6 Cobalamin supplementation

Dogs with dysbiosis may be cobalamin (vitamin $B_{12}$) deficient, and parenteral or oral supplementation of cobalamin is indicated.

The typical dose for cobalamin supplementation in cats is 250 µg per dose.

In dogs, the dose for cobalamin supplementation is 500 µg in small dogs (5–15 kg) and 500–1,200 µg in dogs >15 kg body weight, roughly dependent on body weight.

Cyanocobalamin is used most frequently, but hydroxocobalamin or methylcobalamin can also be used. Cobalamin can be administered by subcutaneous injection with one dose given weekly for 6 weeks and one more dose a month later. Serum cobalamin concentration should be re-evaluated a month after the last dose, and if the serum cobalamin concentration is in the lower part of the reference interval, supplementation should be continued. For oral supplementation, cobalamin should be administered daily for a total of 12 weeks, and serum cobalamin concentration should be rechecked 2–3 weeks after finishing supplementation.

### 7.3.4.6 Prognosis

The prognosis for patients with dysbiosis is excellent if the underlying cause can be effectively treated. However, it should be noted that an underlying cause can rarely be identified in dogs with dysbiosis.

**KEY FACTS**

- The intestinal microbiome is a metabolic organ influencing host health.
- Dysbiosis is an early marker of an abnormal gut environment, and treatment of the underlying disease is required for long-term resolution.
- Fecal dysbiosis can be assessed using a molecular-based Dysbiosis Index.
- Serum cobalamin concentration may be decreased, and serum folate concentration may be increased in patients with small intestinal dysbiosis. If serum concentrations of both vitamins are altered, this is highly suggestive of small intestinal dysbiosis.
- Primary intestinal dysbiosis can be treated using prebiotics, probiotics, synbiotics, antibiotics, or fecal microbiota transplantation.
- Dietary modulation is clinically effective with minimal side effects and should be the first treatment approach to dysbiosis associated with chronic enteropathies.

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
svg.to/9842-07-03-04



## 7.3.5 Non-obstructive motility disorders

Frédéric Gaschen

Dysautonomia is a primary disorder of gastrointestinal (GI) motility and a rare disease with geographically limited prevalence caused by idiopathic degeneration of autonomic ganglia in cats and dogs. Gastrointestinal signs only represent a part of the clinical picture.

Gastrointestinal signs of dysautonomia include vomiting, diarrhea, constipation, tenesmus, and regurgitation. The mortality rate is about 90%.

Regurgitation and constipation appear to be the most frequent gastrointestinal signs of dysautonomia. The mortality rate is about 70%.

Secondary disorders of GI motility include postoperative ileus (POI) and critical illness-related motility disorders. While the return of appetite following abdominal surgery is usually rapid, postoperative GI motility was shown to be decreased in dogs.[1,2,3] Clinical signs include prolonged anorexia, nausea, active or passive vomiting/regurgitation, cranial abdominal discomfort, abdominal distension, and a bloated abdomen. Intestinal sounds are usually absent. In experimental studies, epidural injection of morphine,[4] and laparoscopic surgery (vs. laparotomy) were shown to shorten the duration of POI in dogs.[5,6] Moreover, enteral supplementation of glutamine[7] and administration of GI prokinetics (metoclopramide[3] and motilin-analogues[8,9]) were helpful in the treatment of POI.

In contrast to the situation in human ICU patients, there is no data documenting the existence of critical illness-related motility disorders in dogs and cats. However, small animal clinicians commonly manage paralytic ileus and delayed gastric emptying in critically ill dogs and cats with diseases such as severe acute pancreatitis, gastroenteritis, or peritonitis (▶ Chap. 6.3.2). Clinical signs are similar to those observed in POI, in addition to those of the primary underlying disease. Typically, abdominal radiographs show moderately distended bowel loops filled with gas and liquid content, and abdominal ultrasound reveals distended and hypomotile stomach and intestine. The presence of POI or critical illness-related motility disorders may increase morbidity and mortality and prolong the duration of hospitalization.

Management of POI and critical illness-related motility disorders relies on the following:

1. Treatment of any underlying disease
2. Analgesia as required, with preference given to a lidocaine constant-rate infusion (CRI) over opioids
3. Feeding or tube feeding (e.g., nasoesophageal tube) an easily digestible diet
4. Judicious use of gastric prokinetics, such as metoclopramide (1–2 mg/kg/24h IV as a CRI) alone or in combination with erythromycin (0.5–1 mg/kg IV or PO q8h) or azithromycin (2 mg/kg IV or PO q8h in dogs, 3.5 mg/kg PO q24h in cats).

**References**

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## 7.3.6 Intestinal obstruction

### 7.3.6.1 Intestinal foreign bodies

Melanie Werner, Stefan Unterer

Foreign bodies are the most common cause of intestinal obstructions in dogs and cats. In dogs, solid inorganic foreign bodies are common.

Linear foreign bodies account for almost half (44%) of the cases in cats.[1] Trichobezoars can cause partial or complete intestinal obstructions.

Solid foreign bodies typically lodge in the small intestine. Once they pass the ileocecocolic valve, there is no predilection site for an obstruction. Linear foreign bodies usually do not cause a mechanical blockage but rather lead to gathering and pleating of the intestine around the object (e.g., string), which alters intestinal motility, mucosal fluid secretion, and intestinal wall integrity. Increased pressure on the intestinal mucosa results in impaired lymphatic and blood flow and intestinal wall edema, leading to intestinal ischemia and, ultimately, necrosis and perforation with septic peritonitis. Typical clinical signs include anorexia, abdominal pain, and vomiting. In partial obstruction, clinical signs are less severe. The occurrence of clinical signs after ingestion of the foreign body varies with the site of occlusion. Diarrhea can be seen in chronic partial obstruction.

#### 7.3.6.1.1 Diagnosis

Physical examination findings are non-specific unless the foreign body can be palpated.

Examining the oral cavity (especially the base of the tongue) for linear foreign bodies is crucial.

Laboratory findings include evidence of hemoconcentration, neutrophilia with left shift or neutropenia, hypoglycemia, hypoproteinemia, prerenal azotemia, and hyperlactatemia. Hyperchloremic metabolic alkalosis is detected in about half of the cases.[2] Diagnostic imaging, including survey abdominal radiographs, contrast studies, and ultrasonography, can confirm the diagnosis. In plain radiographs, dilated intestinal loops proximal to the occlusion site (▶Fig. 7-16) may be indicative.[3]

#### 7.3.6.1.2 Treatment and prognosis

Some foreign bodies will pass into the colon. However, most of the time, prompt surgical intervention (enterotomy or even enterectomy) is indicated. Many patients need preoperative stabilization (restoration of hydration, analgesia, correction of electrolyte changes, antibiotics). Early postoperative enteral feeding is associated with a better prognosis and increased anastomotic strength.[4,5]

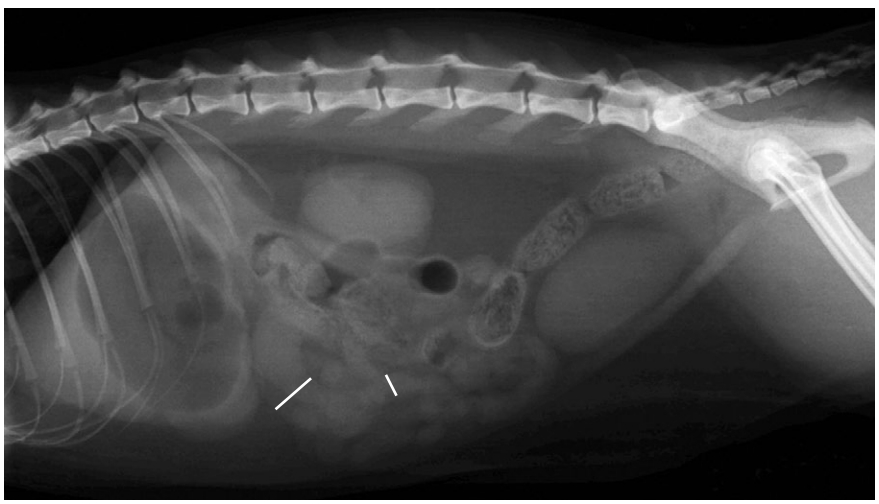


**Fig. 7-16** Lateral abdominal radiograph of a cat with a small intestinal foreign body showing a distended small intestinal loop proximal (**large bar**) in contrast to normal-sized bowel loops distal to the obstruction (**small bar**)

Note: Observation of distended fluid-filled small intestinal loops in combination with empty intestinal segments on diagnostic imaging always indicates an intestinal obstruction. This also applies to a single small intestinal loop diameter of >12 mm in cats, and an intestinal width that exceeds 1.6 times the height of the fifth lumbar vertebral body at its narrowest point in dogs.

### 7.3.6.2 Intestinal intussusception

Melanie Werner, Stefan Unterer

An intestinal intussusception occurs when one (usually proximal) segment of the intestine and associated mesentery (= the intussusceptum) telescope into the lumen of the adjoining (usually distal) segment (= the intussuscipiens). This is a common cause of intestinal obstruction in young animals and infrequently occurs in adult dogs and cats. Predisposing factors include acute intestinal infections (e.g., endoparasites, viral enteritides such as parvovirus enteritis,[6] bacterial infections such as leptospirosis[7]), mechanical or structural lesions (e.g., intestinal foreign bodies or masses), prior intestinal surgery, and acute diarrheic events. In young animals, intestinal intussusceptions can also be idiopathic and are proposed to be due to abnormal intestinal muscular coordination of the not yet fully developed enteric nervous system. In cats, male Maine coons are overrepresented.[8] Intussusceptions can occur in the small or large intestine, but the ileocecocolic junction is most frequently affected. Intussusceptions in this region are classified as:

1. Cecocolic
2. Ileocolic (most common type)
3. Ileocecal (rare)

Intestinal intussusception leads to intestinal obstruction and distension of the intestinal segment proximal to it. The mesentery, including blood and lymph vessels, is included in the intussusceptum. Thus, vascular compromise can occur, typically leading to focal edema and intramural hemorrhage, which result in ischemia and necrosis of the affected intestinal segment.

#### 7.3.6.2.1 Clinical presentation

Affected animals usually present with acute clinical signs. However, subacute or chronic cases also exist, with clinical signs present for days to weeks. Clinical signs include vomiting, progressive hypo- to anorexia, abdominal pain, and mucoid hemorrhagic diarrhea. Intestinal intussusception is suspected if a firm tubular structure is noted during abdominal palpation, particularly in a young animal with a prior history of acute diarrhea.

#### 7.3.6.2.2 Diagnosis

Abdominal radiographs and, if needed, contrast studies may be indicative but are often not diagnostic. Abdominal ultrasonography is the diagnostic method of choice. A target-like lesion consisting of five or more contiguous hyper- and hypoechoic concentric bands or rings in a cross-section is the pathognomonic ultrasonographic finding[9] (▶ Fig. 7-17). In the longitudinal view, contiguous hyper- and hypoechoic parallel lines are seen. Intestinal wall edema may obscure some of these layers resulting in only two or three thick, complete concentric rings to be detected. A complicating perforation or local bacterial translocation may present evidence of peristructural peritonitis and fluid accumulation.

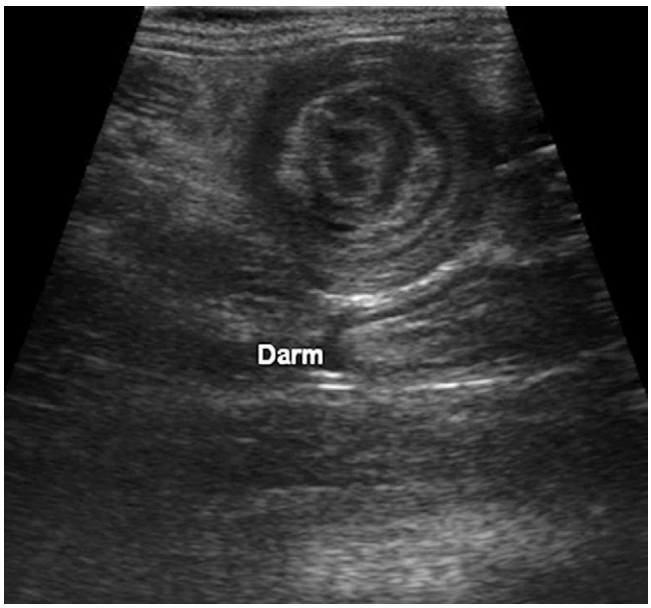



**Fig. 7-17** Characteristic multilayered appearance (contiguous hyper- and hypoechoic concentric rings) of an intestinal intussusception on abdominal ultrasound (transverse view)

In rare cases of ileocolic intussusception, the intussusception may be visible at the anus due to the prolapse of this segment. Thus, differentiating an ileocolic intussusception from rectal prolapse is crucial. Passing a blunt probe between the protruding segment and the anal sphincter can help distinguish both conditions. With an intussusception, the probe can be passed cranially to the level of the pubis without reaching a fornix.

#### 7.3.6.2.3 Treatment and prognosis

Surgical intervention is the treatment of choice. Preoperative correction of dehydration, electrolyte abnormalities, and acid-base imbalances is indicated. Surgery consists of either manual repositioning or resection of the affected area, whereby a major goal is to preserve the ileocecocolic region to avoid coloileal reflux of feces. Short bowel syndrome may result if a long segment of the small intestine needs to be resected (▶ Chap. 7.3.7).

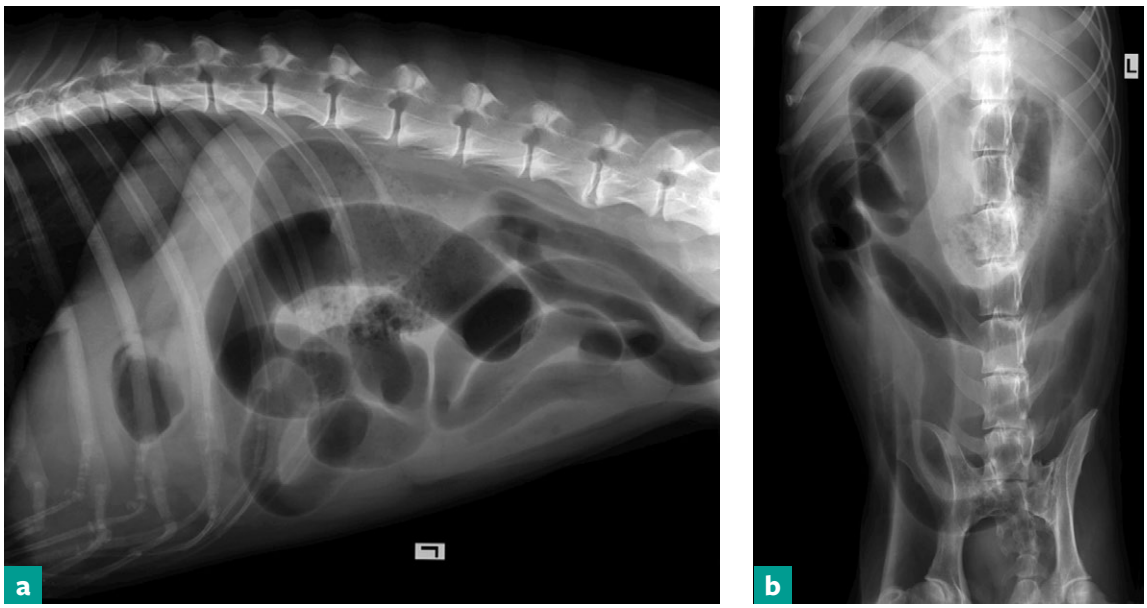



**Fig. 7-18** Abdominal radiographs of a 6-year-old German shepherd dog with acute onset of vomiting, lethargy, and abdominal pain
Marked dilatation of intestinal loops is seen, with the majority of these containing gas and only some containing fecal material and fluid. The cecum is identified on the left side, whereas the descending colon cannot be recognized in its anatomic position. Moderate loss of peritoneal detail is also noted (**a** left lateral and **b** ventrodorsal projection). Exploratory laparotomy revealed a 360° mesenteric volvulus. (Courtesy of Dr. Francesca del Chicca, Vetsuisse Faculty Zurich, Switzerland.)

One study documented a 35% postoperative complication rate with surgical intervention in dogs.[10] Most common were diarrhea, regurgitation, and septic peritonitis, with life-threatening complications in 14% of the cases. The mortality rate was 6%, and dehiscence and recurrent intestinal obstruction occurred in 5% and 3% of the cases, respectively.[10] Postsurgical early enteral feeding is recommended and carries a better prognosis. Surgical enteroplication can prevent recurrent intestinal intussusceptions in dogs.[11]

In contrast to dogs, one study in cats showed enteroplication leading to significant complications and intussusception to recur in 20% of cats despite enteroplication.[8]

### 7.3.6.3 Intestinal torsion

Anna-Lena Ziese, Stefan Unterer

Intestinal torsions can occur as a complete or partial rotation of the intestine around either its own or the mesenteric axis (mesenteric volvulus) and are uncommon disorders in dogs and cats.[12,13]

#### 7.3.6.3.1 Etiology and clinical presentation

While the exact cause for intestinal torsions remains unknown, concurrent gastric dilatation-volvulus (▶Chap. 6.3.3), treatment of intestinal worms, vigorous exercise, closed abdominal trauma, ileocolic carcinoma, lymphocytic-plasmacytic enteritis, exocrine pancreatic insufficiency, gastrointestinal foreign bodies, intussusception, and parvovirus infection have all been associated with intestinal torsion.[12] Large breed dogs appear to be predisposed, with German shepherd dogs being overrepresented.[14]

Torsion of the intestine results in vascular compromise and ischemia of the intestinal tissue. Complete vascular obstruction causes intestinal infarction and subsequent necrosis, with a breakdown of the intestinal barrier leading to the release of bacteria and toxins. With mesenteric volvulus, the obstruction of the cranial mesenteric artery impacts the distal duodenum, jejunum, ileum, cecum, ascending colon, and proximal descending colon.[15] Clinical signs are acute or peracute and include abdominal pain, abdominal distention, haematochezia, retching, and signs of shock.[16] Intestinal torsion is diagnosed based on clinical signs and abdominal radiographs (▶Fig. 7-18) showing severely gas-distended small intestinal loops in a parallel arrangement.[12] Radiographs are mandatory for every patient with signs of an acute abdomen.

#### 7.3.6.3.2 Treatment and prognosis

Patients with suspected intestinal torsion require treatment of shock and immediate surgical intervention. With successful surgery, the most common complication is reperfusion injury with the release of free radicals causing microvascular damage. In general, the prognosis of intestinal torsion is poor to grave due to hypovolemic, septic, and/or toxic shock, and perioperative euthanasia is often considered. The survival rate is more favorable with partial torsions and earlier aggressive treatment and surgical intervention.[17]

**References**

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## 7.3.7 Short bowel syndrome

Anna-Lena Ziese, Stefan Unterer

Short bowel syndrome (SBS) is an overarching term for clinical signs resulting from malabsorption of dietary nutrients due to decreased small intestinal length. Most cases of SBS in dogs and cats result from surgical resection of more than two-thirds of the small intestine, although congenital SBS is also described.[1] SBS can be transient because extensive intestinal resection leads to intestinal adaption with histologic evidence of increased mucosal surface area.[2] In the postoperative period, total parenteral nutrition may be necessary and enteral nutrition should be initiated (▶Chap. 3.2.1) as soon as possible.[3] The accelerated intestinal transit time and reduced absorptive intestinal surface area result in reduced nutrient absorption.

### 7.3.7.1 Clinical presentation and diagnosis

Clinical signs include watery diarrhea, steatorrhea, polyphagia, and weight loss, and clinicopathological findings may include electrolyte imbalances and hypovitaminoses.[4] However, these vary depending on the extent and segment of the intestine removed. Resection of the ileum results in decreased bile acid and cobalamin absorption. If the ileocolic valve, which acts as a physical barrier between the small intestine and colon, is resected, small intestinal bacterial overgrowth and dysbiosis (▶Chap. 7.3.4) can develop.[5] Impaired gastrointestinal hormone metabolism can result in hypergastrinemia and gastric hyperacidity. Even with a known history of intestinal resection, diagnosis of SBS requires ruling out other causes of chronic diarrhea.

### 7.3.7.2 Treatment and prognosis

Treatment of SBS is individual in each patient and aims to provide nutrient supply, control intestinal motility, control bile acid malabsorption, decrease gastric hyperacidity, and prevent vitamin deficiency states. A highly digestible low-fat diet with appropriate mineral supplementation should be fed in small amounts multiple times per day (▶Chap. 3.2.1.2). Patients with ileal resection require vitamin $B_{12}$ supplementation (0.25–1 mg/animal PO q24h or 25–50 µg/kg SC cyanocobalamin q7 days), and some animals benefit from fat-soluble vitamin (A, D, E, and K) supplementation. Also, fermentable bile acid-binding fibers (e.g., psyllium) and/or bile acid-binding drugs (e.g., cholestyramine 100–300 mg/kg PO q12h) are recommended.[3] To decrease intestinal motility and prolong the intestinal transit time, antidiarrheic drugs (e.g., loperamide 0.1 mg/kg PO q6–8h) can be considered. If the ileocolic valve has been resected, antibiotic treatment (e.g., metronidazole 10 mg/kg PO q12h or tylosin 7–15 mg/kg PO q8–12h) is recommended intermittently, as needed. Hypergastrinemia can be treated with $H_2$-receptor antagonists (e.g., famotidine 0.5–1 mg/kg PO q12–24h; cimetidine 5–10 mg/kg SC, IM, or IV q6–8h) or proton pump inhibitors (e.g., omeprazole 1 mg/kg PO q12h).[6] Octreotide (10–20 µg/dog SC q6–8h), a long-acting analog of somatostatin, inhibits intestinal motility and reduces gastrointestinal secretions, and thus may be beneficial in some cases with refractory diarrhea. The prognosis of SBS varies and depends on the remaining intestinal length, ability for intestinal adaption, and response to treatment.

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
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## 7.3.8 Protein-losing enteropathy

Romy M. Heilmann

### 7.3.8.1 Introduction

Protein-losing enteropathy (PLE) is a syndrome that occurs with several disease entities causing leakage of protein-rich lymph into the intestinal lumen (▶Tab. 7-6).[1,2] Enteric protein loss is less common in cats than in dogs and mostly associated with lymphoma.[3] The diagnostic approach to patients with PLE should be based on disease severity and chronicity (▶Fig. 7-19). This algorithm includes evaluating the patient for etiologies of protein catabolism (hepatic insufficiency; ▶Chap. 9.4) or other etiologies for protein loss (protein-losing nephropathy, PLN), which can also be present concurrently with PLE.

### 7.3.8.2 Clinical presentation

Common clinical signs in patients with PLE are weight loss (mainly loss of lean muscle mass; ▶Fig. 7-20), reduced appetite (hypo- or dysrexia) or anorexia, diarrhea, and/or vomiting. Clinical disease activity indices and an undernutrition score can help to assess the severity of these signs.[4] Abdominal pain or distension, tachy- or dyspnea, and decreased or absent respiratory sounds on thoracic auscultation may suggest uni- or bicavitary effusion. Peripheral edema may develop. Neurologic signs (e.g., muscle tremors, tetany, seizures) due to mineral (i.e., $Ca^{2+}$, $Mg^{2+}$) deficiencies occur infrequently. Few dogs with PLE are asymptomatic.

#### 7.3.8.2.1 Diagnostic evaluation

The diagnostic workup of patients suspected of having a disorder that causes PLE requires a sequential approach, including laboratory tests, diagnostic imaging, and often more invasive diagnostics.

#### 7.3.8.2.2 Routine laboratory parameters

The minimum database for dogs with suspected PLE includes hematology, clinical chemistry, urinalysis, and fecal parasitology.[5] These tests help to assess the overall condition of the patient and to rule out other etiologies but are often not specific for PLE or the underlying cause. Mild non-regenerative normocytic/-chromic anemia is a common finding. A non-regenerative microcytic normo- or hypochromic anemia or decreased reticulocyte hemoglobin content suggests iron deficiency. Concurrent mild reactive thrombocytosis and increased BUN concentrations can signal a chronic gastrointestinal bleed. Mild leukocytosis with neutrophilia reflects intestinal inflammation or a stress leukogram. Lymphopenia can be part of the stress leukogram or result from lymphatic leakage.[6] Lack of a stress leukogram (i.e., lack of lymphopenia and/or eosinopenia) may indicate hypoadrenocorticism (HOC).[7] Eosinophilia occurs with endoparasitism, eosinophilic or fungal enteritis, or paraneoplastic effects (e.g., lymphoma). A normal hematology panel does not rule out a significant gastrointestinal disease process.

**Tab. 7-6** Etiologies of protein-losing enteropathy

| | |
|---|---|
| **Primary lymphatic disease** | Primary (idiopathic) intestinal lymphangiectasia<br>• Breed predispositions: Yorkshire terrier, Rottweiler, Chinese shar-pei, Maltese, basenji, German shepherd dog, Norwegian lundehund, soft-coated wheaten terrier |
| | Lipogranulomatous lymphangitis |
| **Mucosal disease causing lymphatic vascular obstruction** | Chronic inflammatory enteropathy (idiopathic inflammatory bowel disease) |
| | Intestinal neoplasia (alimentary lymphoma) |
| | Intestinal crypt disease |
| | Infections associated with enteric protein loss<br>• Viral: Parvovirus<br>• Parasitic: hookworms, *Strongyloides stercoralis, Heterobilharzia americana*<br>• Fungal or algal: *Histoplasma capsulatum, Pythium insidiosum*<br>• Bacterial: *Salmonella* spp., *Campylobacter* spp. |
| **Other diseases** | • Hypoadrenocorticism (Addison's disease)<br>• Right-sided congestive heart failure<br>• Non-steroidal anti-inflammatory drug-induced enteropathy |

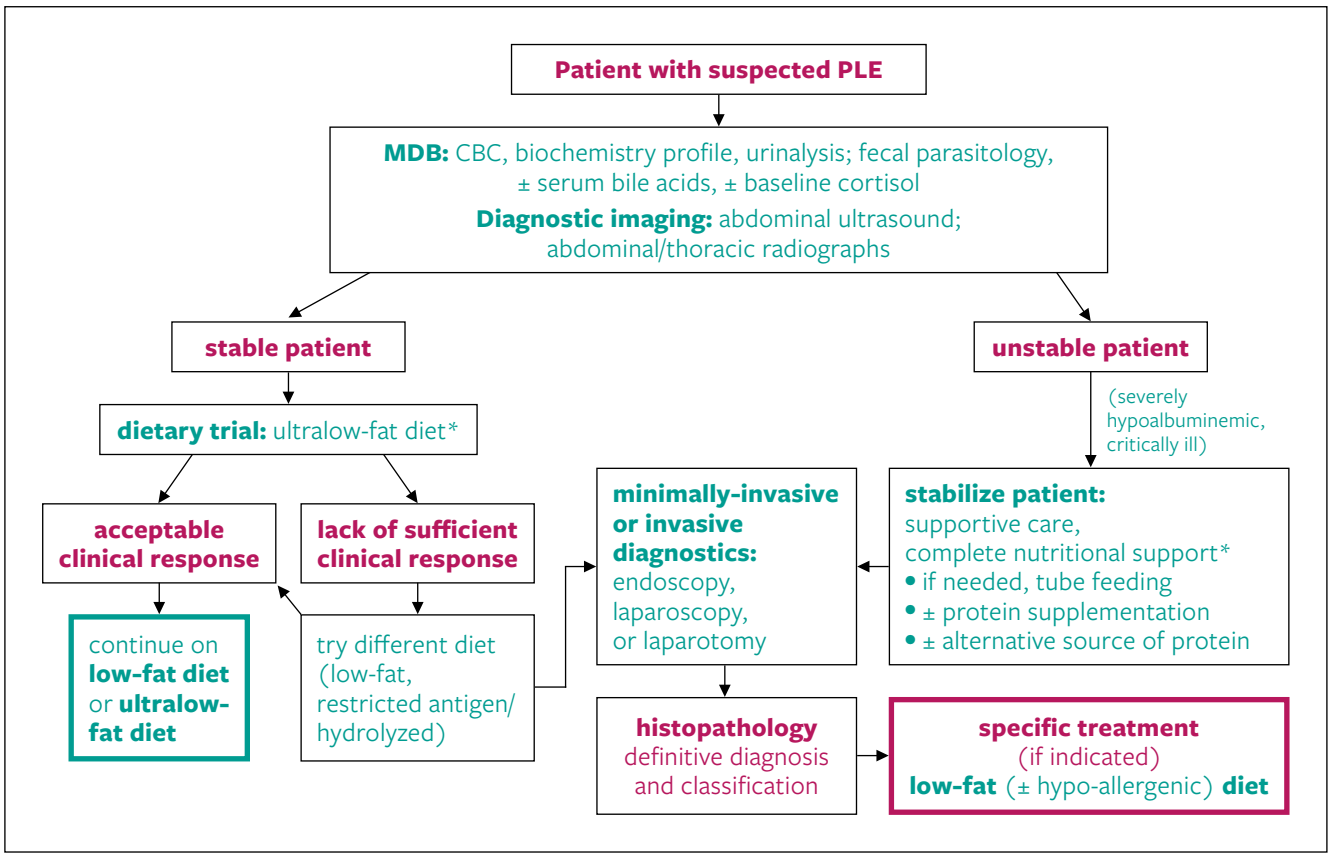



**Fig. 7-19** Approach to diagnostic evaluation and treatment in patients with suspected protein-losing enteropathy

Patients responding to dietary intervention (**turquoise frame**) are classified as food-responsive PLE. Some patients will require immunosuppressive medication (**red frame**) or may even be refractory to treatment.

***** commercial or home-prepared diet; **PLE** = protein-losing enteropathy; **MDB** = minimum database; **CBC** = complete blood cell count



**Fig. 7-20** Nine-year-old mixed breed dog with protein-losing enteropathy (PLE)

Note the significant muscle wasting (temporalis muscle), abdominal distension (marked ascites resulting from severe hypoalbuminemia), and peripheral edema (ventrum) caused by severe PLE.

(Courtesy of Carol and John Knight, Whitney, TX, USA.)

Hypoalbuminemia in dogs with PLE has prognostic relevance,[4,8] and important differentials include hepatic insufficiency and PLN. Hypocalcemia and hypomagnesemia (measured as ionized plasma concentrations)[9] and hypocholesterolemia can occur with PLE. Fasting hypercholesterolemia might indicate PLN. Hypercalcemia is a possible paraneoplastic syndrome (negative prognostic indicator) with PLE due to intestinal T-cell lymphoma,[10] differentials for this finding include HOC and granulomatous disease. Increased serum liver enzyme activities can reflect reactive hepatopathy. Elevated serum bile acids concentrations and decreased liver synthetic substance concentrations indicate hepatocellular dysfunction.[5] Hypokalemia and -natremia can result from vomiting or diarrhea; hyperkalemia and hyponatremia suggest typical HOC. Metabolic acidosis is the most common acid-base disturbance in PLE patients.

Urinalysis with a urine sediment examination (± bacterial culture) and urine protein-to-creatinine ratio (after exclusion of a urinary tract infection) can diagnose or rule out PLN.

Routine fecal parasitology (direct smear/fecal wet mount, fecal flotation) can identify endoparasite infections (▶Tab. 7-6) as a cause of PLE,[5] and analysis of three fecal samples collected within 5 days improves the diagnostic accuracy. *Giardia* spp. (detected by fecal flotation, antigen ELISA, or immunofluorescence assay) are an unlikely cause but can complicate PLE. Fecal bacteriology should be reserved for the diagnosis of specific enteropathogens and is rarely indicated (▶Chap. 7.3.1.2). Adherent-invasive *E. coli* causing granulomatous colitis can lead to hypoalbuminemia (▶Chap. 8.3.1.2). In endemic areas, infection with *H. americana* or *H. capsulatum* (▶Chap. 7.3.1.5.2) can also cause PLE.

Serum baseline cortisol concentrations >2 µg/dL or ACTH-stimulated cortisol concentrations >6 µg/dL exclude a diagnosis of HOC, which can mimic PLE.[5] Serum-specific pancreatic lipase concentration can assess patients with suspected or confirmed PLE for pancreatitis and trypsin-like immunoreactivity concentration to diagnose or rule out exocrine pancreatic insufficiency. Serum concentrations of cobalamin (vitamin $B_{12}$) and folate (vitamin $B_9$) as markers of intestinal absorptive capacity have diagnostic and therapeutic value. Hypocobalaminemia affects 22–75% of dogs with PLE.[2,11] Suboptimal serum cobalamin states require supplementation to replete body cobalamin stores and aid with mucosal regeneration. Paired methylmalonic acidemia due to a lack of intracellular cobalamin is a superior test for cobalamin deficiency,[11] but is currently not widely available in veterinary medicine. Hypofolatemia is detected in ~14% of dogs with chronic enteropathy;[11] and if marked, warrants oral supplementation. Concurrent hyperfolatemia and hypocobalaminemia suggest intestinal dysbiosis (▶Chap. 1.3.2).

Increased fecal alpha$_1$-proteinase inhibitor ($\alpha_1$PI) concentrations (mean of ≥19.0 µg/g in samples collected from 3 onsecutive days)[12] signal an enteric loss of protein. This test can detect PLE before clinical or clinicopathologic evidence of the disease develops[12] and with concurrent hepatopathy or PLN. A 3-day mean fecal $\alpha_1$PI concentration of <4.0 µg/g excludes a diagnosis of PLE, and the serum-to-fecal $\alpha_1$PI ratio improves the test accuracy for PLE in hypoalbuminemic dogs (if naïve to corticosteroids).[12] However, careful interpretation of a positive result is advised in puppies as fecal $\alpha_1$PI concentrations are higher in puppies than in adults.[11]

#### 7.3.8.2.3 Other diagnostic tests

Analysis of peritoneal or pleural fluid from a diagnostic abdomino- or thoracocentesis includes routine macroscopic and laboratory assessment (i.e., specific gravity, protein concentration, total and nucleated cell counts), cytology, and in some cases also, bacterial culture. Cavitary effusions in patients with PLE are typically transudates.

Routine coagulation tests (i.e., clotting times and concentrations of fibrinogen, antithrombin, fibrin degradation products, and D-dimers) are not useful unless a coagulopathy or thromboembolic complication is suspected.[13] Documenting a PLE-associated hypercoagulability requires thromboelastography.[14] Serum 25-hydroxyvitamin D levels can detect hypovitaminosis D.[15]

Endemic prevalences dictate specific infectious disease testing (e.g., *H. capsulatum, P. insidiosum*) in patients with suspected or diagnosed PLE.

Food-specific serum or salivary immunoglobulin titers are not predictive of food responsiveness in dogs with PLE.

The serum concentration of C-reactive protein (CRP), a non-specific inflammatory marker, is often increased in dogs with PLE, particularly if requiring immunomodulatory treatment.[16] Fecal calprotectin is a more specific marker of intestinal inflammation,[11] but similar to CRP, adds little value to current diagnostic algorithms for PLE.

#### 7.3.8.2.4 Diagnostic imaging

Routine diagnostic imaging is essential to assess the overall health of the patient and rule out other etiologies that can mimic PLE. Abdominal radiographs are not specific for diagnosing PLE but can show a loss of serosal detail with abdominal effusion or reveal other differentials (e.g., intestinal foreign body). Thoracic radiographs should be performed if pleural effusion, lymphoma, or pulmonary thromboembolism are suspected.

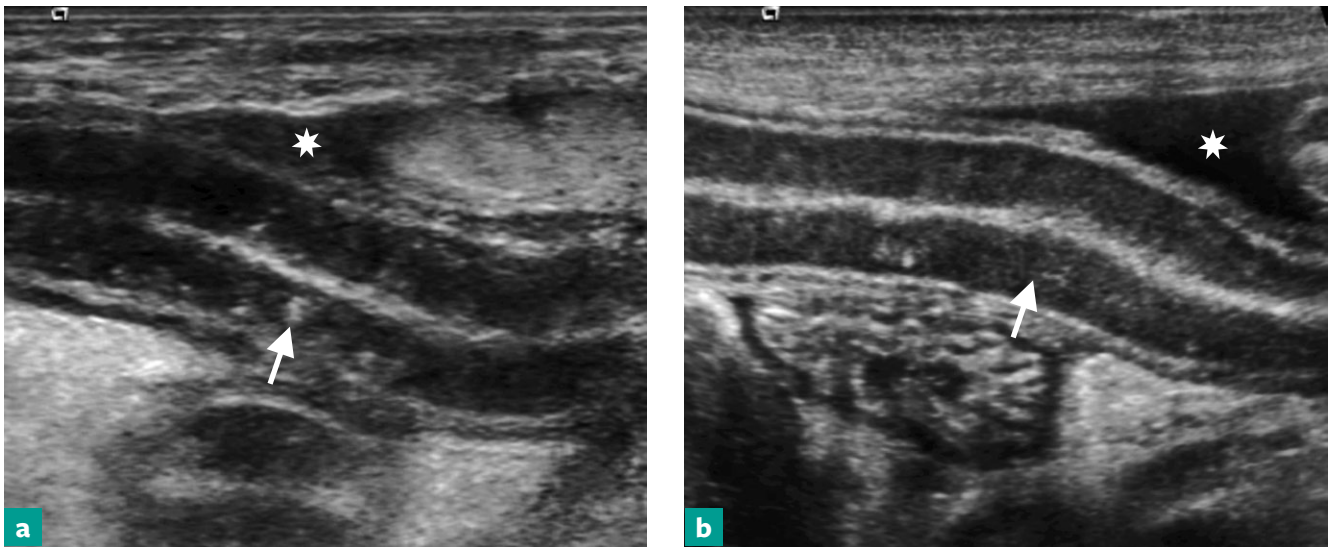



**Fig. 7-21** Ultrasonographic appearance of the intestinal wall in a dog with protein-losing enteropathy

Note the increased intestinal wall thickness with (**a**) hyperechoic mucosal stipples (**arrow**), free intra-abdominal fluid (peritoneal effusion; **asterisk**), and (**b**) hyperechoic mucosal striations (**arrow**).

Abdominal ultrasonography is more sensitive and specific to detect lesions of PLE (▶Fig. 7-21).[17] This modality can assess gastrointestinal wall thickness and layering, evidence of gastrointestinal or extra-alimentary masses, intra-abdominal lymphadenopathy, or peritoneal effusion. Ultrasonography allows for evaluating echotexture, structure, and size of other intra-abdominal organs (e.g., liver, biliary tract, pancreas). Peritoneal fluid, intra-abdominal masses, or altered lymph nodes can be aspirated using ultrasound guidance.

#### 7.3.8.2.5 Histopathology

Endoscopy, with the collection of tissue biopsies, allows for a definitive diagnosis in many patients. This procedure requires a stable patient and carries a lower procedural risk than a surgical approach (i.e., laparoscopy or -tomy) needed to evaluate lesions outside endoscopic reach (e.g., intestinal lipogranulomatous lymphangitis[18]; ▶Fig. 7-22). Both esophagogastroduodenoscopy and ileocolonoscopy should be performed, as lesions of PLE may be localized to one segment (▶Fig. 7-23). The sensitivity and specificity of endoscopy to detect lymphangiectasia are only moderate.[19] Lesions outside endoscopic reach can also be detected by video capsule endoscopy (▶Chap. 1.5).

Endoscopic sampling for histopathology requires a sufficient number of adequate biopsies to detect or exclude lesions of PLE reliably.[20] Typical changes include dilated lacteals, crypt abscesses, and variable degrees of inflammation (▶Fig. 7-24). Distinguishing inflammation and granuloma formation due to lymphatic leakage (primary lymphangiectasia) from an inflammatory infiltrate causing blockade to lymphatics (secondary lymphangiectasia) can be challenging.[21] Molecular diagnostics (immunohistochemistry, PCR for antigen-receptor rearrangements) may be needed to characterize the disease process further.

### 7.3.8.3 Treatment

Life-long dietary management with a high-protein (25–30% on a caloric basis), low-fat (≤20% fat on a caloric basis; i.e., ≤20g fat per 1000 kcal), possibly with supplemental medium-chain triglycerides diet is the cornerstone of PLE treatment.[22–24] This strategy will break the cycle of intestinal protein leakage and catabolism. Sequential implementation of treatment is recommended (▶Fig. 7-19). Clinical, clinicopathologic, and histologic variables are unreliable for predicting treatment responses.[2,5,20]

#### 7.3.8.3.1 Nutritional management

An easily digestible ultra-low fat (≤10g fat per 1000 kcal) diet (▶Tab. 7-7) or a homemade ration (e.g., tilapia and rice or low-fat chicken, rice, cottage cheese, white/sweet potato) can help to restore a positive protein balance.[2,23] The dietary choice will depend on the patient's appetite and preferences. A board-certified nutritionist should be consulted if a homemade diet is considered for long-term feeding. Response rates with the dietary management of non-infec-

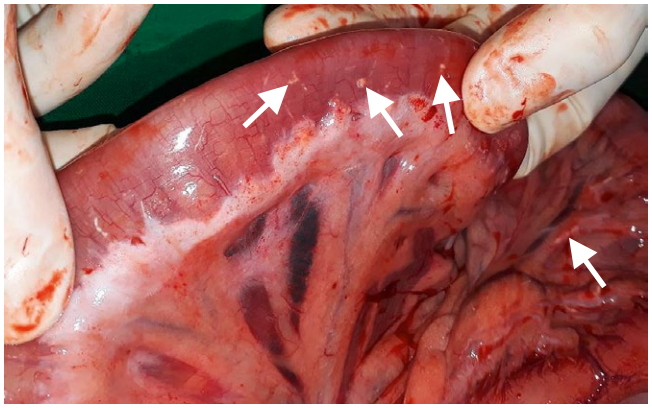


**Fig. 7-22** Focal intestinal lipogranulomatous lymphangitis (FLL) in a 6-year-old Maltese with protein-losing enteropathy

A variant of intestinal lymphangiectasia, FLL is characterized by disseminated nodular lesions (lipogranulomas) close to serosal and mesenteric lymphatics (**arrows**). These lesions result from an inflammatory response to chronic leakage of lymph and obstruction of lymphatics. Diagnosis of FLL and differentiation from neoplasia requires surgical biopsy.

(Courtesy of Dr. Cora Siebenaller, Marienberg, Germany.)

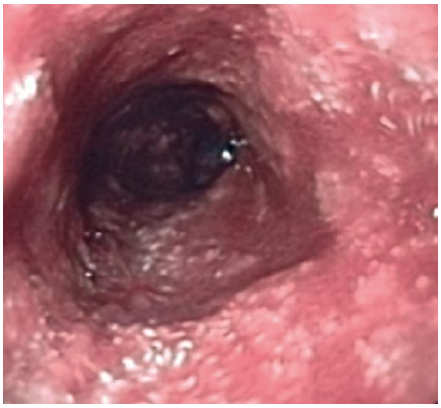


**Fig. 7-23** Endoscopic view of the duodenum in a dog with protein-losing enteropathy

Typical findings are white pinpoint foci reflecting dilated lacteals. Visibility of lymphatics was enhanced by a small amount of cream given orally 12 hours before endoscopy.

(Reprinted from Erdmann & Heilmann [2017][5] with permission from Thieme, Stuttgart, Germany.)

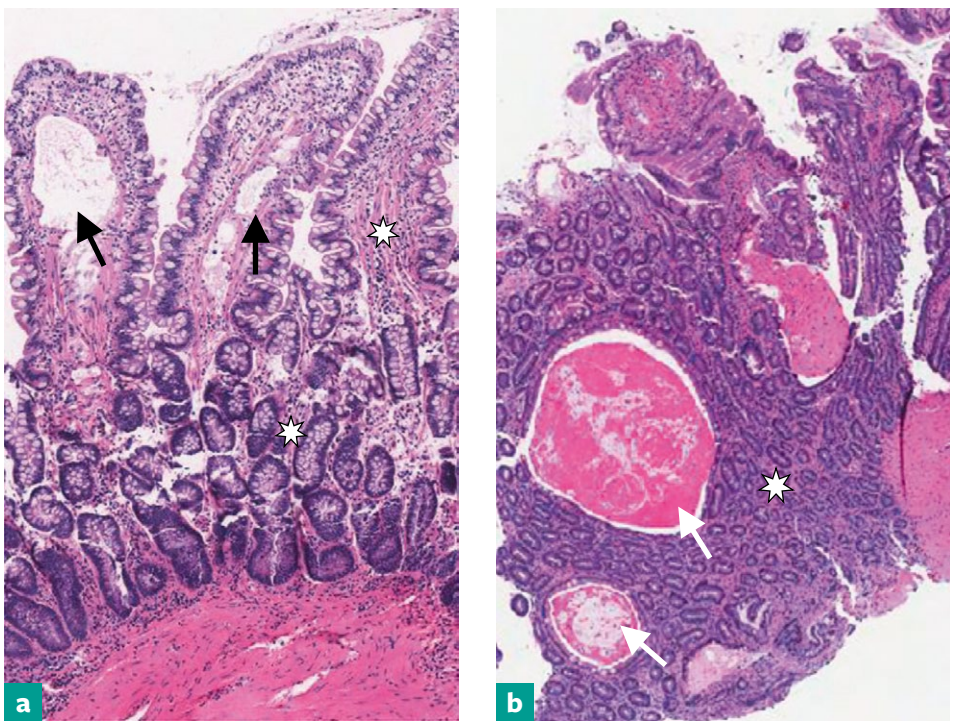



**Fig. 7-24** Histopathologic inflammatory and structural lesions of protein-losing enteropathy

Typical mucosal changes include (**a**) dilated lacteals (**arrows**), (**b**) cystic crypts filled with sloughed epithelial cells, leukocytes, and debris (crypt abscesses; **arrows**), and (**a** and **b**) increased cellularity of the lamina propria (**asterisks**).

**Tab. 7-7** Fat and protein contents of a home-prepared ultra-low-fat diet and commercially available low-fat or hypoallergenic diets.[2,22] Contents on a caloric basis should be considered for comparison between diets.

| Diet | Formula | Fat content on a DM basis (%) | Fat content on a caloric basis (% kcal) | Protein content on a DM basis (%) | Protein content on a caloric basis (% kcal) |
|---|---|---|---|---|---|
| **Home-cooked ultra low-fat diet** | | | | | |
| Chicken breast, white potato | wet | 1.6* | ~4* | 41.4* | ~58* |
| **Commercial low-fat diet** | | | | | |
| Royal Canin® Gastro-intestinal low fat | dry | 7.1 | 17 | 24.2 | 24 |
| | wet | 6.5 | 16 | 28.8 | 29 |
| Purina® EN low fat | dry | 6.8 | 16 | 28.4 | 28 |
| | wet | 8.6 | 20 | 44.0 | 43 |
| Hill's® i/d™ low fat | dry | 7.4 | 17 | 25.9 | 25 |
| | wet | 8.5 | 20 | 25.1 | 24 |
| **Commercial hypoallergenic/low-fat diet** | | | | | |
| Purina® HA | dry | 10.5 | 24 | 21.3 | 20 |
| Royal Canin® Hypoallergenic | dry | 17.5 | 34 | 26.2 | 34 |
| | wet | 15.1 | 34 | 24.6 | 22 |
| Hill's® z/d | dry | 14.4 | 32 | 19.1 | 17 |
| | wet | 14.1 | 31 | 20.0 | 18 |

* based on a composition of one part chicken breast plus two parts white potato; **DM** = dry matter.
Royal Canin®, St. Charles, MO, USA; Purina®, St. Louis, MO, USA; Hill's®, Topeka, KS, USA.



tious, non-neoplastic PLE are high (73–85%).[22–24] Success is further improved with multiple small meals given throughout the day.[2] Critically ill patients may require supplemental or exclusive feeding of a full elemental diet (e.g., Vivonex®), semi-elemental diet, or polymeric formula (e.g., Ensure®). If cost is not a concern, elemental diets can also be given intermittently or, if needed, continuously.

#### 7.3.8.3.2 Medical management

Anti-inflammatory or immunosuppressive treatment should be initiated in patients with PLE that show an inflammatory infiltrate on biopsies and no clinical response to dietary intervention within 2–4 weeks.[22,23] Absent any clear evidence for an immune-mediated etiology of PLE,[2] immunosuppressive treatment (▶Tab. 7-8) should be carefully considered. Glucocorticoids have catabolic, hyperlipidemic, and also prothrombotic effects. Thus, other immunomodulatory drugs (e.g., cyclosporine) can serve as first-line drug choices. Mycophenolate can cause significant gastrointestinal adverse effects and is not a good choice to treat inflammatory PLE. Combination immunomodulatory treatment should be reserved for cases refractory to dietary and mono-drug therapy.[1,2,25] There is no evidence for an antibiotic-responsive PLE.[5] Thus, antimicrobial treatment trials are generally not recommended. The beneficial effects of supplemental fiber (e.g., psyllium) or pro-/prebiotics remain to be investigated.

Supportive care should address vomiting/nausea, thrombotic risk, and suboptimal B vitamin status. Empirical deworming is also recommended. Mineral imbalances causing clinical signs should be corrected. Support of plasma oncotic pressure (i.e., colloidal IV fluids, human albumin) and other treatment options (e.g., pentoxifylline) may be carefully considered with severe hypoalbuminemia and marked cavitary effusion. Coagulopathy, as a complication of critical illness, requires transfusion of fresh frozen plasma. Octreotide may be beneficial as a rescue treatment in dogs with inflammatory PLE that are refractory to immunomodulatory treatment. The therapeutic efficacy of heparin has not been systematically evaluated in small animal PLE.

**Tab. 7-8** Treatment options for patients with protein-losing enteropathy

| Treatment indication | Drug options | Dose |
|---|---|---|
| Vomiting, nausea | Antiemetic<br>• Maropitant<br>• Metoclopramide<br><br>Ondansetron | <br>• 1 mg/kg SC or 2 mg/kg PO q24h<br>• 0.2–0.5 mg/kg SC or PO q6–8h or 5–20 µg/kg/h IV<br><br>• 0.3–0.5 mg/kg SC or IV q12–24h |
| Thromboprophylaxis | • Clopidogrel<br>• Acetylsalicylic acid<br>• Enoxaparine | • 1–3 mg/kg PO q24h<br>• 0.5–1 mg/kg PO q12h<br>• 0.8 mg/kg SC q6–8h |
| Suboptimal serum cobalamin status (serum cobalamin concentration <400 ng/L) | Cyanocobalamin | 50 µg/kg SC weekly for ≥6 weeks or<br>50 µg/kg PO q24h for ≥12 weeks |
| Moderate to marked hypofolatemia | Folate or folic acid | 200–400 µg PO q24h for 7–28 days |
| Marked or symptomatic hypocalcemia/hypomagnesemia | • Calcium gluconate<br><br>• Magnesium sulfate or magnesium chloride | • 12–25 mg/kg PO q12h or 5–15 mg/kg (0.5–1.5 ml/kg of a 10% solution) slowly IV<br>• 0.03–0.04 mEq/kg/h (0.015–0.02 mmol/kg/h) IV |
| Anti-inflammatory/ immunosuppressive treatment | Cyclosporine | 5 mg/kg PO q12–24h |
| | Chlorambucil | 4–6 mg/m$^2$ PO q24h for 1–3 weeks, then taper |
| | Azathioprine | 2 mg/kg PO q24h for 1–2 weeks, then decrease to q48h |
| | Prednisone/prednisolone | Initial dose: 1–2 mg/kg PO q12–24h, then attempt tapering by 25% q2–4 (2–8) weeks |
| | Budesonide | 3 mg/m$^2$ PO q24h for at least 2–3 weeks |
| Somatostatin analog for refractoriness to immunomodulation | Octreotide | 2–4 µg/kg SC q8–12h |

**PO** = per os; **IV** = intravenous; **SC** = subcutaneous

### 7.3.8.4 Prognosis

The prognosis for dogs with PLE varies with the underlying etiology, severity of clinical signs, response to treatment, disease relapse with appropriate dietary management or with tapering of immunomodulatory therapy. Potential complications of PLE include pulmonary thromboembolism with a risk of acute death. Negative prognostic factors are increased BUN concentration, hypocalcemia/-magnesemia, hypovitaminosis D, hypocobalaminemia, and severe undernutrition.[2,4,5,9,15,24–26]

### References

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svg.to/9842-07-03-08

### KEY FACTS

- Protein-losing enteropathy (PLE) most frequently results from chronic intestinal inflammation and/or lymphangiectasia in dogs, but is less common in cats.
- Routine laboratory parameters and diagnostic imaging are not specific for PLE but are essential to assess the overall patient condition and rule out other etiologies.
- The final diagnosis of PLE requires histopathology, which also dictates the prognosis for an individual patient.
- Dietary management with a high-protein, low-fat diet is the cornerstone of PLE management.
- Lack of evidence for an immune-mediated etiology of PLE warrants careful consideration of immunosuppressive treatment.

## 7.3.9 Neoplasia of the small intestine

Emma Warry

### 7.3.9.1 Introduction

Intestinal neoplasia is uncommon, with most reports suggesting an incidence between 0.3–1% for dogs and cats.[1] Of the non-lymphoid small intestinal (SI) tumors, carcinomas predominate in both species.[2]



Leiomyosarcomas and gastrointestinal stromal tumors (GIST) comprise the second most commonly reported non-lymphoid gastrointestinal malignancy in dogs.[2–4] Other reported canine small intestinal tumors include leiomyomas, fibrosarcomas, undifferentiated sarcomas, mast cell tumors (MC tumors), carcinoids, neurilemomas, and extramedullary plasmacytomas.[1,2,5–7]

Although the small intestine comprises about 90% of the length of the intestinal tract, most canine non-lymphoid intestinal tumors, other than MC tumors, are located in the colon or rectum, not in the more proximal segments.[1,5,18] This is true in human beings as well, where small bowel tumors account for only 3% of all gastrointestinal malignancies.[19]



In cats, the second most commonly reported non-lymphoid malignancy is mast cell tumor (MC tumor). Although uncommon, leiomyosarcomas and gastrointestinal stromal tumors have been reported in cats, as have MC tumors, hemangiosarcomas, adenomatous polyps in the duodenum, and extraskeletal osteosarcomas.[8–17]

Previous reports have indicated that 90% of feline intestinal tumors occur in the small intestines.[1] However, a recent study evaluating 441 feline intestinal tumors found an equal distribution between small intestine (SI) and large intestine (LI).[20] A significant predisposition for lymphoma (▶ Chap. 11.3) and sarcoma in the SI, and polyps, papilloma, and adenocarcinoma in the LI was identified in this study.[20]

### 7.3.9.2 Incidence

Multiple hypotheses have been proposed to explain the low incidence of SI tumors in dogs and humans. Proposed factors include the rapid transit time of potential carcinogens in the proximal segments compared with the colon, an inability of the SI flora to transform procarcinogens into their active metabolites, the presence of microsomal enzymes in the small intestine that detoxify carcinogens, and local immunosurveillance by IgA-secreting lymphocytes and B-cells in the distal ileum.[19,21] The apparent higher incidence of SI tumors in cats compared with dogs and humans remains unexplained. However, the data discussed above is in alignment with what is seen in other species.[20]

The most common primary SI tumors in dogs and cats, except for lymphoma (▶ Chap. 11.3), are those of epithelial origin, most of which are malignant.[1] Of the four types of **malignant epithelial tumors** (adenocarcinoma, mucinous adenocarcinoma, signet-ring cell carcinoma, and undifferentiated or solid carcinoma), adenocarcinomas (ACA) predominate. These tumors often cause annular constriction and may become quite large before they are clinically detectable. Feline intestinal ACAs are histologically subtyped as tubular, undifferentiated, or mucinous.[11,22,23] Of these, mucinous ACA is the least common.[23] Approximately one-third of feline intestinal ACAs have areas of osseous or cartilaginous metaplasia.[1] Tumor grading based on the degree of cellular differentiation may not be clinically relevant. In a series of cats with intestinal ACAs, papillary ACAs were described as the most differentiated tumors, yet they were associated with the highest rate of metastasis.[24,25]

Leiomyomas and leiomyosarcomas originate from smooth muscle and were historically thought to be the most common mesenchymal tumors affecting the canine gastrointestinal (GI) tract.[2,4,26] However, it is now understood that many tumors previously diagnosed as leiomyosarcoma are, in fact, GISTs, with a smaller number being reclassified as non-GIST/non-leiomyosarcoma mesenchymal tumors.[27,28] GISTs arise from the interstitial cells of Cajal, which are found in the SI and LI.[28–30] Positive reactivity for CD117 (KIT) is the basis for distinguishing a GIST from a leiomyosarcoma.[28–31] Recently, the DOG-1 (discovered on GIST-1) antibody has been shown to have improved specificity and sensitivity for diagnosing of GISTs.[32] Human GISTs almost exclusively affect the stomach and small intestine, whereas the stomach is rarely involved in dogs.[29–31] Reported distribution of canine GISTs between the SI and LI varies between studies, with some referencing the SI as the more common location and vice versa.[28–33] Leiomyosarcomas are more consistently

described to arise in the SI, with one study reporting 92% of these tumors being identified here.[28] There may be a predilection for leiomyosarcomas in the jejunum, the most common location reported in many studies.[28]

The incidence of GISTs in cats is not known. There is a single case report of a cat with a jejunal GIST treated with surgical excision.[17] However, given that intestinal mesenchymal tumors in cats are rare, the incidence of GISTs is likely very low.

As most tumors of the SI in dogs and cats are malignant, understanding their **metastatic potential** is important. The presence of metastasis at diagnosis in canine GISTs ranges from less than 10% to greater than 50%.[27,30,33–36] In humans, it is well established that GISTs can have a spectrum of behavior, which is likely also the case in dogs. Metastasis is reported to occur in the liver, abdominal lymph nodes, omentum, and spleen.[29,31,35] The reported metastatic rate for leiomyosarcoma at the time of diagnosis is 50%, but it is possible that many of these tumors could have been GISTs that were misdiagnosed.[34,37] Metastasis was intra-abdominal and reported in the liver, spleen, omentum, and abdominal lymph nodes. With canine SI adenocarcinoma, metastasis at the time of diagnosis is approximately 58%, and regional lymph nodes are the most common site, followed by the mesentery and omentum.[38,39] Metastasis to the testicles has also been reported in a small number of dogs.[40] Approximately 50% of cats with SI adenocarcinoma have metastasis at the time of diagnosis, with the most common location being abdominal lymph nodes.[22,41]

Small intestinal neoplasia is generally a disease of older animals, occurring at a mean age of approximately 9 years in dogs and a mean and median age of 8.7 and 11 years, respectively, in cats.[2,3,11,20] Some tumor types, especially leiomyosarcomas, have been reported in very young animals.[22] Accordingly, age should not be used to exclude a diagnosis of SI neoplasia. No clear breed predispositions have been identified for canine SI cancer except with MC tumors, for which miniature breeds, especially the Maltese, are at increased risk.[5] Siamese cats appear to be predisposed to intestinal cancer.[2,11,20,21] Conflicting views exist regarding gender predispositions for SI cancer in dogs and cats, with some reports indicating a male predisposition and others noting a female predisposition.[1–3,21,22] In humans, there is a slight male predominance for malignant small bowel tumors.[19]

#### 7.3.9.3 Clinical presentation

Weight loss, vomiting, and anorexia are the most common presenting complaints associated with SI cancer in dogs and cats.[2,3,20,23] In dogs, weight loss and vomiting are more common with duodenal or jejunal lesions, whereas, in cats, there is equal site distribution for masses associated with these presenting complaints.[2] Other clinical signs reported with SI cancer include melena, abdominal distension, and lethargy.[2,3,20,25,41]

**Paraneoplastic syndromes** are reported with smooth muscle tumors, including hypoglycemia (leiomyoma and leiomyosarcoma) and nephrogenic diabetes insipidus (leiomyosarcoma).[25,41,42] Dogs with paraneoplastic hypoglycemia can present with central nervous system (CNS) signs such as seizures and ataxia.[25,43,44] Hypoglycemia may also occur secondary to tumor-related peritonitis, especially with smooth muscle tumors, which can grow quite large and subsequently rupture.[25] Local peritonitis is reported in up to 50% of dogs undergoing surgical excision for leiomyosarcoma.[34] Polyuria (PU) and polydipsia (PD) were noted in over one-third of the dogs with GI leiomyosarcoma in one report and have been described in other reports of smooth muscle tumors.[25,42,44] In one case, the cause of PU/PD was tumor-related nephrogenic diabetes insipidus, but the cause has remained undetermined in others.[25,42,44]

Hemoperitoneum has also been described as a presenting complaint in a small number of dogs with SI tumors.[34]

#### 7.3.9.4 Diagnosis

Physical examination findings may aid in the diagnosis, as a palpable mass is found in approximately half of all cases.[2,3,20]

Plain radiographs are generally less sensitive than abdominal palpation or ultrasonography to detect intestinal masses, especially in cats.[2,20] However, plain radiographs were sufficient to warrant surgical exploration in 65% of cats in one report.[23] Contrast radiography may enhance tumor visualization and was diagnostic for tumor-related obstruction in 13/15 cats (87%) in one study.[20]

**Abdominal ultrasonography** is currently the gold standard for diagnostic imaging of intestinal neoplasia. It permits a more accurate assessment of intestinal wall layering and facilitates differentiating neoplasia from non-specific enteritis.[45] Abdominal ultrasonography identified intestinal neoplasia in 87–90% of cases in two reported case series.[3,45] Dogs in which intestinal wall layers are no longer visible are reportedly over 50 times more likely to have intestinal neoplasia than non-specific enteritis.[45] Segmental intestinal wall thickening of mixed echogenicity in cats supports a diagnosis of ACA over that of lymphoma.[46]

Definitive diagnosis is generally made by **fine-needle aspiration** of an ultrasound-imaged mass or **histopathological examination of a tissue biopsy** obtained during laparoscopy or exploratory laparotomy.

Abdominocentesis should be performed on any patient where free fluid is detected within the peritoneal cavity and evaluated for septic peritonitis, carcinomatosis, and sarcomatosis. Diagnosis of carcinomatosis or sarcomatosis will change the treatment approach and prognosis.

Preoperative lab work should include a complete blood cell count (CBC), serum chemistry profile, and urinalysis. Anemia and leukocytosis are the predominant CBC abnormalities noted in dogs and cats.[2,20] Leukocytosis is generally characterized by neutrophilia.[2] Lymphopenia was noted in 7/11 affected cats (64%) in one report.[23] Neutropenia, a degenerative left shift, or toxic changes in neutrophils should alert the clinician to the likelihood of tumor rupture and septic peritonitis, commonly reported with leiomyosarcomas.[25]



Biochemical abnormalities in dogs may include hypoproteinemia due to intestinal protein loss or decreased hepatic production and hypoglycemia occurring either as a paraneoplastic syndrome or secondary to sepsis or hepatic failure.[3,25]



In cats, hypoproteinemia, hyperglycemia, azotemia, hypercholesterolemia, and increased activities of alanine transaminase and alkaline phosphatase have been reported.[2,20,23]

### 7.3.9.5 Staging and treatment

**Preoperative staging procedures** should include a thorough physical examination to assess for unusual sites of metastasis, three-view thoracic radiographs, and abdominal ultrasonography. The mesenteric lymph nodes are the most frequent site of intestinal carcinoma metastasis.[2,7,23] The rate of intra-abdominal metastasis to lymph nodes, liver, and mesentery exceeds 58% in dogs and 70% in cats with intestinal ACA.[3,7,20] Metastatic rates are slightly lower with leiomyosarcomas, ranging from 18–54%.[3,25,41] Lung metastasis is an uncommon finding at the time of diagnosis.[3,7,20,23,41]

**Surgery** is the only beneficial treatment option for non-lymphoid SI cancer.[3,47] Conversely, surgery is generally unrewarding for visceral MC tumors in dogs, with a reported median survival time (MST) of 18 days.[48] The goals of exploratory laparotomy when SI neoplasia is expected are:

1. To facilitate complete excision of an identified mass.
2. To visualize and biopsy affected organs so that a definitive diagnosis and staging can be achieved.
3. To confirm a diagnosis. Surgical margins should ideally include 4–8 cm of normal-appearing tissue.[49]

**Complete abdominal exploration** should be performed to assess for metastatic disease. Lymph nodes draining the affected site should be excised or at least biopsied, regardless of size. In general, the duodenum is drained by the hepatic and pancreaticoduodenal nodes, the jejunum is drained by the jejunal lymph nodes found at the origin of the jejunal vessels, and lymphatic drainage of the ileum is into the jejunal and colic nodes.[50] Although metastases can have a negative impact on the overall outcome, several reports caution against recommending euthanasia at the time of surgery based on the presence of metastatic disease alone. This is especially true for dogs with leiomyosarcoma, where survival times exceeding 3 years have been reported, even in cases with metastatic disease.[37] For patients with ACA and metastasis, a 1-year survival rate of 20% has been reported for dogs and a mean survival time of 1 year for cats.[3,20] Tissues should be submitted for histopathological evaluation, and when bowel rupture has occurred, bacterial culture and antimicrobial sensitivity testing is indicated.

**Immunohistochemistry (IHC)** may be needed to reach a definitive diagnosis in some cases. The IHC markers of value for intestinal masses include:

1. Cytokeratin for epithelial tumors.
2. Vimentin, desmin, and α-smooth muscle actin for spindle cell tumors.
3. CD117 (KIT) and DOG-1 for GISTs.[27–29,32,51,52]

The roles of chemotherapy and radiation therapy have not been defined for non-lymphoid SI cancer in dogs and cats.[3,47] When chemotherapy has been attempted for visceral MC tumors in dogs, the results have been poor.[48] A recent retrospective evaluation of the role of carboplatin chemotherapy following surgical excision of intestinal ACA in dogs found no significant difference in outcome compared with dogs that received surgery alone.[38]

Toceranib phosphate has been evaluated in dogs with GIST, and a clinical benefit was reported in 71% of dogs with gross disease.[36] The role of toceranib in the setting of microscopic disease for GIST remains unknown.

#### 7.3.9.6 Prognosis

The prognosis for canine small intestinal (SI) cancer is primarily related to tumor type. Canine SI adenocarcinoma has a reasonable outcome following surgery with or without the addition of chemotherapy, with a reported median survival time (MST) of 544 days.[38] In this same population, 1-year and 2-year survival was 60% and 36%, respectively.[38] Although not statistically significant, likely due to small case numbers, dogs with lymph node metastasis at the time of surgical excision had an MST of 134 days versus 960 days for those without lymph node metastasis.[38] 73% of dogs in this study died or were euthanized due to metastatic or recurrent local disease, suggesting that most dogs eventually succumb to disease progression.[38]

In cats with small intestinal adenocarcinoma (ACA), surgical excision results in a significantly longer median survival time than cats with no surgery (365 days vs. 22 days).[41] Cats that undergo surgical excision and survive 2 weeks post-surgery have reported survival times ranging from 2.5–15 months, with a case report of one cat still alive 28 months post-surgery.[22] In cats with ACA, metastatic disease is not reported to have a similarly profound effect on prognosis as in dogs. However, one report indicated a 5-month mean survival time in cats with metastasis compared with 10 months for those without metastasis.

As stated above, GISTs seem to have a spectrum of behavior. Reported MSTs for dogs undergoing surgery alone range from 11–37 months.[27] When only dogs surviving the perioperative period are evaluated in survival data, MST is numerically longer but not statistically significant.[27] Recently, the role of toceranib was evaluated in a gross disease setting.[36] The progression-free interval for dogs experiencing a clinical benefit of toceranib administration was 110 weeks (25 months).[36] When dogs were treated with toceranib following surgery in a microscopic disease setting, the progression-free interval was 67 weeks (15.5 months).[36]

Factors that have an impact on outcomes in dogs with GIST include

1. Survival of the perioperative period
2. Presence of metastasis at diagnosis
3. Mitotic index[36]

Leiomyosarcomas are associated with the most favorable prognosis, with a reported MST from 12–21.3 months for dogs surviving the immediate postoperative period.[25,34] Dogs with documented metastasis at the time of surgery had an MST of 21.7 months.[34]

Non-malignant lesions, including polyps and leiomyomas, are curable with surgery. In one series of cats with duodenal polyps, surgery provided a complete resolution of signs in 13/15 cats (87%), and none were reported to have disease recurrence.[14] Similarly favorable outcomes are reported for dogs with leiomyomas.[31,42]

**KEY FACTS**

- Most small intestinal tumors in dogs and cats are malignant, and understanding their metastatic potential is important.
- Weight loss, vomiting, and anorexia are the most common presenting complaints associated with small intestinal cancer.
- Definitive diagnosis is generally made by fine-needle aspiration of an ultrasound-imaged mass or histopathological examination of a tissue biopsy obtained during laparoscopy or exploratory laparotomy.
- Surgery is the only beneficial treatment option for non-lymphoid small intestinal cancer.

**References**

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# 8 Large intestine and anorectum

Diseases of the large intestine are common in both dogs and cats. The clinical signs are obvious and unpleasant to owners, usually resulting in a prompt visit to the veterinarian. The most common clinical sign of large intestinal disease is diarrhea, usually characterized by increased frequency of defecation, decreased quantity of stool per defecation, tenesmus, hematochezia, and excess mucus (▶Chap. 2.3). Concurrent involvement of the small intestine may additionally result in melena and weight loss (▶Chap. 2.4). Vomiting, abdominal pain, flatulence, increased borborygmus, and reduced appetite may also accompany some large bowel diseases. Constipation, the second major clinical sign of large intestinal disease, may be associated with a variety of dietary and environmental factors, neurological or musculoskeletal disorders, and may progress to megacolon (▶Chap. 2.5). This chapter will discuss the normal anatomy and physiology of the large intestine and many common colonic diseases of dogs and cats.

## 8.1 Anatomy

Timothy Bolton, Michael S. Leib

The large bowel ranges in length from 28–90 cm in dogs and 20–45 cm in cats.[1,2] It begins at the ileocolic junction and terminates at the anus (▶Fig. 8-1 and ▶Fig. 8-2). Anatomically, the large bowel is divided into the cecum, colon, and rectum.

**The cecum** is a sigmoid-shaped diverticulum of the proximal colon and joins the colon through the cecocolic orifice, which is surrounded by a muscular sphincter. This junction is close to the ileocolic orifice, which is also surrounded by a sphincter. The cecum is variable in length and measures 8–30 cm in dogs and 2–4 cm in cats.

**The colon** is divided into ascending, transverse, and descending portions in conjunction with their connecting flexures. These subdivisions are identified based on their relative position within the body. The **ascending colon** is a short segment that begins at the ileocolic sphincter and courses cranially to the right (hepatic) colic flexure. Spatially, the cecum and ascending colon lie to the right of the median plane and close to the descending duodenum, right limb of the pancreas, and stomach. From the right colic flexure, the **transverse colon** runs cranial to the root of the mesentery to the left (splenic) colic flexure, where it joins the descending colon. The transverse colon is close to the left limb of the pancreas, stomach, and loops of small intestine. The **descending colon**, the longest segment, passes caudally, following the left lateral abdominal wall into the pelvic inlet, where the rectum begins. It is usually covered by the greater omentum and lies adjacent to the ascending portion of the duodenum. The uterus or prostate and the urinary bladder lie ventral to its terminal portion.

Blood is supplied to the large bowel by the cranial and caudal mesenteric arteries. Venous drainage occurs through the cranial and caudal mesenteric veins, which empty into the portal vein. Lymphatic drainage occurs through the right, middle, and left colic lymph nodes.

Histologically, the large bowel is similar to the small bowel and contains **mucosal**, **submucosal**, **muscular**, and **serosal layers**. The anatomical modifications of the colonic mucosa, which increase its absorptive surface area, are not as distinctive as those in the small bowel. The colonic mucosa is devoid of villi, and the microvilli of colonic epithelial cells are less abundant than their counterparts in the small bowel. Despite the **absence of villi**, numerous crypts extend from the absorptive surface through the entire thickness of the mucosa. These **crypts of Lieberkühn** contain epithelial, mucus, and endocrine cells. Compared to the small bowel, mucus cells, also called goblet cells, are more prominent, and endocrine cells are fewer. The deeper portion of the crypts consists mainly of undifferentiated cells. These cells migrate along the crypts as they proliferate and mature, ultimately giving rise to the aforementioned epithelial, mucus, and endocrine cells. At the mucosal surface, the cells undergo apoptosis, degenerate, and are sloughed into the lumen. Cell turnover in the colon is slower than in the small intestine, requiring 4–7 days. Within the lamina propria, moderate numbers of diffusely distributed lymphocytes and plasma cells can be found.[3,4]

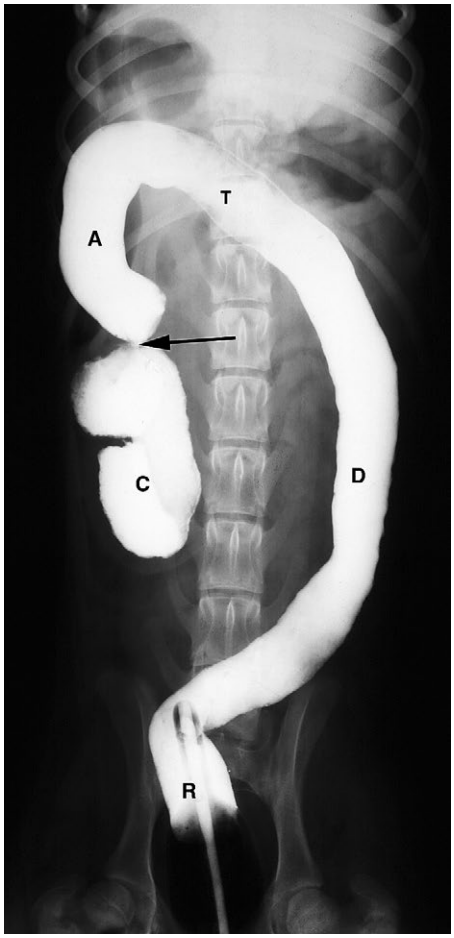



**Fig. 8-1** Barium enema in a dog

This figure shows a ventrodorsal abdominal radiograph after a barium enema in a dog showing the cecum (**C**), ascending colon (**A**), transverse colon (**T**), descending colon (**D**), rectum (**R**), and cecocolic junction (**arrow**).




**Fig. 8-2** Barium enema in a cat

Ventrodorsal abdominal radiograph after a barium enema in a cat showing the ileocolic junction (**thin arrow**), the short cecum (**thick arrow**), and the short ascending colon (**A**).



Both the intrinsic and extrinsic nervous systems regulate large bowel function. Intrinsic innervation occurs through the intramural network of neurons contained in the **myenteric plexus**, which lies between the longitudinal and circular muscle layers and the **submucosal plexus**. Intrinsic control allows the large bowel to autonomously regulate functions based on intraluminal conditions. These include the degree of distension and the type and quantity of fluid and other intraluminal contents. Extrinsic neural control occurs through the **autonomic nervous system**. Parasympathetic innervation to the proximal portion of the large bowel is through the vagus nerve, with the remainder of the large bowel supplied by the pelvic nerves. Sympathetic innervation arises from the paravertebral ganglia and follows the splanchnic nerves to the wall of the large intestine. Parasympathetic preganglionic fibers and sympathetic postganglionic fibers synapse on cell bodies and neurons of the intrinsic nervous system.

## References

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## 8.2 Physiology

Michael S. Leib, Timothy Bolton

The major functions of the large intestine are extraction of water and electrolytes from the ileal effluent, storage of feces, and defecation. In addition, microbial fermentation of organic matter that escapes digestion and absorption in the small intestine also occurs in the large intestine. Absorptive processes and microbial metabolism occur in the proximal colon, whereas fecal storage and elimination occur in the distal colon. These functional differences may be attributed to regional differences in patterns of colonic motility.

### 8.2.1 Motility

The majority of muscular contractions arising in the proximal colon are retrograde peristaltic contractions, which are initiated in the transverse colon and are propagated towards the cecum.[1] Termed **antiperistalsis**, this type of motility slows the transit of colonic contents and enhances mucosal absorption of fluid and electrolytes. The transverse colon plays the most important role in the proximal colon for mixing, storage, and dehydration of fecal contents.

Throughout the colon, **rhythmic segmentation**, originating in the circular muscle layer, moves the contents short distances in both antegrade and retrograde directions, preventing rapid transit. This promotes the absorption of the remaining water and electrolytes. Coordinated peristalsis can be observed in any part of the colon but is the predominant pattern of motility in the mid-portion of the colon. Peristaltic waves are tonic rings of constriction transmitted by the longitudinal muscle layer, which serve to move colonic contents aborally.

**Spontaneous giant migrating contractions**, or mass movements, are the predominant form of motility in the distal large intestine. These powerful, smooth muscle contractions originate in the orad colon and migrate in an aborad direction over a segment or the entire length of the colon, moving colonic contents towards the rectum in preparation for defecation.[2]

Intrinsic smooth muscle properties, intrinsic neurons, extrinsic nerves, and neuroendocrine polypeptides influence colonic contractile activity. Control of peristalsis and rhythmic segmentation in the colon is determined by **slow-wave activity**, an inherent myoelectric property of smooth muscle. Slow waves are generated by ion fluxes across the smooth muscle cells. The frequency of slow-wave activity determines the rate of contraction, while the number of spike potentials superimposed upon slow waves and generated during the depolarization phase, determines the strength of contractions. Slow waves are less frequent in the proximal colon than in the distal colon, which helps to impede transit and promotes the absorption of water and electrolytes.

In contrast to the small bowel, slow waves in the large bowel are generated in the circular muscle layer. There are multiple pacemakers in the colon that propagate slow waves over a short distance. However, a single pacemaker exists in the transverse colon, from which slow waves are spread most often in an orad direction and are associated with antiperistalsis. Giant migrating contractions result from prolonged bursts of electrical activity, which span several slow wave cycles and appear to be independent of slow-wave activity. Differences in the intrinsic mechanical properties of colonic longitudinal and circular smooth muscle have been demonstrated in cats and contribute to regional specialization of motility. This is most notable in the proximal colon, where the antiperistaltic activity of the longitudinal smooth muscle layer predominates over the segmental activity of the circular muscle layer.

The **intrinsic nervous system** is essential for normal colonic motility and can function independently of the extrinsic nervous system. Reflexes mediated through efferent cholinergic neurons stimulate segmental contractions and peristalsis. Stimulation of mechanoreceptors in the muscular layers that respond to distension or of chemoreceptors within the mucosa that respond to luminal contents result in muscular contractions.

In addition to acetylcholine and norepinephrine, a variety of other **neurotransmitters** have been identified that are released from the neurons of the intrinsic nervous system. Many of these are peptides and include neurotensin, cholecystokinin, substance P, somatostatin, and 5-hydroxytryptamine (5-HT).[3,4] The response of colonic smooth muscle to neurotransmitters varies throughout the colon. Regional differences have been observed in smooth muscle responses to neurotensin and cholecystokinin, both of which are more potent stimuli of proximal colonic compared to distal colonic smooth muscle activity.[5] These differences may, in part, explain the different motility patterns and functions in the proximal and distal colon.

Extrinsic neural and hormonal regulation of colonic motility is poorly understood. In general, extrinsic parasympathetic activity stimulates and sympathetic activity inhibits, segmental contractions. The major function of the extrinsic nervous system is in the distal colon, where it participates in the defecation reflex.

The **defecation reflex** may be initiated in response to the ingestion of a meal (gastrocolic reflex) as well as luminal distension in the distal colon and rectum. Increased tension in the rectal wall stimulates intramural receptors that transmit

impulses along afferent parasympathetic pathways within the pelvic nerve to the sacral spinal cord. Efferent nerve fibers contained within the pudendal, hypogastric, and pelvic nerves complete the reflex arc. Stimulation of these fibers initiates a motor response that causes contraction of colonic and rectal smooth muscle, with concomitant relaxation of the internal and external anal sphincters. These events allow the evacuation of feces from the rectum and distal colon. Defecation is usually preceded by giant migrating contractions of the distal colon.[2] The defecation reflex can be inhibited by voluntary contraction of the external anal sphincter. Receptive relaxation of the distal colon and rectum accommodates fecal storage until the next defecation reflex is initiated.

### 8.2.2 Water and electrolyte transport

The large intestine normally absorbs a smaller quantity of water than the small intestine but does so much more efficiently. Approximately 90% of the water entering the large bowel is absorbed.[1,6] Water absorption in the large bowel occurs passively across an **osmotic gradient** principally created by sodium absorption. The large bowel has a **maximum absorptive capacity** for water. When fluid flow from the small intestine exceeds this absorptive capacity, when there is excessive colonic fluid secretion or colonic absorption decreases, diarrhea ensues. Therefore, the capacity of the large bowel to absorb water principally determines whether or not diarrhea is present with either small or large bowel diseases.

**Sodium absorption** in the proximal colon appears to occur principally via chloride-coupled sodium transport. This process results from two separate ion transport mechanisms working in concert to facilitate sodium and chloride movement across the apical membrane of the epithelial cells. An even exchange of sodium with potassium and chloride with bicarbonate maintains electrical neutrality.

The large bowel **secretes potassium** by way of an active conductance mechanism at the apical membrane of the colonocytes. In contrast, active potassium absorption occurs in the distal colon through a $K^+/H^+$ exchange.

Mineralocorticoids and glucocorticoids stimulate sodium absorption and potassium secretion in the distal colon. These substances affect colonic transport by increasing the permeability of the apical membrane to sodium and potassium and by enhancing the activity of the $Na^+/K^+$ ATPase pump. Colonic epithelial cells also secrete bicarbonate. Bicarbonate neutralizes the acid produced by colonic bacteria, which can be irritating to the mucosa. The secretion of bicarbonate is coupled to the absorption of equal numbers of chloride ions and may occur independently of sodium absorption.

### 8.2.3 Mucus secretion

Mucus is the principal secretory product of the large bowel. Mucus acts as a lubricant and facilitates the passage of large bowel contents, and protects the mucosa from mechanical or chemical injury. Various agents (microorganisms, enterotoxins) can be bound by mucus, thus preventing their attachment, entry into, or adverse effects upon the colonic mucosa.[6,7] Commensal microorganisms directly stimulate goblet cell differentiation and mucus secretion.[8] The large bowel is capable of secreting large volumes of mucus, water, and electrolytes when inflamed. This response serves to dilute the irritating factor and promote colonic distension and evacuation of colonic contents. Marked increases in mucus secretion can also be caused by the stimulation of parasympathetic activity.

### 8.2.4 Colonic microbiome

Characterization of the intestinal microbiota has been greatly enhanced by the advent of new molecular techniques that have replaced traditional culture methods. One such technique, called **high-throughput RNA sequencing**, has been utilized to target a conserved but extremely variable bacterial 16S ribosomal RNA (16S rRNA) gene. The ability of this technique to identify bacteria based on their unique 16S rRNA gene sequence has vastly expanded our understanding of gastrointestinal (GI) bacteria identity and diversity.[9,10] At least several hundred different bacterial phylotypes have been identified within the GI tract of dogs and cats. Despite this diversity, healthy dogs and cats have a stable microbiota, with genetically related dogs more similar than genetically unrelated dogs.[11]

Most (>99%) **GI bacteria** originate from five phyla (*Firmicutes*, *Proteobacteria*, *Bacteroidetes*, *Actinobacteria*, and *Fusobacteria*).[10,12]



The phyla *Firmicutes*, *Bacteroidetes*, and *Fusobacteria*, are common in canine feces.[12]



The phyla *Proteobacteria* and *Firmicutes* are common in feline feces.[12]

Moving from duodenum to colon, the absolute number, and diversity of bacteria increase, with the colon containing the highest bacterial concentration in the GI tract with up to

$10^{11}$ organisms per gram of feces.[13] Anaerobic (spore and non-spore-forming) bacteria (*Clostridium* spp., *Bacteroides* spp., *Fusobacterium* spp., and *Lactobacillus* spp.) predominate, accounting for up to 90% of the canine and feline colonic bacterial flora.[14,15] Aerobic bacteria (family *Enterobacteriaceae* and *Streptococcus* spp.) are also present in the colon, albeit in much smaller numbers.[15]

In addition to bacteria, the GI tract is home to **fungi, viruses, protozoa, parasites, and archaea**. Some microorganisms, such as viruses, have not been well delineated; however, recent studies have better characterized the fungal component of the microbiome. Phylum *Ascomycota* is most abundant in dogs and is the only phylum present in cats, while the genus *Candida* is most abundant in dogs. Genera *Saccharomyces* and *Aspergillus* are most abundant in cats.[16,17] The influence of these non-bacterial microorganisms on the host and their roles, if any, in GI disease remains unclear. Preservation of a normal colonic microbiota is important for maintaining host health and preventing disease induced by bacterial colonization with pathogenic organisms. Numerous interrelated factors impact the microbiota composition and health, including developmental stage, environmental conditions, diet, orally administered or enterohepatically circulated antibacterial agents, and disease states.

Recent studies have investigated some of these important factors. For instance, as kittens age, the colon becomes increasingly populated with obligate anaerobes, such as *Bacteroides* spp., which are capable of metabolizing complex carbohydrates.[18] Such change is most significant in the descending colon, where anaerobic conditions are most prevalent.[19] Furthermore, kittens living together from birth until 8 weeks of age were found to have a similar microbiota composition; however, following weaning, the primary determinant became the diet.[20] Thus, environmental conditions play an important role in neonatal microbiota composition, with shifts being driven by the diet. Lastly, healthy adult dogs fed a meat-based raw food diet had decreases in the abundance of bacteria associated with dietary fiber digestion. This suggests that the microbiota can adjust to the macronutrient composition of the diet being fed.[21,22]

Many metabolic products are produced by commensal bacteria and include **short-chain fatty acids (SCFA)**, secondary bile acids, lactate, and ammonia. Some of these are important in global host health, colonocyte function, and modulation of mucosal innate and adaptive immune responses. Colonic microbiota ferment soluble fibers into SCFA (i.e., propionate, butyrate, and acetate). Luminal SCFAs are subsequently absorbed by colonocytes, either being metabolized for energy or transported via the blood to distant body tissues. The physiologic functions of SCFAs include stimulation of colonocyte proliferation, absorption of water and electrolytes, maintenance of the colonic epithelial barrier, regulation of intestinal motility, suppression of inflammation via upregulation of anti-inflammatory regulatory T-($T_{reg}$-) cells, and provision of ~7–10% of the animal's total energy requirements.[10,23,24] Conversely, diminished SCFA production by colonic bacteria, as can occur with GI disease, promotes the establishment of a proinflammatory state.[12]

Colonic bacteria also convert primary bile acids to **secondary bile acids**. Multiple beneficial effects are exerted by these secondary bile acids, including anti-inflammatory properties, decreased sporulation of *Clostridium difficile*, and promotion of glucagon-like peptide 1 (GLP-1) secretion.[10] GLP-1 is an incretin hormone produced by cells of the distal ileum and colon that promotes insulin secretion, thus contributing to glucose homeostasis. As with SCFAs, diminished secondary bile acid production by colonic microbiota during disease results in the perpetuation of a proinflammatory state.[10] In addition to the synthesis of metabolic products beneficial to animal health, the colonic microbiota resist colonization by pathogenic organisms through colonization resistance.[24] The mechanisms by which colonization resistance deters pathogenic organisms include creating an inhospitable environment (i.e., antimicrobial secretion, pH alteration, hydrogen sulfide gas release, and SCFA synthesis) for nonresident bacteria and competition for mucosal attachment sites and nutrients.[24]



**CLINICAL PEARLS**

The use of antibiotics with an anaerobic or broad spectrum may upset this sensitive balance and result in an overpopulation of potential pathogens.

Colonic bacteria play a significant role in the development, maintenance, and modulation of the **innate and adaptive mucosal immune responses**. Several innate mechanisms have been described, such as colonization resistance and the effects of microbiota-synthesized SCFAs on colonic motility and mucosal epithelial barrier preservation. The resident microbiome also directly stimulates goblet cell differentiation and secretion of the protective mucus layer in the colon.[8] Adaptive mucosal immune responses directed by large intestinal microbiota include antibody production by B-lymphocyte-derived plasma cells and naïve T-lymphocyte differentiation into anti-inflammatory $T_{reg}$-cells, resulting in immunotolerance.[9] The resident microbiota also contributes to immunotolerance by reducing phagocyte migration to mesenteric lymph nodes for B- and T-lymphocyte activation.[25]

**Intestinal dysbiosis** is defined as a change in the intestinal microbiome that results in adverse effects on host health.[12] It is characterized by changes in the relative proportion of particular organisms, resulting in reduced species diversity. The development of pathogenic features and reduction/loss of important commensal organisms are two changes that can occur to the microbiota in intestinal dysbiosis.[12] Animal models have demonstrated that mucosal inflammation and intestinal dysbiosis are interrelated; however, there is evidence that inflammation can be the cause or consequence of dysbiosis. In dogs, intestinal dysbiosis is a common finding with a variety of enteropathies, such as idiopathic inflammatory bowel disease.[12]

### 8.2.5 Immune function

Over the past 15 years, the immune function of the GI tract has been further elucidated. Intestinal immunity serves two interconnected functions: **rapid responsiveness to invading pathogens** balanced with **tolerance to food antigens and resident microbiota**. Both innate and adaptive immune responses are required; however, the latter is determined by signals generated from food antigens and microbes. To remain in a healthy state, an animal must respond aggressively to pathogens and remain quiescent (immunotolerant) to the resident microbiota and food antigens.[9]

**Mechanical defense mechanisms** in the colon include the mucosal barrier, intrinsic motility, mucus production, and the resident bacterial microbiota. Immunologically, the purpose of these mechanisms is to prevent colonization by pathogenic organisms. Of these, however, the resident microbiota is most important (▶ Chap. 8.2.4).

Innate and adaptive immune responses in the colon are extremely complex, requiring numerous cell types to function. The **gut-associated lymphoid tissue** (**GALT**) provides immune surveillance and defense in the GI tract, consisting of inductive sites (Peyer's patches, lymphoid follicles, and mesenteric lymph nodes) and effector sites (lamina propria).[26] In the inductive sites are B- and T-lymphocytes, specialized epithelial cells (called M-cells), dendritic cells, and innate lymphoid cells.[12] The last three cells are antigen-presenting cells (APCs), meaning that they sample antigens in the GI lumen and present them to B- and T-lymphocytes in the inductive sites.[27,28] In response to antigens presented by APCs, B-lymphocytes differentiate into antibody-producing plasma cells, and T-lymphocytes differentiate into helper T-cell populations (Th1, Th2, Th17) that direct either a pathogenic or protective cytokine response. The B- and T-lymphocyte responses comprise the humoral and cell-mediated arms of the adaptive mucosal immune response.

**Immunoglobulin A** (**IgA**) is the primary antibody secreted from the GI mucosa. IgA prevents luminal bacteria from penetrating the colonic epithelial barrier and is required for the maintenance of a healthy microbiome.[29,30] Dendritic cells in lymphoid follicles, utilizing surface receptors called pattern recognition receptors (PRRs), bind microbe-associated molecular patterns (MAMPs) present on luminal resident microbiota or pathogens.[12,26] Subsequent cytokine secretion by dendritic cells induces B-lymphocyte differentiation into IgA-producing plasma cells. A second mechanism for IgA production by B-lymphocyte-differentiated plasma cells occurs in the Peyer's patches. However, T-cells are required for this to occur.[26] The IgA produced by both mechanisms is transported transcellularly through colonic epithelial cells into the GI lumen, where it coats bacteria and prevents mucosal penetration.[26] The presence of normal colonic microbiota is essential to mucosal IgA production and secretion.

Following antigen penetration of the mucosal barrier, non-IgA immunoglobulins become involved in the humoral immune response. **IgM**, **IgG**, and **IgE** participate in host defense by the processes of opsonization, complement fixation, and promotion of an inflammatory response, all properties that IgA lacks. IgE is also important in the mediation of immediate hypersensitivity reactions. When antigen binds to IgE molecules fixed to mast cells, degranulation occurs, releasing inflammatory mediators (e.g., histamine, serotonin, and leukotrienes). This release of inflammatory mediators by mast cells is important in the expulsion of an invading microbe.

**Cell-mediated immunity** in the colon is mediated by cytokine-secreting T-cells. Naïve T-cells differentiate into helper subsets (Th1, Th2, Th17, Treg) in response to antigens presented by APCs. The specific antigen signaling through PRRs and MAMPs induces either a protective or pathogenic immune response. A protective response, or immunotolerance, occurs when resident microbiota and food antigens are recognized by the immune system as innocuous. In this situation, naïve T-lymphocytes differentiate into Treg-cells.[12,26] Treg-cells secrete anti-inflammatory cytokines, such as IL-10 and TGF-β, resulting in a protective immune response or tolerance.[12,26] Immunotolerance is necessary to prevent mucosal injury due to an inflammatory response to benign food antigens or commensal bacteria. A breakdown in immunotolerance is part of the pathogenesis of idiopathic inflammatory bowel disease (IBD; ▶ Chap. 11.2).

A **pathogenic immune response** occurs due to a breakdown in immunotolerance, such as in IBD, or if an invading pathogen is present. In this situation, naïve T-cells differentiate into Th1, Th2, or Th17 helper T-cells, depending on the type of pathogen.[26] These subsets produce inflammatory

cytokines responsible for recruiting phagocytic cells to the GI tract to eradicate the pathogen. For example, parasitic infections promote Th2-cell differentiation and secretion of IL-4, IL-5, and IL-13. Recruitment of mast cells, basophils, and eosinophils to kill the parasite occurs in response to these cytokines.[26] Viruses and pathogenic bacteria promote Th1- and Th17-cell differentiation, respectively, with subsequent secretion of IL-17, IL-22, and TNF-α. Recruitment of macrophages and cytotoxic T-lymphocytes to kill the virus or bacteria occurs in response to these cytokines.[26]

**KEY FACTS**

- The major functions of the large intestine are extraction of water and electrolytes from the ileal effluent, storage of feces, and defecation.
- A normal colonic microbiome is important for maintaining host health and preventing disease induced by the colonization with pathogenic bacteria.
- Intestinal immunity plays a central role in the animal's general health. The intestinal immune system is required to mount an immediate first-line response to fight invading pathogens, but remains quiescent (immunotolerant) to the resident microbiota and food antigens.

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
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## 8.3 Diseases of the large intestine

### 8.3.1 Acute and chronic colitis

Michael S. Leib, Timothy Bolton

Acute and chronic colonic inflammation (colitis) commonly results in large bowel diarrhea in dogs and cats. Signs of colitis include excess fecal mucus, hematochezia, tenesmus, increased frequency of defecation, and reduced volume of feces per defecation. Vomiting, anorexia, dehydration, and abdominal pain are observed less commonly. With concurrent small bowel involvement, melena and weight loss (chronic cases only) may also occur.

Acute colitis is most commonly caused by dietary indiscretion or intolerance (▶Chap. 7.3.2, ▶Chap. 11.1), toxin or foreign body ingestion, drug administration (antibiotics or non-steroidal anti-inflammatory drugs [NSAIDs]), whipworm infestation (dogs only, ▶Chap. 8.3.1.1), *Clostridium perfringens* enterotoxicosis (▶Chap. 7.3.1.2.2), acute hemorrhagic diarrhea syndrome (▶Chap. 7.3.3), or may be idiopathic. Infections with *Salmonella* spp. or *Campylobacter* spp. (▶Chap. 7.3.1.2) are uncommon causes of acute colitis and may cause signs of both small and large bowel diarrhea. Diagnosis is based on patient history, fecal examination, and response to dietary management with a highly digestible, low fat and moderate-fiber diet, or exclusion of a source of dietary indiscretion. Colonoscopy and mucosal biopsy are rarely performed, so histological documentation of colonic inflammation is not often acquired, and the speculative diagnosis of acute colitis is based on the rapid resolution of clinical signs (e.g., diarrhea).

Chronic colitis is usually associated with idiopathic inflammatory bowel disease (IBD; ▶Chap. 11.2) or *Clostridium perfringens* enterotoxicosis. Uncommon causes of colitis include histiocytic ulcerative colitis (▶Chap. 8.3.1.2), pythiosis (phycomycosis, ▶Chap. 7.3.1.5.3) and colitis associated with histoplasmosis (▶Chap. 7.3.1.5), the colorless unicellular alga *Prototheca* spp. (▶Chap. 7.3.1.5.3), *Heterobilharzia americana* (schistosomiasis, ▶Chap. 7.3.1.4), or *Leishmania infantum*.

### 8.3.1.1 Whipworm infection

Michael S. Leib, Timothy Bolton

#### 8.3.1.1.1 Pathophysiology

*Trichuris vulpis* infestation is one of the most common causes of acute or chronic large bowel diarrhea and colitis in dogs.[1,2] Puppies and adult dogs that live in contaminated environments are commonly affected and often re-infected.

Cats rarely have whipworms.

The parasite's life cycle is direct. Adult worms shed eggs intermittently, which can result in false-negative fecal examinations. The eggs have thick, yellow-brown shells, are barrel-shaped, with polar plugs, and are approximately 80 × 35 µm (▶Fig. 8-3). Whipworm eggs can persist for years in the environment, but prolonged sunlight will kill them. Areas that cannot be easily cleaned, such as lawns and dirt kennels, can become contaminated, providing a source for reinfection. The eggs embryonate in the soil within 3–8 weeks to form an infectious larva within the egg.[3] After a dog ingests the infective eggs, the larvae hatch in the small intestine, burrow into the mucosa for 2–10 days, emerge again, and attach to



**Fig. 8-3** Whipworm eggs
Close-up of a group of whipworm eggs in a fecal flotation

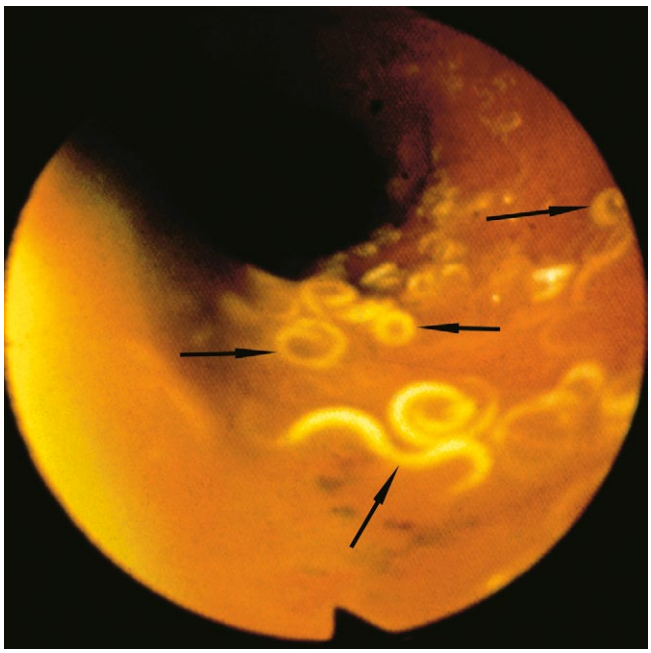


**Fig. 8-4** Whipworms
Endoscopic appearance of adult whipworms (**arrows**) in the ascending colon of a dog

the mucosa in the cecum and ascending colon, where they complete their maturation.[4] Female worms begin producing eggs 70–114 days after the infection has been acquired. Estimates of daily egg production range from 1,000–4,000. Adult worms may live up to 18 months.

Pathogenicity is related to the tunneling of the thin anterior portion of the adult worm into the epithelium of the cecum or ascending colon, producing localized inflammation, mucosal hyperplasia, and in some cases, focal granulomatous reactions.[4,5] Adult worms measure 45–75 mm in length (▶Fig. 8-4). The worms feed on tissue fluid, blood, and cellular debris. The parasites may be found throughout the large intestine in dogs harboring large numbers of worms.

Many infected dogs do not show any clinical signs. The factors contributing to the development of clinical signs include the number of worms present, the location of worms, the degree of inflammation produced, the level of anemia or hypoproteinemia, the nutritional status of the host, and the presence of other GI parasites.[4]

**CLINICAL PEARLS**

Although the zoonotic potential of *Trichuris vulpis* is still being debated, it has been implicated as a cause of visceral larval migrans and patent intestinal infections of human beings.[3–5] Clients should be warned of the possible public health significance, and appropriate sanitary measures should be taken when disposing of fecal material.

#### 8.3.1.1.2 Clinical presentation and diagnostic evaluation

Some infected dogs do not develop clinical signs. However, diarrhea with hematochezia and excess mucus occurs frequently. Abdominal pain, vomiting, inappetence, and weight loss can also be observed.[4] Diarrhea may be intermittent in chronic cases. Anemia can result in pale mucous membranes and lethargy and is often associated with a larger worm burden.

Whipworm eggs can be identified using routine fecal flotation procedures. Whipworm eggs have higher specific gravity than other common nematodes and require higher specific gravity solutions for optimal flotation.[6] Zinc sulfate flotation

(with centrifugation) has been demonstrated to be more sensitive than other flotation techniques for identifying whipworm eggs.[7] An ELISA detecting whipworm coproantigens (proteins) has been developed and can detect infection prior to egg production.[6] However, if multiple fecal examinations fail to identify eggs or coproprotein, empiric treatment for whipworms should be instituted prior to performing additional diagnostic tests for chronic diarrhea. A presumptive diagnosis of whipworm infection can be made if clinical signs improve within 2–3 days of appropriate anthelminthic treatment. Adult worms may be seen in the cecum and ascending colon during colonoscopy if a dog with an occult infection has not been treated before colonoscopy (▶Fig. 8-4). Peripheral blood eosinophilia may be present. Anemia and hypoproteinemia may develop in cases with severe whipworm infestation.

#### 8.3.1.1.3 Treatment and prognosis

Numerous therapeutic agents are effective against whipworms in dogs.[5] Commonly used treatments include fenbendazole (50 mg/kg PO q24h for 3 days) and a combination of febantel, pyrantel pamoate, and praziquantel (Drontal® Plus, Bayer, USA, at 25 mg/kg febantel PO once).[8] In some countries, products are available containing combinations of emodepside with either praziquantel (Profender®, Bayer, USA, at 1 mg/kg PO emodepside once) or toltrazuril (Procox®, Bayer, USA at 0.45 mg/kg PO emodepside once).[9,10]

Fenbendazole is a safe and efficacious drug with broad-spectrum activity against common gastrointestinal (GI) nematodes, *Giardia* spp., and some tapeworms. Febantel is converted to fenbendazole in the liver. The combination of febantel and pyrantel is synergistic and allows treatment with a single dose. When febantel is combined with praziquantel, it offers broad-spectrum activity against common GI nematodes and tapeworms.

Treatment should be repeated after 3 weeks and again after 3 months. The effects of most anthelminthics on the larval stages of whipworms remain unknown.[4] After anthelminthic administration has removed the adult worms, larvae can still develop into adult parasites and reestablish infestation. Frequent disposal of feces will help reduce the risk of reinfection. In severe recurrent cases, monthly heartworm prophylaxis with milbemycin oxime (each dosage based on a sliding scale of body weight, given PO q30d) will help control the whipworm infection.[11] Also, topical heartworm preventative solutions containing moxidectin will control whipworms.

Clinical signs rapidly resolve following appropriate therapy. Re-infestation is common in dogs that live in contaminated environments.

**KEY FACTS**

- The most common clinical sign of large intestinal disease is diarrhea, usually associated with increased frequency of defecation, decreased quantity of stool per defecation, tenesmus, hematochezia, and excess mucus.
- *Trichuris vulpis* infestation is one of the most common causes of acute or chronic large bowel diarrhea in dogs. Diagnosis requires fecal flotation with high specific gravity solutions using centrifugation or detection of whipworm coproantigens by ELISA.
- Anthelminthic administration is used to remove adult worms. However, larvae can still develop into adult parasites and reestablish infestation. Frequent disposal of feces will help reduce the risk of reinfection.

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
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### 8.3.1.2 Granulomatous colitis

Alison C. Manchester

Granulomatous colitis (GC) is an uncommon form of chronic inflammatory enteropathy (▶Chap. 11.2) that typically has an underlying infectious etiology. This chapter will mainly focus on canine GC, but the same general principles can be applied to feline patients.

#### 8.3.1.2.1 Clinical presentation

GC presents similarly to other forms of chronic colitis. Associated clinical signs include increased frequency of defecation and poorly formed to liquid bowel movements with or without mucus. Hematochezia, tenesmus, dyschezia, and fecal urgency can also occur. Clinical signs may be constant or wax and wane. Unlike other causes of large bowel diarrhea, dogs with GC may experience weight loss. Physical examination findings (e.g., uveitis, peripheral lymphadenopathy, skin lesions) and clinicopathological abnormalities may point to systemic disease. Anemia and hypoalbuminemia may be seen with *E. coli*-associated GC (▶Chap. 7.3.1.2.5), hypercalcemia with canine schistosomiasis (▶Chap. 7.3.1.4), and peripheral eosinophilia with pythiosis (▶Chap. 7.3.1.5.3).

Dogs with *E. coli*-associated GC tend to be <4 years old with life-long clinical signs. The disease is primarily seen in boxers[1–3] and French bulldogs[4–6] but has been diagnosed in many breeds worldwide.

A similar disease has been described in three adult cats: a Persian crossbred[7] and two domestic shorthairs.[8,9]

### 8.3.1.2.2 Etiology and pathophysiology

GC occurs secondary to various persistent exogenous and endogenous irritants, most commonly, long-standing infections (▶Tab. 8-1). In rare cases, autoimmune and neoplastic diseases, as well as reactions to foreign bodies, can be associated with GC. Thus, immunosuppression of patients with granulomatous intestinal infiltrates should be avoided until infectious etiologies have been excluded to the best of the clinician's ability.

The connection between GC and an infectious agent is most thoroughly described in dogs with *E. coli*-associated GC. When first reported in a colony of boxer dogs in 1965, a bacterial etiology was suspected due to the macrophage-predominant inflammation and intracellular bacteria-like structures seen on colonic histopathology.[1] However, no causative agent was identified, and, for years, GC in boxer dogs (also referred to as **histiocytic ulcerative colitis**) was considered a severe form of immune-mediated IBD. Nonetheless, reports of treatment successes with antimicrobials surfaced.[1,10,11] Subsequently, investigations using culture-independent techniques (immunohistochemistry, fluorescence *in situ* hybridization [FISH], and 16S sequencing) documented *E. coli* within colonic mucosal macrophages (▶Fig. 8-5).[12,13] *E. coli* that are able to invade and persist intracellularly are implicated in the pathogenesis of this form of GC for a few reasons. Firstly, dogs treated with appropriate antimicrobials can achieve lasting histological and clinical remission,[6,11,13–15] which is associated with clearance of intramucosal *E. coli*.[14,16] Intramucosal bacteria are also rarely identified in dogs with other forms of colitis,[13] and disease could not be experimentally induced with *Mycoplasma* spp.[17] Finally, exhaustive searches have failed to consistently isolate other enteropathogens such as *Salmonella* spp., *Yersinia* spp., and *Mycobacterium* spp. from affected dogs.[1,12]

*E. coli* isolates from affected dogs are non-clonal, lacking diarrheagenic virulence genes, with in vitro propensity to invade epithelial cells and persist in macrophages is similar to that of *E. coli* from healthy dogs.[13,16,18] Genome-wide association screening of affected boxers and bulldogs has identified a region of interest encoding the CD48/SLAM family of genes, implicated in the selective detection and killing of *E. coli* by murine macrophages and a risk of IBD in humans.[19–21] Preliminary evidence in cultured macrophages derived from a GC boxer with the CD48/SLAM risk haplotype supports a hypothesis of impaired killing of *E. coli*.[18] Thus, the current understanding of *E. coli*-associated GC involves opportunistic *E. coli* gaining access to and persisting in colonic mucosal macrophages of susceptible hosts.

**Tab. 8-1** Infectious causes of granulomatous colitis in dogs

| Infectious cause | Examples |
|---|---|
| Bacterial | • *Salmonella* spp.<br>• *Yersinia* spp.<br>• *Mycobacterium tuberculosis*<br>• *Escherichia coli** |
| Algal | • *Prototheca zopfii*<br>• *Pythium insidiosum* |
| Protzoal | • *Entamoeba histolytica*<br>• *Tritrichomonas blagburni** |
| Trematode | *Heterobilharzia americana* (schistosomiasis) |
| Fungal | *Histoplasma capsulatum** |
| Viral | Feline infectious peritonitis (FIP)* |

Infectious agents marked with an asterisk (*) are documented causes of granulomatous colitis in cats.

### 8.3.1.2.3 Diagnostic evaluation

GC is an uncommon cause of chronic large bowel signs. Thus, other differentials should be ruled out before pursuing the advanced diagnostics required to confirm GC (▶Chap. 2.3). The diagnostic work-up should be tailored to the patient, depending on signalment, extra-GI clinical signs, and geographical region. A thorough digital rectal examination must be completed, as dogs with rectal and perianal tumors (▶Chap. 8.4.4) can present with colitis-like clinical signs. *E. coli*-associated GC rises higher on the differential diagnosis list when young dogs with chronic large bowel diarrhea show no improvement with typical empirical colitis therapies (▶Chap. 8.4.1.1.2).

After an initial diagnostic work-up and, if indicated, treatment trials, the next diagnostic step in these patients is endoscopic evaluation (▶Chap. 1.5) of the rectum, colon,

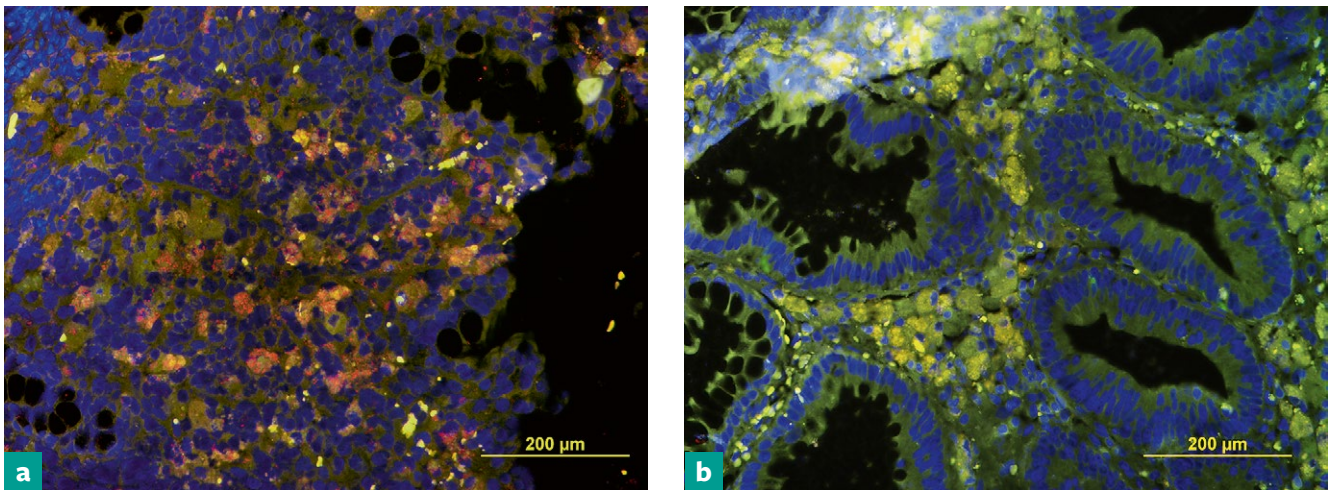



**Fig. 8-5** Fluorescence *in situ* hybridization photomicrographs of endoscopically obtained colonic mucosa from two boxer dogs suspected to have *E. coli* -associated granulomatous colitis

Sections were treated with a Cy-3 labeled *E. coli/Shigella* spp.-specific probe (**red**) and a non-eubacterial control probe (FAM-Non-EUB-338, **green**). Nuclei are stained with DAPI (**blue**).

**a** Dog 1: section highlighting multifocal clusters of *E. coli* dispersed throughout the mucosa, often intracellularly, consistent with a diagnosis of *E. coli*-associated granulomatous colitis.

**b** Dog 2: *E. coli*-FISH in this sample reveals no invasive bacteria but substantial autofluorescence (**green**) amid patchy inflammation.

**FISH** = Fluorescence *in situ* hybridization; **E. coli** = *Escherichia coli*; **DAPI** = 4',6'-diamidino-2-phenylindole
(Courtesy of Dr. Kenneth W. Simpson, Cornell University, NY.)

cecum, and terminal ileum. Colonoscopic abnormalities in dogs with *E. coli*-associated GC range from areas of friable mucosa with hemorrhagic foci to eccentric wall thickenings to diffuse ulcerations.[3,22] The colon may be stiff from scarring and fibrotic contracture, impairing insufflation and full visualization.[15] Because lesions can be patchy, at least ten good quality biopsies should be obtained for histopathological evaluation. If GC is suspected, 2–3 biopsies should be saved in Luria-Bertani or another sterile transport medium for bacterial culture. For further information of advanced testing for GC testing please visit the website of the Gastrointestinal Laboratory at Texas A&M University (https://vetmed.tamu.edu/gilab/service/assays/histopathology-service/).

## Histopathology

GC is diagnosed when macrophages, lymphocytes, plasma cells, and neutrophils infiltrate the colonic wall. GC is subcategorized based on special staining with periodic acid-Schiff (PAS; ▶Chap. 1.8.1). GC with PAS-negative macrophages indicates the need for an exhaustive search for infectious agents other than *E. coli* (▶Tab. 8-1). Tests to consider include additional special staining of biopsies (e.g., Gomori's methenamine silver, Giemsa, acid-fast), fungal antigen testing, urine and/or blood culture (particularly for febrile patients), fecal testing (culture, PCR), and lymph node aspirate cytology and, if indicated, histopathology.

Colonic lesions in dogs with *E. coli*-associated GC are typified by large, foamy, PAS-positive macrophages, accompanied by granulocytes and lymphocytes, in the lamina propria and submucosa.[1,2,13] Severe mucosal ulceration with or without secondary colonization by luminal bacteria and goblet cell loss are other classical findings.[22,23] Granulomatous inflammation may also be present in the cecum, ileum, and mesenteric lymph nodes.[1,24,25]

## Infectious agent visualization

After determining if GC is PAS-positive or PAS-negative, the diagnostician's next goal is to visualize the infectious agents. This may be accomplished with routine histopathology, but other techniques offer greater sensitivity and specificity. FISH uses fluorescent-tagged, oligonucleotide probes specific for 16S eubacterial ribosomal DNA sequences to highlight the presence of organisms in paraffin-embedded, formalin-fixed tissues (▶Fig. 8-5). This technique provides information on bacterial morphology and location in biopsies replete with inflammation and cellular debris. The combination of PAS-positive GC with intramucosal *E. coli* documented with FISH provides a definitive diagnosis of *E. coli*-associated GC.

### Bacterial isolation (culture)

Beyond visualization, a comprehensive diagnosis of GC involves the isolation and characterization of the infectious organisms. Bacterial culture and antimicrobial susceptibility testing of colonic biopsies from dogs with *E. coli*-associated and possibly other forms of GC allows for targeted antimicrobial therapy. This is particularly important given the frequent occurrence of fluoroquinolone-resistant *E. coli* in affected dogs.[15,16,26] When culture yields multiple isolates, therapy is directed at the most resistant isolate. It must be emphasized that culture results from GC samples are not informative without the context provided by clinical, histological, and FISH findings.

### 8.3.1.2.4 Treatment and prognosis

Successful treatment of GC hinges upon eliminating the inflammatory trigger, whether that be bacterial, fungal, algal, or trematodal. For recommendations regarding treatment of non-*E. coli*-associated GC, readers are directed to other chapters in this book and disease-specific reviews.[27–31]

Elimination of intramucosal *E. coli* is the primary therapeutic goal for dogs with *E. coli*-associated GC. This is accomplished by administering antimicrobials

1. to which *E. coli* are susceptible to and
2. that can reach intracellular *E. coli*.

Antimicrobials accumulating within macrophages include fluoroquinolones (FQ), potentiated sulfonamides, tetracyclines, chloramphenicol, rifampicin, and carbapenems.[32,33]

For dogs without FQ-resistant *E. coli*, the recommended treatment is **enrofloxacin** at 7.5–10 mg/kg PO q24h for 6–8 weeks.[6,10,11,14] Clinical improvement is expected within approximately 7 days of initiating therapy. Still, the drug must be continued to complete the course and maximize the probability of achieving lasting clinical remission. Lack of response to enrofloxacin raises concern for incorrect diagnosis or FQ-resistance. If not already completed, advanced diagnostics should be performed at this point. If *E. coli*-associated GC was definitively diagnosed, repeat colonic biopsy for culture and FISH is prioritized. Proctoscopy offers an alternative means of biopsy collection, which may be completed with the patient under sedation.

In cases involving FQ-resistant *E. coli*, therapy is guided by the susceptibility profiling results. FQ-resistance is often associated with resistance to macrophage-penetrating antimicrobials.[18,34] This may limit antimicrobial options to **carbapenems**, which should only be prescribed as a last resort, given their importance in treating human infections. Contemporaneous ciprofloxacin, tetracycline, and trimethoprim treatment were more effective in killing intramacrophage *E. coli* from Crohn's disease patients than ciprofloxacin alone.[32] Thus, combination protocols may be effective in dogs with multidrug-resistant *E. coli*. Clinical remission has been documented in FQ-sensitive or -resistant *E. coli*-associated GC dogs treated with chloramphenicol, doxycycline, amoxicillin-clavulanic acid, meropenem, and various antimicrobial combinations.[1,2,11,15,18] It must be kept in mind that in vitro susceptibility test results do not guarantee in vivo efficacy.

Evidence-based recommendations regarding **adjunctive therapies** for dogs with *E. coli*-associated GC are lacking. Sulfasalazine appears to dampen host inflammatory responses in addition to exerting direct anti-bacterial effects,[35] though no controlled trials have evaluated the efficacy of this drug in this disease. In the author's experience, supplemental psyllium fiber can reduce the severity of clinical signs.

Ideally, a **post-treatment biopsy** is performed to document the resolution of GC. Dogs with *E. coli*-associated GC experiencing clinical remission show reduced inflammatory infiltrates, no invasive bacteria, and replenishment of goblet cells. However, histologic improvement lags behind clinical improvement.[14,34]

As with treatment, the **prognosis** for animals with GC hinges upon identifying and the ability to eliminate the inciting cause of granulomatous inflammation. Prognosis is guarded in cases where an underlying etiology is not identified. Dogs with *E. coli*-associated GC can achieve clinical remission with antimicrobial therapy and go on to live normal lives without relapse.

**KEY FACTS**

- *E. coli*-associated granulomatous colitis is a rare but treatable, breed-associated disease.
- Targeted antimicrobial treatment can allow dogs with *E. coli*-associated granulomatous colitis achieve lasting clinical remission.

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
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## 8.3.2 *Clostridium perfringens* enterotoxicosis

Michael S. Leib, Timothy Bolton

*Clostridium perfringens* type A enterotoxin has been associated with food poisoning in humans. It has also been frequently associated with chronic large bowel diarrhea in dogs and occasionally in cats (▶Chap. 7.3.1.2.2).[1] Both naturally occurring and hospital-acquired cases have been described.[2] In the author's clinic, approximately 13% of dogs evaluated with chronic large bowel diarrhea were diagnosed with *C. perfringens* enterotoxicosis. This percentage is thought to be underestimating the true incidence of disease as the dogs evaluated were a referral population. Many dogs with diarrhea treated with antimicrobials (e.g., metronidazole) by their primary veterinarian most likely responded to therapy and were not referred for further evaluation.

Several epidemiological studies have characterized the prevalence of *C. perfringens* fecal enterotoxin in dogs with various types of diarrhea, hospitalized dogs without diarrhea, and healthy outpatients yielding variable results.[3–6] While the presence of enterotoxin in these three groups was similar in one study, another investigation showed a higher incidence of fecal enterotoxin in the group of dogs with diarrhea. In these studies, fecal enterotoxin was detected in 5–14% of dogs without diarrhea and up to 34% of diarrheic dogs.[7] The authors believe that a similar epidemiological study of dogs with chronic large bowel diarrhea would demonstrate a much stronger association between fecal enterotoxin and diarrhea.

A syndrome of acute hemorrhagic diarrhea in dogs (AHDS, ▶Chap. 7.3.3) has been strongly associated with the presence of *C. perfringens* fecal enterotoxin.[3] This syndrome was characterized by severe acute hemorrhagic diarrhea, hematemesis, severe dehydration, high mortality, and necrotizing hemorrhagic enteritis and mesenteric lymphadenopathy on necropsy. Conflicting results have been found relating the role of *C. perfringens* enterotoxin in dogs with AHDS (formally called hemorrhagic gastroenteritis).[8,9] Recently, novel pore-forming toxin genes, called *netE* and *netF,* have been found in *C. perfringens* type A strains isolated from dogs with AHDS.[10]

Thus, a simple and universally accepted description of the role of *C. perfringens* enterotoxin as a cause of canine and feline diarrhea has not yet emerged, and some of the syndrome's characteristics remain controversial. Many questions will hopefully be answered after completion of case-based studies in which a definitive diagnosis is determined, the animals treated with appropriate antibiotics, and the clinical outcome assessed.

### 8.3.2.1 Pathophysiology

*Clostridium perfringens* is an anaerobic, spore-forming, gram-positive bacillus.[6] It is considered part of the normal fecal microbiome in both dogs and cats. Five toxigenic types (A–E) have been differentiated based on the production of 1–4 major toxins. Each biotype can also produce other toxins, with at least 16 toxins having been identified.[11] The majority of **enterotoxin** (**CPE**) is produced by type A strains. The gene (*cpe*) encoding CPE is carried on large plasmids. The enterotoxin is produced during sporulation and causes intestinal fluid accumulation, mucosal inflammation, alterations in mucosal tight junctions, increased mucosal paracellular permeability, and consequently, diarrhea.[12] In some experimental models, the enterotoxin has its greatest effects within the small intestine. Although the stimuli for sporulation and enterotoxin production are unknown, it is thought that disruption of the colonic microenvironment may allow the proliferation of enterotoxigenic strains.[7] Such disruption can occur secondary to underlying diseases, such as idiopathic inflammatory bowel disease (▶Chap. 11.2), or following antimicrobial administration.

### 8.3.2.2 Clinical presentation and diagnostic evaluation

Acute and chronic large bowel diarrhea commonly occur with *C. perfringens* enterotoxicosis. Defecation occurs frequently and is often accompanied by tenesmus. Feces contain excess mucus and hematochezia, occasionally appearing to be mostly fresh blood and little fecal material. In chronic cases, diarrhea can be intermittent and episodic or occur on most days. Vomiting, weight loss, flatulence, and abdominal pain are seen less frequently. Small bowel diarrhea or mixed bowel diarrhea (signs of both small and large bowel diarrhea) may occur (▶Chap. 2.3).

The diagnosis is confirmed by detecting **fecal enterotoxin by ELISA** (TechLab, Blacksburg, VA) or the **cpe gene by PCR** in a dog or cat with typical clinical signs in which other causes of diarrhea have not been identified. It has been recommended that the use of both tests together increase diagnostic accuracy as a strong association existed between diarrhea in dogs and the detection of both CPE and its gene (*cpe*).[6] Both the ELISA and PCR tests are available through commercial diagnostic laboratories. In animals with intermittent clinical signs, fecal samples should be collected when diarrhea is present, as the enterotoxin may not be detected during asymptomatic periods. There is some evidence that refrigeration may lead to unreliable results in 10–14% of samples.[13]

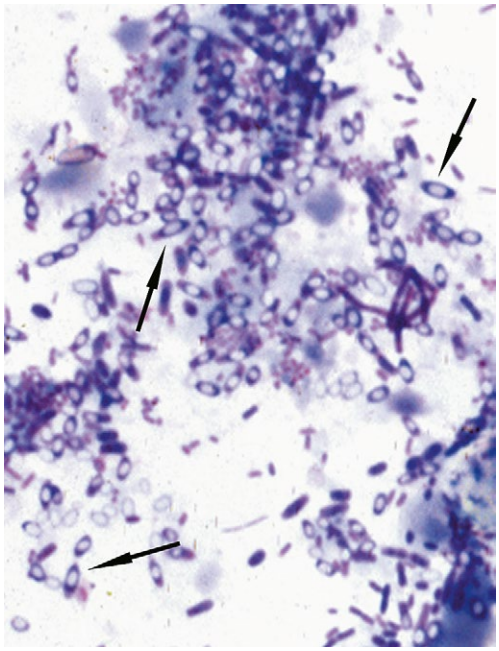


**Fig. 8-6** *Clostridium perfringens* endospores
Large numbers of clostridial endospores (**arrows**) in a rectal cytology specimen stained with a rapid Wright stain

In the past, it has been suggested that the diagnosis of enterotoxicosis should be suspected when >3–5 spores per oil immersion field are seen in a rectal cytology specimen. The spores are larger than most bacteria and assume a "safety pin" appearance (▶Fig. 8-6). However, epidemiological studies have not demonstrated a consistent relationship between the number of fecal spores and the presence of enterotoxin.[4,5] But signs of large bowel diarrhea in dogs were associated with larger numbers of spores on rectal cytology.[3] These epidemiological studies were performed on dogs with unspecified types of diarrhea. The authors strongly believe that if the diarrhea group had included dogs only with signs of large bowel diarrhea (the most common clinical sign associated with *C. perfringens* enterotoxicosis), there would have been a stronger relationship between the presence of diarrhea and the number of spores. Also, in the authors' experience, huge numbers of spores found on rectal cytology samples from dogs with typical clinical signs are often associated with a positive test for fecal enterotoxin and rapid clinical response to antibiotic treatment. However, the presence of fecal enterotoxin, typical clinical signs, and response to antibiotic treatment may also occur in dogs without any or many spores on a rectal cytology sample. Although endoscopic examination of affected animals has been infrequently performed, the colon may be grossly and histologically normal or may show a hyperemic, hemorrhagic, or ulcerated mucosa with histopathological findings of catarrhal or suppurative colitis.[1]

### 8.3.2.3 Treatment and prognosis

Clinical signs may resolve spontaneously without antibiotic treatment. Affected animals with severe clinical signs usually respond to **antimicrobial therapy** rapidly, within 3–5 days. Metronidazole at 6 mg/kg PO q8–12h, ampicillin at 22 mg/kg PO q8h, or amoxicillin at 11–22 mg/kg PO q8–12h for 7–10 days are all effective treatments.[1]

**NOTE**
Recent studies have shown a high rate of resistance to tetracyclines.[7]

Animals that develop recurrent clinical signs after antimicrobial treatment may require repeat therapy (one or two additional times). Long-terms antimicrobial therapy (e.g., with tylosin [Tylan® powder, Elanco, USA] for 3–6 months, at 10–20 mg/kg PO q12h) may be needed but should be carefully considered due to the potentially detrimental effects of antibiotics.[14] Tylosin powder has a bitter taste and may need to be mixed with a small quantity of canned food or placed into a gelatin capsule. The lack of an immediate response to antimicrobial treatment should prompt further diagnostic evaluation for underlying GI disease.[14]

Some chronic recurrent cases benefit from feeding a **high-fiber diet**. The proposed mechanisms of action for dietary fiber include bacterial fermentation of fiber, leading to acidification of the colon, which may inhibit sporulation, or an alteration of the bacterial microbiota (potentially correcting intestinal dysbiosis) that inhibits *C. perfringens* proliferation.

The prognosis for patients with *C. perfringens* enterotoxicosis is usually excellent. Most severely affected animals respond to therapy within several days. At present, clinical findings have not been identified that can predict which patients will require repeat therapy.

**KEY FACTS**
The pathophysiology of *Clostridium perfringens* enterotoxicosis is not fully understood. However, it is a common cause of chronic large bowel diarrhea in dogs that responds quickly to therapy.

**References**
The complete list of references for this chapter can be downloaded from vetline.de:
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## 8.3.3 *Tritrichomonas blagburni* infection

M. Katherine Tolbert

### 8.3.3.1 Etiology and clinical presentation

*Tritrichomonas blagburni* (▶Fig. 8-7) is a flagellated protozoal parasite and a global cause of chronic diarrhea in cats.[1,2] The proposal to rename this organism in cats from *T. foetus* to *T. blagburni* has not been universally accepted yet.[3] Although the true prevalence of *T. blagburni* infection in cats is unknown, it is suspected to be relatively high. In one study, 31% of 117 cats examined at an international cat show were found to be infected with *T. blagburni*.[4]

While cats of any age, breed, or sex can be infected, young cats that are densely housed (e.g., cats in catteries, animal shelters, or multi-cat households) are at an increased risk.[2,4] Infection is most commonly identified in young cats (i.e., those that are <2 years of age), but older cats can also be infected. *T. blagburni* primarily colonizes the surface of the colonic mucosa, leading to chronic large bowel diarrhea or mixed-bowel diarrhea (▶Chap. 2.3). Without appropriate treatment, cats can remain persistently infected. While the diarrhea may spontaneously resolve, infected cats will often experience recurrent bouts of diarrhea after being exposed to stress. In the absence of co-infection, cats infected with *T. blagburni* generally appear healthy but show an increased frequency of defecation with loose to liquid stools, which can contain blood and mucus. Fecal incontinence can also be observed. The anal region can also appear edematous and may become painful with severe diarrhea. A rectal prolapse (▶Chap. 8.4.1.2) may occur in some cases.

### 8.3.3.2 Diagnosis

Diagnosis of a *T. blagburni* infection can be made by identification of trophozoites on a direct fecal smear examination, fecal culture, PCR analysis of fecal material, or a colonic mucosal biopsy. Freshly voided, unrefrigerated stool or stool collected from a fecal loop or colonic flush can be used for cytologic examination.

The disadvantages of direct **fecal smear** examination include a low sensitivity (14%), low specificity (*Giardia* spp. or the nonpathogenic *Pentatrichomonas hominis* can be misdiagnosed as *T. blagburni*), and the fact that only fresh fecal samples can be used. The sensitivity might be improved by analyzing multiple fresh fecal smears and by obtaining the fecal sample from the proximal colon through a fecal collection loop (preferred)[7] or colonic flush. Video clips that demonstrate how to perform the colonic flush technique and the classic motility of the parasite can be found online at https://cvm.ncsu.edu/research/labs/clinical-sciences/tfoetus/.

Trichomonads are observed with a forward, propulsive motion during microscopy, whereas Giardia has a 'falling leaf' motility pattern.

*T. blagburni* can also be **cultured in-house** using the commercially available culture system InPouch™ TF (Biomed Diagnostics, San Jose, CA). The pouches should be inoculated with <0.1 g of freshly voided feces and then incubated at 25°C or 37°C. The pouches need to be evaluated under a microscope every day, when incubated at 37°C or every other day when incubated at 25°C. Results are usually obtained between 1–11 days after setting up a pouch. Although fecal culture is more sensitive and specific than direct fecal smear examination, difficulties in the interpretation of results, the necessity of using freshly voided feces, the potential for a false negative due to bacterial overgrowth or the presence of low numbers of trophozoites, and the fact that the results

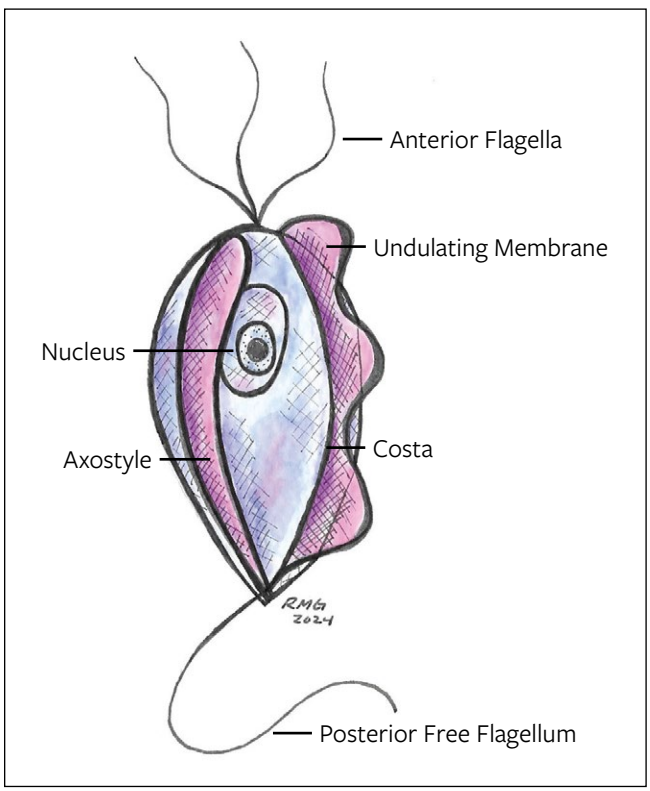



**Fig. 8-7** *Tritrichomonas blagburni*

This line drawing shows a detailed outline of a *Tritrichomonas blagburni* organism. As seen in https://www.youtube.com/watch?v=aF06jlbcF8E, the three flagella and the undulating membrane are defining characteristics that can be used to differentiate *Tritrichomonas blagburni* from other protozoal organisms such as *Giardia* spp. on fecal examination.

(Courtesy of Dr. Randi M. Gold, Texas Veterinary Medical Diagnostic Laboratory, College Station, TX, USA.)

might not be available for up to 11 days, are important disadvantages of this method. Experimental growth of *Pentatrichomonas hominis* in the InPouch™ cultures has also been reported.[7] Therefore, a positive result should be confirmed cytologically or by PCR.

*T. blagburni* DNA can be amplified from fecal samples by **PCR**.[9] PCR has been shown to be the most sensitive method for detecting *T. blagburni* in fecal samples and is ideally suited for the diagnosis of *T. blagburni* infection.[8] The advantages of PCR testing compared to culture include a higher sensitivity, faster turnaround time, and easier handling and storing of samples since DNA is relatively stable at various temperatures. In high-density housing environments, samples from two up to three cats can be batched to aid in evaluating the population for infection. The PCR can detect both live and dead organisms and has a very high analytical sensitivity. While PCR tests for *T. blagburni* are not standardized, many of the assays offered by commercial laboratories can detect as little as ten *T. blagburni* organisms per 100 mg fecal sample. However, the PCR test is not 100% sensitive. In cases with a high index of suspicion for infection, repeat testing is recommended. For all diagnostic tests, cats should not have received antimicrobials for ≥10 days, and the fecal sample should be devoid of litter.

**Co-infections,** such as *Giardia* spp. and coccidia, are commonly present in *T. blagburni* infected cats. Therefore, part of the diagnostic workup for *T. blagburni* infection should include evaluation for the presence of other enteropathogens.

### 8.3.3.3 Therapy

Administration of ronidazole (30 mg/kg PO q24h for 2 weeks) can be effective in both resolving diarrhea and eradicating *T. blagburni*.[9] There has been some anecdotal evidence that ronidazole may cause neurological side effects. However, these side effects appear to be reversible once therapy is discontinued and are more frequently observed when using higher than recommended dosages or frequencies of administration. Ronidazole is not approved for use in domestic animals, and it is recommended to obtain signed consent from the owner before initiating therapy. Several compounding pharmacies offer ronidazole. The stability and efficacy of the compounded product vary widely, and acquisition of the compounded drug from a highly reputable compounding pharmacy is recommended. About 20–33% of infected cats do not respond to treatment.[4,6] Poor compounding can result in treatment failure. Other reasons for ronidazole failure include insufficient dose or duration of therapy, the presence of a co-infection, poor compliance or drug failure, the presence of a ronidazole-resistant strain, or re-infection from another cat in the household who may be asymptomatic. Other cats in the household/cattery should also be tested for *T. blagburni* to ensure that the affected cat does not become re-infected. If all of the above are ruled out, and a resistant infection is suspected, not much can be offered that will help to eliminate the infection. Most cats have spontaneous resolution of diarrhea but may continue to harbor the infection and relapse with diarrhea during stressful periods. Diet changes and antibiotics might prolong harboring of the infection. *T. blagburni* infection is largely dependent on resident bacteria for intestinal colonization and persistence. Thus, targeted alteration of the resident microbiome (e.g., fecal microbial transplantation, high dose species-specific probiotics[10]) shows promising results in improving infection. However, clinical trials are needed to further explore the benefits of these therapies. Whether a second round of ronidazole treatment might be beneficial has not been studied to date.

#### KEY FACTS

- *Tritrichomonas blagburni* (formerly named *Tritrichomonas foetus*) is a flagellated protozoal parasite and a global cause of chronic diarrhea in cats that primarily colonizes the surface of the colonic mucosa.
- Without appropriate treatment, cats can remain persistently infected. While the diarrhea may spontaneously resolve, infected cats will often experience recurrent bouts of diarrhea after being exposed to stress.
- Diagnosis can be made by identification of trophozoites on a direct fecal smear examination, fecal culture, PCR analysis of fecal material or colonic mucosal biopsy. Freshly voided, unrefrigerated stool or stool collected from a fecal loop or colonic flush can be used for cytologic examination.
- Administration of ronidazole (30 mg/kg PO q24h for 2 weeks) can be effective in both resolving diarrhea and eradicating *T. blagburni*. Targeted alteration of the resident microbiome might help in cases of re-infection. To minimize the risk of re-infection, other cats in the household/cattery should also be tested for *T. blagburni*.

#### References

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## 8.3.4 Irritable bowel syndrome

Michael S. Leib, Timothy Bolton

Irritable bowel syndrome (IBS) is a commonly diagnosed but poorly understood functional disorder in dogs.[1] Other terms used to describe this syndrome include spastic colon, nervous colitis, and mucus colitis.[2] It has been estimated that 10–15% of dogs with chronic large bowel diarrhea have IBS.[3] Approximately 15% of human adults in the United States report symptoms consistent with IBS.[4] IBS in humans has been traditionally defined as colonic dysfunction in the absence of identifiable structural, biochemical, or microbiological causes. Some affected individuals have predominantly abdominal pain and diarrhea, while others have constipation, while some have alternating diarrhea and constipation. There are no data-based clinical reports or pathophysiologic studies of this syndrome in the veterinary literature.

In dogs, IBS is a diagnosis of exclusion, as known causes of large bowel diarrhea must be eliminated before a presumptive diagnosis of IBS can be made. It is possible that dogs diagnosed with IBS:

1. may truly have a syndrome similar to IBS in human beings,
2. may have a closely related and possibly overlapping syndrome called fiber-responsive chronic large bowel diarrhea (FRLBD, ▶Chap. 8.3.4), or
3. may have another colonic disorder that has not been correctly diagnosed.

### 8.3.4.1 Pathophysiology

There have been no pathophysiological studies concerning IBS in dogs. Factors that may contribute to IBS in humans include a genetic predisposition, visceral hypersensitivity, food intolerance, altered gut-brain axis with gut dysmotility, dysfunction of innate immunity, psychosocial factors, or an imbalance of GI neurotransmitters.[4,5] Abnormal colonic myoelectrical activity leads to abnormal intestinal motility, which is likely the ultimate cause of the clinical signs.[2] Recent evidence suggests that intestinal dysbiosis (decrease or loss of colonic microbial diversity and species richness) may play an important role in humans.[5]

### 8.3.4.2 Clinical presentation and diagnostic evaluation

In dogs, the most common clinical sign of IBS is chronic intermittent large bowel diarrhea (▶Chap. 2.3) with excess fecal mucus, tenesmus, an urgency to defecate, and increased frequency of defecation, and hematochezia in some cases.[2] Intermittent bloating, nausea, vomiting, and abdominal pain may also occur. Often, stressors can be identified in the patient history, and they may be associated with the development of cyclic clinical signs. Affected dogs may be hyperexcitable, unmanageable, or possess abnormal personality traits. However, dogs without these abnormalities or stressors identified in the medical history can also develop IBS.[3]

It cannot be overemphasized that IBS in dogs is a diagnosis of exclusion. A thorough diagnostic plan for chronic large bowel diarrhea must be followed before a presumptive diagnosis of IBS can be made. Fecal examinations must be negative for parasite infestations, and laboratory evaluation should eliminate the possibility of systemic disorders (▶Chap. 1.3). Dietary trials with a highly digestible fat-restricted diet or a hypoallergenic diet (▶Chap. 3.2.1) and deworming against whipworms (▶Chap. 8.3.1.1) should be instituted before making a diagnosis of IBS. Finally, colonoscopic examination and mucosal biopsies must be normal (▶Chap. 1.5, ▶Fig. 8-8).

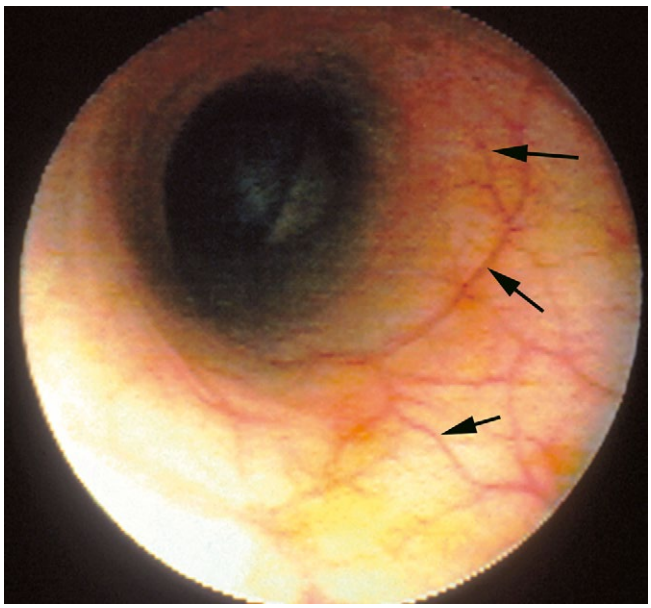


**Fig. 8-8** Normal colonic mucosa

Endoscopic appearance of normal colonic mucosa in a dog with idiopathic large bowel diarrhea. The mucosa is smooth and glistening, and submucosal blood vessels are clearly visible (**arrows**).

**CLINICAL PEARLS**

In some cases of IBS, spasms of the colonic wall may occur after contact with the endoscope.

In the author's experience, response to a high-fiber diet does not eliminate the presence of IBS. However, it may support a diagnosis of FRLBD instead. The relationship between IBS and FRLBD will be discussed in the next section.

### 8.3.4.3 Treatment

The intermittent nature of clinical signs often makes assessment of IBS therapy difficult. Multiple treatments often need to be tried before control of the clinical signs is achieved. If a stress factor or abnormal personality trait can be identified, **behavioral modification** can be beneficial. Unfortunately, many stressors cannot be eliminated, and many clients are unable or unwilling to alter their behaviors or attempt to alter their pet's behavior. Thus, dietary and pharmacological therapy is commonly used. The author has recommended supplementing highly digestible diets with a source of soluble fiber. In many cases, feeding **high-fiber diets** can lead to a reduction in dosages and frequency of administration of pharmacological agents required or may eliminate the need for drug therapy. An in-depth discussion of dietary fiber can be found in the next section on FRLBD.

The severity and frequency of diarrhea can also be reduced by **motility-modifying agents**, such as loperamide or diphenoxylate. These drugs reduce diarrhea by increasing colonic segmentation. They can often be given for several days and discontinued after the diarrhea resolves.[2]

**CLINICAL PEARLS**

Caution should be utilized when administering loperamide to collies and herding breeds with potential ivermectin sensitivity. Mutations in genes controlling P-glycoprotein drug transporters can allow increased loperamide concentrations to cross the blood-brain barrier, leading to neurotoxicity.

Pain can often be relieved by **antispasmodic agents**, and **sedatives** can reduce the effects of stressors. Librax® (Valeant Pharmaceuticals, USA) contains the sedative chlordiazepoxide (5 mg) and clidinium bromide (2.5 mg), an anticholinergic antispasmodic agent. A suggested dosage is 0.1–0.25 mg/kg of clidinium or 1–2 capsules of Librax® PO (for dogs >10 kg body weight) q8–12h.[2,6] The drug can be given when the owner first notices abdominal pain or diarrhea, or when stressful conditions are anticipated or encountered, and it can usually be discontinued after a few days. Other anticholinergics such as propantheline at 0.25 mg/kg PO q8–12h, hyoscyamine at 0.003–0.006 mg/kg PO q8–12h, or dicyclomine D at 0.15 mg/kg PO q8–12h have also been suggested.[1,2] Anticholinergics can decrease or inhibit GI motility, which may worsen diarrhea. Other side effects are uncommon. In human patients with IBS, the side effects include xerostomia, urinary retention, blurred vision, headache, psychosis, nervousness, and drowsiness. On occasion, nausea and vomiting prevent the administration of oral medications. Parenteral anti-emetics can be given to relieve nausea and vomiting and allow the administration of oral medications.[2]

**Newer efficacious treatments** utilized in humans with IBS include some of the following: Eluxadoline, a peripherally acting drug with mixed opioid effects and minimal oral bioavailability, thought to reduce visceral hypersensitivity without disruption of intestinal motility.[7] Rifaximin is a broad-spectrum, non-absorbable antibiotic believed to correct or improve intestinal dysbiosis.[5] Alosetron is a serotonin 5-HT3 receptor antagonist, used in women, which is thought to improve or normalize visceral pain, colonic transport, and GI secretions. It has been associated with causing ischemic colitis.[8] Perhaps some of these therapies might be effective in dogs with IBS that do not respond to historically used treatment options.

### 8.3.4.4 Prognosis

The prognosis for a cure of IBS in dogs is guarded. Affected dogs may have intermittent clinical signs for years. Environmental, dietary, and pharmacological therapy often results in control or a reduction of clinical signs. Those dogs that respond to fiber supplementation have a good prognosis for reducing or eliminating their clinical signs. Future clinical or pathophysiologic studies in dogs will hopefully lead to more effective treatments that will improve the prognosis for dogs that do not respond to dietary fiber supplementation.

**KEY FACTS**

- In dogs, irritable bowel syndrome is a diagnosis of exclusion, and known causes of chronic large bowel diarrhea must be eliminated before a diagnosis of irritable bowel syndrome can be made.
- Treatment options include behavioral modification, highly digestible diets with a source of soluble fiber, motility modifying agents, antispasmodic drugs, and, if indicated, sedatives to reduce the effects of stressors.

**References**

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## 8.3.5 Fiber-responsive large bowel diarrhea

Michael S. Leib, Timothy Bolton

Some dogs with chronic idiopathic large bowel diarrhea can be successfully managed by feeding a highly digestible diet supplemented with soluble fiber.[50,51] Such patients are diagnosed as having fiber-responsive chronic large bowel diarrhea (FRLBD). Dogs of all ages have been affected, with a median age of 6 years. [51] Common breeds include German shepherd dogs, miniature schnauzers, cocker spaniels, and miniature or toy poodles. The syndrome of FRLBD is closely related to and overlaps with irritable bowel syndrome (IBS).

### 8.3.5.1 Pathophysiology

Some of the dogs with FRLBD (especially those with abnormal personality traits or exposed to environmental stressors) can be diagnosed with IBS. Presently, the relationship between IBS and FRLBD is unclear, and overlap of cases exists. However, many of the dogs with FRLBD have hematochezia, a clinical sign historically considered uncommon in dogs with IBS.[43,44] Also, dogs with IBS only rarely have been historically described as responding to dietary fiber supplementation alone.[43] Thus, dogs with FRLBD may represent a separate syndrome or a subset of IBS patients that respond to dietary fiber supplementation. The pathophysiology of FRLBD is unknown. However, based on the current understanding of the GI microbiome and the clinical response of dogs with FRLBD to soluble fiber supplementation, intestinal dysbiosis (decrease or loss of colonic microbial diversity and species richness) may play an important etiologic role.

### 8.3.5.2 Clinical presentation and diagnostic evaluation

The predominant clinical sign of dogs with FRLBD is chronic intermittent large bowel diarrhea with hematochezia, excess fecal mucus, and tenesmus.[51] Approximately 25% of dogs may have daily diarrhea. Occasionally, vomiting, decreased appetite, abdominal pain, and anal pruritus can occur. Abnormal personality traits and environmental stress factors are found in approximately 40% of affected dogs. Only rarely do owners describe their dogs as nervous or highly strung. Separation anxiety, submissive urination, noise sensitivity, fear of thunderstorms, or aggression occur rarely.

In most cases, it is not possible to relate stressors or abnormal personality traits to the development or intensification of diarrhea. Some stressful factors that have been identified include household visitors, travel, moving, construction, recent adoption, installation of an invisible fence, death of another household pet, or visits to the groomer, veterinarian, or dog show. On physical examination, abdominal and rectal palpation should be normal.

The diagnosis of FRLBD is based on the exclusion of known causes of large bowel diarrhea after a thorough diagnostic evaluation, including colonoscopy (▶Fig. 8-8) and mucosal biopsy (▶Chap. 1.5.3). If no cause of diarrhea is identified, the diagnosis of idiopathic large bowel diarrhea is made. If the diarrhea responds to fiber supplementation, the diagnosis is amended to FRLBD.

### 8.3.5.3 Treatment

Dietary fiber is a collective term for a wide variety of plant polysaccharides and lignins that are resistant to mammalian digestive enzymes.[52] There are many types of dietary fiber, each with diverse chemical, physical, and physiologic properties. **Water-soluble fibers** include pectin, gums, mucilage, and some hemicelluloses.[52] They are found in the parenchymatous portions of fruits and vegetables, and in the seeds of leguminous plants. Soluble fibers adsorb a large quantity of water, improving fecal consistency. **Water-insoluble fibers** include cellulose, lignin, and some hemicelluloses, and are found in cereal grains and seed coats. Insoluble fibers greatly add to the fecal volume. Thus, dietary fiber can increase fecal bulk, which increases colonic distension, the major stimulus for normal colonic motility. With increased colonic distension, an improved motility pattern in dogs with FRLBD may result in normal defecation and resolution of clinical signs.

Soluble dietary fiber is a **prebiotic**, fermented by colonic bacteria, resulting in altered composition and/or activity of bacteria. Prebiotics are not digested by mammalian digestive enzymes and "feed" the colonic bacteria, potentially correcting intestinal dysbiosis. Fermentation of soluble fiber by colonic bacteria produces short-chain fatty acids (SCFA), such as butyrate, which is an energy source for colonic epithelial cells. SCFAs also lower colonic pH, induce anti-inflammatory T regulatory (Treg) cells, increase sodium resorption, and increase mucosal blood flow. Prebiotics have other potentially beneficial effects within the colon, including increasing the thickness of the colonic mucous layer, elongating microvilli, increasing epithelial cell numbers, preventing the adherence of pathogenic bacteria, increasing water resorption, and increasing beneficial numbers of *Bifidobacteria* organisms.[53–55]

**Psyllium** comes from the seeds or husks of the plant *Plantago ovata* and consists of approximately 90% soluble fiber. Psyllium was beneficial in treating children with idiopathic

chronic nonspecific diarrhea.[56] Because the beneficial effects persisted after the withdrawal of fiber supplementation, the authors postulated that psyllium led to an alteration of the colonic microbiome. Psyllium has also been shown to be beneficial in human adults with nonspecific chronic diarrhea, ulcerative colitis in remission, some patients with IBS, burn patients receiving enteral nutrition, patients being tube fed, and some patients with other diarrheal disorders.[51]

A highly digestible fat-restricted diet supplemented with psyllium hydrophilic mucilloid (Metamucil®; 1–3 tablespoons/day) will rapidly benefit most dogs with FRLBD.[51] In the cases reported by the author, the median amount of Metamucil® added to the diet was 1.33 g/kg/day (range: 0.31–4.9 g/kg/day). Approximately 85% of dogs had an excellent or very good response to psyllium supplementation. In cases that do not respond to fiber supplementation, drug therapy for IBS may need to be added to the treatment protocol.

Some dogs can have the amount of supplemented fiber reduced and possibly withdrawn entirely, while others require long-term supplementation. Some dogs can also be switched from a highly digestible diet to a regular maintenance diet without relapsing diarrhea. Although not studied in dogs requiring long-term fiber supplementation, a dietary trial with a commercially available high-fiber diet can be attempted after the clinical signs have been controlled using soluble fiber supplementation and the diagnosis of FRLBD has been confirmed. High-fiber commercially available diets may be more convenient for clients to feed. Most high-fiber diets contain insoluble fiber. However, some newer diets contain soluble fiber or prebiotics (e.g., Hills Gastrointestinal Biome®). Dietary trials with these high-fiber diets might show beneficial results in dogs with FRLBD.

#### 8.3.5.4 Prognosis

The prognosis for dogs with FRLBD is very good to excellent for those that respond to soluble fiber supplementation. Since no specific clinical findings have been identified that can predict whether an individual dog will respond to fiber therapy, a therapeutic trial is necessary. The prognosis is more guarded for those patients that do not respond or only partially respond to fiber supplementation and require drug therapy for IBS.

**KEY FACTS**

- Dogs with fiber-responsive chronic large bowel diarrhea (FRLBD) likely represent a separate syndrome or a subset of IBS patients that respond to dietary fiber supplementation The predominant clinical sign of dogs with FRLBD is chronic intermittent large bowel diarrhea with hematochezia, excess fecal mucus, and tenesmus.
- A highly digestible fat-restricted diet supplemented with 1–3 tablespoons/day of psyllium will benefit most dogs with FRLBD.

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
svg.to/9842-08-03-05

### 8.3.6 Feline megacolon

Andreas H. Hasler

#### 8.3.6.1 Definition and etiology

Megacolon denotes an enlarged, dilated colon. This dilation is associated with a loss of function. The most obvious dysfunction is decreased or absent transport of feces, and hence, the main clinical sign of megacolon is constipation or obstipation (▶ Chap. 2.5). The goal of the diagnostic evaluation and treatment is to identify the underlying cause and, if possible, restore proper transport of feces.

**NOTE**

**Constipation** is characterized by infrequent, incomplete, or difficult defecation, with the passage of hard or dry bowel movements (feces). Constipation does not necessarily imply permanent loss of function.

**Obstipation** is pronounced constipation that is difficult to manage or does not respond to medical treatment. Obstipation is caused by prolonged retention of hard, dry bowel movements. Defecation becomes impossible for patients with this condition.[1]

There is no single or uniform etiology of megacolon in the cat. From a clinical perspective, it is important to differentiate the loss of colonic muscle tone (i.e., colonic inertia) from outlet obstruction (▶Tab. 8-2), as this dictates treatment. An extensive list of differential diagnoses should be considered in an individual animal. However, it should be kept in mind that most cases are idiopathic, orthopedic, or neurologic in origin. Idiopathic megacolon is the most common diagnosis, occurring in approximately 60–70% of affected cats. Neurologic disorders constitute approximately 11% of the cases, and those due to an outlet obstruction are 23% of the cases.[2]

**Tab. 8-2** Differential diagnoses for megacolon in the cat

| |
|---|
| **Colonic inertia** |
| Idiopathic megacolon |
| Neurologic diseases<br>• Spinal cord diseases<br>– Lumbosacral disease<br>– Cauda equina syndrome<br>– Sacral spinal cord deformities (Manx cat)<br>• Hypogastric or pelvic nerve disorders<br>– Traumatic injury<br>– Malignancy<br>– Dysautonomia<br>• Submucosal or myenteric plexus neuropathy<br>– Dysautonomia<br>– Aging |
| Metabolic or endocrine disease<br>• Metabolic<br>– Dehydration<br>– Hypokalemia<br>– Hypercalcemia<br>• Endocrine<br>– Hypothyroidism<br>– Obesity<br>– Nutritional secondary hyperparathyroidism |
| Secondary to prolonged colonic distention (e.g., outlet obstruction) |
| **Outlet obstruction** |
| Pelvic fracture malunion |
| Colonic, rectal, or anal stricture or neoplasia |
| Foreign body or improper diet |
| Anal or rectal atresia |

### 8.3.6.2 Pathophysiology

Normal cats can retain feces in the colon for several days without any demonstrable adverse effects.[3] With prolonged retention of feces, absorptive processes dehydrate and solidify the feces. The fecal volume can become so large that passage through the pelvic canal is physically impossible, and the colon becomes dilated. If this dilation exists for a prolonged period of time, irreversible changes can occur. The degree of colonic dilation and duration of time needed to produce irreversible changes are not known. Based on empiric observations, a period of approximately 6 months has been suggested.[4]

The pathogenesis of idiopathic megacolon has not been fully elucidated, and this condition may not be a uniform disease. Histologically (hematoxylin and eosin [H&E] staining), the colon reveals few abnormalities.[5,6] In vitro isometric stress measurements have been performed on colonic smooth muscle obtained from cats with idiopathic dilated megacolon.[6] These studies suggest that the disorder of feline idiopathic megacolon is a generalized dysfunction of colonic smooth muscle.

Some authors[5] found neuronal depletion in the form of reduced numbers of interstitial cells of Cajal. As pacemakers of slow waves, their reduction may decrease contraction and lead to constipation.

The role of the intestinal microbiota has not been evaluated in cats with megacolon. However, in other species, there is little doubt that there is a connection between the gut microbiome and intestinal motility.[7]

### 8.3.6.3 Clinical history

Constipation, obstipation, and megacolon may be observed in cats of any age, sex, or breed. However, most cases are observed in middle-aged (mean 5.8 years) male cats (70% male, 30% female) of domestic shorthair (46%), domestic longhair (15%), or Siamese (12%) breed.[2] Affected cats are usually presented for reduced, absent, or painful defecation for a period of time ranging from days to weeks or months. Some cats are observed making multiple, unproductive attempts to defecate, while other cats may sit in the litter box for prolonged periods of time without assuming a defecation posture. Dry, hardened feces are observed inside and outside of the litter box.

**CLINICAL PEARLS**

Occasionally, chronically constipated cats have intermittent episodes of hematochezia or diarrhea due to mucosal irritation caused by fecal concretions. This may give the pet owner the erroneous impression that diarrhea is the primary problem.

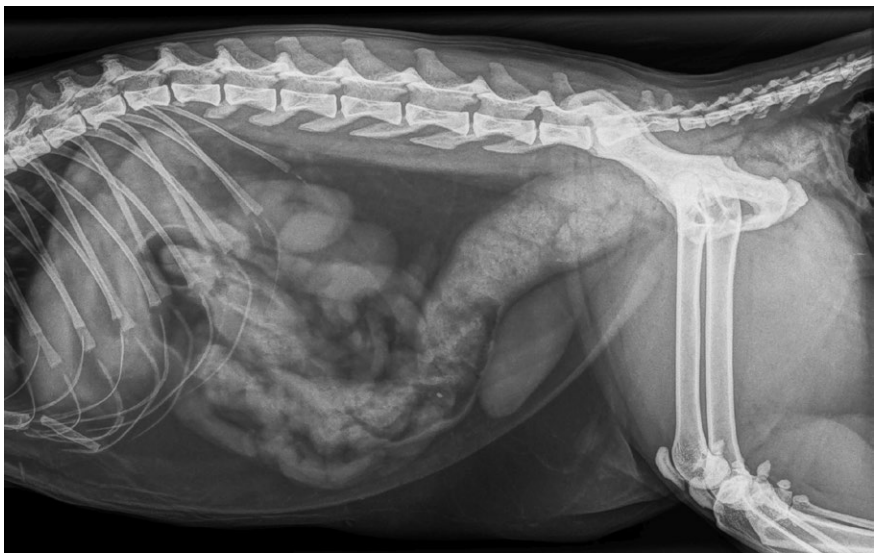


**Fig. 8-9** Lateral abdominal radiograph of a constipated cat

Note the dilation of the colon and a feces-filled rectum.

Some cats show fecal incontinence. In the author's experience, these cats have a dilated feces-filled rectum in addition to the dilated colon (▶Fig. 8-9). A prolonged inability to defecate may result in other systemic signs, including anorexia, lethargy, weight loss, and vomiting. In outdoor cats that do not have access to a litter box or in multicat households, these clinical signs may be the presenting complaints rather than constipation.

#### 8.3.6.4 Clinical presentation

Colonic impaction is a consistent physical examination finding in affected cats. In severely obese cats, physical palpation may be difficult. Other findings will depend on the severity and pathogenesis of constipation. Dehydration, weight loss, debilitation, abdominal pain, and mild to moderate mesenteric lymphadenopathy may also be observed in cats with severe idiopathic megacolon. Colonic impaction may be so severe as to render it difficult to differentiate impaction from colonic, mesenteric, or other abdominal neoplasia. Cats with constipation due to dysautonomia may have other signs of autonomic nervous system failure, such as urinary and fecal incontinence, regurgitation due to megaesophagus (▶Chap. 5.3.8), mydriasis, decreased lacrimation, prolapse of the nictitating membrane, and bradycardia.

#### 8.3.6.5 Diagnosis

The minimal diagnostic workup should include a neurologic examination, rectal palpation, and abdominal radiographs. The neurologic examination should focus on lower motor neuron signs (e.g., spinal cord injury and pelvic nerve trauma). Rectal palpation should be performed in all cats, but sedation or anesthesia may be necessary to prevent pain and incomplete palpation. The examination should include the anal area (anal sacs, anal sphincter, and evaluation for perianal fistulas), the rectum (evaluation for herniation, stricture, inflammation, foreign body), and the pelvic canal (pelvic floor, prostate, and urethra).

**Abdominal radiographs**, including the pelvis, are indicated to

**a)** assess the amount of fecal impaction,
**b)** assess the anatomic regions, i.e., the colon and/or rectum (▶Fig. 8-10),
**c)** rule in or exclude pelvic narrowing, and
**d)** educate the client.

It should be emphasized that the diameter of the colon has a wide range in normal and in constipated cats.[8] One study found normal colonic diameters to vary between 11–30 mm, and in constipated cats to range from 27–57 mm. To improve the diagnostic accuracy, the authors suggest comparing the colonic diameter on radiographs to the length of the 5th lumbar vertebra (L5). A high diagnostic accuracy was achieved when a cut-off of 1.28 times the length of L5 was used (▶Fig. 8-10).

**Ancillary studies** may be indicated in some cases. Extraluminal mass lesions may be further evaluated by abdominal ultrasonography and ultrasound-guided biopsy (▶Chap. 1.4.6.3), whereas intraluminal mass lesions are best evaluated endoscopically. Colonoscopy (▶Chap. 1.5) may also be used to evaluate the colon and anorectum for suspected inflammatory lesions, strictures, sacculations, and



**Fig. 8-10** Lateral abdominal radiograph of a constipated cat

Note the markedly dilated colon with a maximum diameter that is about twice the length of the 5th lumbar vertebra (L5).

diverticula. Barium enema contrast radiography (▶Chap. 1.4) may be used if colonoscopy is not possible. Cerebrospinal fluid analysis, computed tomography (CT) or magnetic resonance imaging (MRI), and electrophysiological studies should be considered in animals with evidence of neurologic signs. Finally, colonic biopsy or anorectal manometry will be necessary to diagnose suspected cases of aganglionic megacolon.

While most patients with obstipation and megacolon are unlikely to have significant clinicopathologic changes (i.e., CBC, serum biochemistry profile, and urinalysis parameters), these tests should be performed in cats presented for further evaluation of constipation. Metabolic causes of constipation, such as dehydration, hypokalemia, and hypercalcemia, may be detected in some cases. Though hypothyroidism is a rare cause of constipation in cats, basal serum thyroxine (T4) concentration and other thyroid function tests should also be considered in cats with additional clinical signs consistent with a diagnosis of hypothyroidism.

**CLINICAL PEARLS**

Constipation could theoretically also develop following successful treatment of feline hyperthyroidism.

### 8.3.6.6 Treatment

Treatment is directed towards

1. removal of feces and restoring fecal passage,
2. addressing the underlying cause, and
3. preventing further episodes of constipation.

#### 8.3.6.6.1 Removal of feces

Once megacolon has developed, these cases are often unresponsive to rectal suppositories or repeated enemas, and nasopharyngeal tube application of polyethylene glycol solution or manual extraction of impacted feces is required. Hence, hospitalization may be warranted. Intravenous fluid therapy prior to further intervention may help restore hydration and prevent further compaction of feces.

**Enemas**

Severe cases should be adequately rehydrated and then anesthetized with an endotracheal tube in place to prevent aspiration should colonic distension induce vomiting. Several types of enema solutions may be chosen. Any solution used for the enema should be warmed to body temperature. The procedure is most likely to take 30–60 minutes and warming the patient during anesthesia may be helpful. Enemas given too rapidly may not soften the feces adequately as they are expelled quickly. Solutions that may be used:

1. warm tap water (5–10 ml/kg), which carries the risk of water intoxication,
2. warm isotonic saline or Ringer's solution (5–10 ml/kg),
3. polyethylene glycol solution (5–10 ml/kg),
4. dioctyl sodium sulfosuccinate (5–10 ml/cat), or
5. lactulose solution (5–10 ml/cat). Enema solutions should be administered with a well-lubricated 10–12 Fr rubber catheter or a Higginson pump.

Massage of the colon and repeating the enema is often necessary.

Enemas containing sodium phosphate are contraindicated in cats because of their propensity for inducing severe hypernatremia, hyperphosphatemia, and hypocalcemia in this species.[9]

Oral application of a sufficient amount of polyethylene glycol solution (e.g., MiraLAX®, CoLyte®, or GoLYTELY®®) is rarely possible in cats.

An elegant alternative is to apply the polyethylene glycol solution via a nasoesophageal tube as a slow drip (6–10 ml/kg/h) over several hours. Defecation usually results within 6–12 hours. In a retrospective study of nine cats,[10] the median time to defecation was 8 hours, and the median total dose of polyethylene glycol 3350 was 80 ml/kg.[11] Adverse effects were limited to vomiting in one cat and hyponatremia in five cats.

### Manual extraction

As with enemas, if manual extraction of feces is indicated, these cases should be adequately rehydrated and then anesthetized with an endotracheal tube in place. An enema (see above) is administered into the colon while the fecal mass is manually reduced by abdominal palpation. Instruments to grab or break up feces should have round tips, such as sponge forceps. Careful insertion and retrieval are advised. Repeated enemas in between help to keep the colon dilated and reduce the risk of perforation. A second intervention may be needed if complete evacuation of feces is not achieved within reasonable anesthetic time.

#### 8.3.6.6.2 Addressing the underlying cause

Any disease or condition contributing to the development or worsening of megacolon should be addressed. Partial pelvectomy or pelvic reconstructive procedures can be used for pelvic fracture malunion.[4] Mass excision, segmental proctectomy or colectomy, or bougienage (preferred by the author) or ballooning can be performed to excise obstructive mass lesions or strictures. Foreign bodies should be removed, and diet changes made when indicated. The major dilemma in treating an outlet obstruction is whether the dilated colon can function properly after removing the obstruction. In cases of pelvic fracture malunion, it has been recommended that removing the obstruction (i.e., pelvic resection) be performed in cats with clinical signs of constipation present for <6 months, with colectomy being reserved for those cats with a longer history of clinical signs.[4] However, these guidelines have been established empirically based on a small number of cases.

#### 8.3.6.6.3 Preventing further episodes of constipation

Medical treatment aims at softening the feces by administering some form of laxatives (including food additives) and/or activating the colonic wall smooth muscle via prokinetic drugs.

### Food and food additives

Dietary fiber (▶Chap. 3.2.1) binds water and softens the feces, promoting the intestinal secretion of mucin by stimulating mucosal protein synthesis. The fiber is broken down in the proximal colon and provides a substrate for microbial fermentation.[12] These substrates stimulates the growth of the intestinal microbiota and contributes significantly to the fecal dry weight. Besides, dietary fiber promotes the excretion of bacterial fermentation products, such as short-chain fatty acids (SCFA), which can stimulate intestinal motility. Possible mechanisms of SCFAs in gut motility may involve the intestinal release of 5-HT.[13] One study of 66 cats fed a psyllium-enriched extruded dry diet showed an improvement in 93% of the cats with no additional medication and in 80% of the cats that received other medications.[14]

However, there is a debate, and testimonials on the internet diverge about the ideal type of food. The American College of Veterinary Surgery (ACVS) states that a low residue diet is the preferred type of food (https://www.acvs.org/small-animal/megacolon). The rationale for feeding a low residue diet is based on the assumption that a weakened colon benefits from a reduced luminal volume to be transported aborally.

### Laxatives

Most laxatives work either by softening the feces or stimulating intestinal motility, hence counteracting the mechanisms involved in constipation. There are a plethora of products available for the treatment of constipation. Laxatives have been classified as:

1. Lubricant
2. Bulk-forming
3. Emollient
4. Stimulant
5. Osmotic

For over 30 years, emphasis has been placed on the differentiation of the many mechanisms of laxative actions.[1] However, there are no comparative clinical trials, and studies on the safety of laxatives are also scarce.[11] Regardless of the mechanism of action, the cats' daily medication with a laxative is a major problem for many cat owners.

**Lubricant laxatives** Mineral oil and white petrolatum (paraffin in Europe) are the two major ingredients of lubricant laxatives. By decreasing colonic water absorption and coating of the feces, they improve fecal transport and aid in constipation treatment. The main indication is hairball removal. The lubricating properties of these agents impede colonic water absorption and permit greater ease of fecal passage. However, these effects are usually moderate, and, in general, lubricants are beneficial only in mild cases of constipation.



**NOTE**

The use of mineral oil should probably be limited to rectal administration because of the risk of aspiration pneumonia with oral administration, especially in depressed or debilitated cats.

**Bulk-forming laxatives** Most of the available bulk-forming laxatives are dietary fiber supplements containing poorly digestible polysaccharides and cellulose derived principally from cereal grains, wheat bran, and psyllium.[15] Fiber-supplemented diets are available commercially, or the pet owner may wish to add psyllium (1–4 teaspoons per meal), wheat bran (1–2 tablespoons per meal), or pumpkin (1–4 tablespoons per meal) to canned cat food. Cats need to be well hydrated when opting for fiber supplementation to maximize the therapeutic effect. Fiber supplementation is most beneficial in mildly constipated cats prior to the development of obstipation and megacolon. Instead of mixing bulk to the food, a commercial high-fiber diet (see above) might be more convenient to use and results in a more reliable and consistent composition of the food.

**Emollient laxatives** Emollient laxatives are anionic detergents that increase water and lipid miscibility in the ingesta, thereby enhancing lipid absorption and impairing water absorption. Dioctyl sodium sulfosuccinate and dioctyl calcium sulfosuccinate are examples of emollient laxatives available as oral and enema formulations. Anecdotal experience suggests that dioctyl sodium sulfosuccinate therapy may be most useful in animals with acute but not chronic constipation. As with bulk-forming laxatives, animals should be well-hydrated before emollient laxatives are administered. It should be noted that the clinical efficacy has not been definitively established for emollient laxatives. Dioctyl sodium sulfosuccinate, for example, inhibits water absorption in isolated colonic segments in vitro. However, it may be impossible to achieve tissue concentrations large enough to inhibit colonic water absorption in vivo. Further studies are required to determine the clinical efficacy and therapeutic role of dioctyl sodium sulfosuccinate in feline constipation management.

**Stimulant laxatives** The stimulant laxatives (bisacodyl, phenolphthalein, castor oil, cascara, and senna) are a diverse group of agents that have been classified according to their ability to stimulate propulsive intestinal motility. Bisacodyl, for example, stimulates nitric oxide-mediated epithelial cell secretion and myenteric neuronal depolarization. Diarrhea results from the combined effects of increased mucosal secretion and colonic propulsion. At a dose of 5 mg q24h PO/cat, bisacodyl is the most effective stimulant laxative in the cat. It may be given alone or in combination with fiber supplementation. However, daily administration of bisacodyl should probably be avoided because of the risk of myenteric neuron injury with chronic use.

**Hyperosmotic laxatives** This group of laxatives consists of the magnesium salts (e.g., magnesium citrate, magnesium hydroxide, or magnesium sulfate), the poorly absorbable polysaccharides (e.g., lactose or lactulose), and polyethylene glycol solutions (which are also used for colonoscopy preparation). Magnesium salts are not currently recommended in the treatment of feline constipation and idiopathic megacolon. Lactose is not effective as a laxative agent in cats. The organic acids produced from lactulose fermentation stimulate colonic fluid secretion and propulsive motility. Lactulose administered at a dose of 0.5 ml/kg body weight PO q8–12h fairly consistently produces soft feces in the cat. Lactulose may cause increased intestinal calcium (and magnesium) absorption and lead to hypercalcemia in cats. While many cats were successfully treated with lactulose in the past, a survey showed that many cat owners claimed better results after switching to a polyethylene glycol product. The safety of chronic oral polyethylene glycol administration has been documented in healthy cats.[11] The powder was mixed with food, and palatability was good. Starting doses were 3 ± 1 g/day/cat, and final doses were 0.8–3.8 g/day/cat. Dosages for lactulose and polyethylene glycol have to be individually tapered and adapted based on the course of the disease.

## Colonic prokinetic agents

Previous studies of feline colonic smooth muscle function suggested that stimulation of colonic smooth muscle contraction improves colonic motility in cats affected with idiopathic dilated megacolon.[6] Unfortunately, many of the currently available gastrointestinal (GI) prokinetic agents have not proved useful in the treatment of feline constipation because of either significant side effects (e.g., bethanechol) or the prokinetic effect being limited to the proximal GI tract (e.g., metoclopramide, domperidone, or erythromycin).

**The 5-HT4 serotonergic agonists** (e.g., cisapride, prucalopride, tegaserod, and mosapride) appear to have the advantage of stimulating motility from the gastroesophageal sphincter to the descending colon with relatively few side effects. **Cisapride**, for example, increases gastroesophageal sphincter pressure, promotes gastric emptying, and enhances small intestinal and colonic propulsive motility. Cisapride enhances colonic propulsive motility by activating colonic neuronal or smooth muscle 5-HT receptors in several animal species.[16] In vitro studies showed that cisapride stimulates feline colonic smooth muscle contraction, although it has not been conclusively shown that cisapride stimulates feline colonic propulsive motility in vivo.[17] A large body of anecdotal experience suggests that cisapride effectively stimulates colonic propulsive motility in cats affected with mild to moderate idiopathic constipation. Cats with long-standing obstipation and megacolon are not likely to show much improvement with cisapride therapy. Cisapride was widely used to manage canine and feline gastric emptying, intestinal transit, and colonic motility disorders throughout most of the 1990s.[16] The drug was withdrawn from the market in the USA, Canada, and certain western European countries in July 2000 following reports of untoward cardiac side effects in human patients. Similar cardiac effects have been characterized in experimental dogs, but in vivo effects have not been reported in dogs or cats. The withdrawal of cisapride created a need for new GI prokinetic agents. However, cisapride continues to be available in some European countries and from compounding pharmacies throughout the United States.

**Prucalopride** and **mosapride** are alternative 5-HT medications. In vitro effects on isolated colonic smooth muscle have been reported[18] and clinical studies, though with only small numbers of cats. Mosapride was given at a dose of 5 mg PO q12h to 15 cats with chronic constipation.[19] In 14 cats, there was no recurrence of constipation while receiving mosapride. None of the cats experienced prolongation of the QT-interval or GI adverse effects.

**Misoprostol** is a **prostaglandin E1 analog** that reduces the incidence of NSAID-induced gastric injury. The main side effects of misoprostol therapy are abdominal discomfort, cramping, and diarrhea. Studies in dogs suggest that prostaglandins can initiate a giant migrating complex pattern and increase colonic propulsive activity. In vitro studies showed that misoprostol stimulates feline and canine colonic smooth muscle contractions. Given its limited toxicity, misoprostol may be useful in cats (and dogs) with severe refractory constipation.

**Ranitidine and nizatidine** are classic **histamine H2 receptor antagonists** and can also stimulate colonic motility in dogs and cats. These drugs stimulate contraction by inhibiting tissue acetylcholinesterase and the accumulation of acetylcholine at the motor endplate. It remains unclear how effective these drugs are in vivo, although both $H_2$ receptor antagonists stimulate feline colonic smooth muscle contraction in vitro. Cimetidine and famotidine, members of the same class of drugs, lack this effect.

## Altering the colonic microbiome

Modulating the enteric microbiome is a treatment option that has gained interest in the last few years. One study with a commercial probiotic showed significant clinical improvement in cats with chronic constipation.[5] Fecal microbial transplantation (FMT) is recommended in selected cases in human medicine. There are reports of FMT in cats for colitis treatment[20] but currently none for the treatment of feline megacolon.

## Surgery

Colectomy should be considered in cats that are refractory to medical therapy. Colectomy is also indicated in cats with a concurrent perineal hernia and is performed before perineal herniorrhaphy is considered. Different colectomy techniques have been described in detail elsewhere.[1,3] In the cat, total and subtotal colectomy with preservation of the ileocolic valve can be a successful surgical treatment for idiopathic megacolon.[3,21] Subtotal colectomy entails sparing the ileocolic valve to reduce the risk of small intestinal dysbiosis or bacterial overgrowth. However, this recommendation has been challenged.[3]

Arguments for a total colectomy are
**a)** it is easier to perform,
**b)** it allows a tension-free anastomosis, and
**c)** it is more likely to prevent recurrent constipation.

There are testimonials from cat owners on the internet where subtotal surgery was not successful and total colectomy resolved the clinical problem. Regardless of the type of surgery, cats have a generally favorable prognosis for recovery following colectomy. Most cats start eating within 24–48 hours after surgery. Most cats produce semisolid unformed feces after 1 week and soft formed feces by 6–12 weeks after surgery, although mild to moderate diarrhea may persist for weeks to months postoperatively in some cases. Overall, feces are often softer, and defection frequency increases to 2–4 times per day in colectomized cats.

#### 8.3.6.7 Prognosis

Many cats have one or two episodes of constipation without further recurrence, although others may progress to complete colonic failure. Cats with mild to moderate constipation generally respond to conservative medical management (i.e., dietary modification, emollient or hyperosmotic laxatives, and colonic prokinetic agents). Early use of colonic prokinetic agents (in addition to one or more laxative agents) is likely to prevent the progression of constipation to obstipation and megacolon in these cats. Some cats may become refractory to these therapies; these cats eventually require colectomy. Cats have a generally favorable prognosis for recovery following colectomy.

**KEY FACTS**

- Megacolon is a disorder found most often in male, middle-aged cats, although it may affect cats of any age, gender, or breed.
- Most cases of feline megacolon are idiopathic.
- Medical therapy consists of colonic reduction of impacted fecal material, laxative therapy, prokinetic treatment, and surgery.
- Cats may have transient diarrhea following subtotal colectomy, but most recover normal intestinal function following such surgery.

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
svg.to/9842-08-03-06

### 8.3.7 Neoplastic diseases of the large intestine

Emma Warry

#### 8.3.7.1 Introduction

Unlike in humans, large intestinal (LI) tumors in dogs and cats are rare.[1–4] The incidence of LI neoplasia is unknown as all tumors of the alimentary system tend to be reported together regardless of location.[5,6] Malignant epithelial tumors are the most common non-lymphoid neoplasms of the LI in dogs and cats.[1–4] The World Health Organisation (WHO) describes the following malignant tumor types: acinar (tubular) adenocarcinoma (ACA), papillary ACA, mucinous ACA, signet-ring cell carcinoma, undifferentiated carcinoma, and adenosquamous carcinoma.[7]

The tumor growth pattern can be further subclassified as polypoid or non-polypoid.[7,8] Tumors with a polypoid growth pattern prescribe to the "adenoma-carcinoma sequence" theory, where carcinogenesis results in the progression of a benign precursor lesion to a malignant tumor.[7–10] Whereas tumors with a non-polypoid growth pattern follow *de novo* carcinogenesis, where a malignant lesion develops without the initial presence of a precursor.[8–10]

Benign epithelial tumors, including adenomatous polyps and *carcinoma-in-situ*, account for a large proportion of the remaining LI neoplasia cases. Adenomatous polyps are found primarily in the rectum, whereas *carcinoma-in-situ* can be found in the colon or rectum.[11]

Other non-lymphoid neoplasms reported in the canine LI include leiomyosarcoma, leiomyoma, gastrointestinal stromal tumor, extraosseous osteosarcoma, colonic hemangiosarcoma, lymphangiosarcoma, ganglioneuroma, and extramedullary plasmacytoma.[11–16]



In cats, non-lymphoid LI neoplasia has historically been reported to occur less frequently than in the SI.[17–19] However, recent information (▶Chap. 7.3.9) suggests more of an equal distribution with a significant predisposition of ACA in the LI.[17] Other tumor types reported in the LI of cats include mast cell tumors, squamous cell carcinomas, hemangiosarcomas, leiomyosarcomas, and fibrosarcomas.[17,18,20]

### 8.3.7.2 Incidence

Colorectal cancer (CRC) in people is the second most common cause of cancer death in the United States.[21] Most cases arise spontaneously.[21] Risk factors have been identified and can be considered either modifiable or non-modifiable.[21] CRC induced by modifiable risk factors occur most frequently. Established risk factors include smoking, diet, alcohol consumption, physical inactivity, and excess body weight.[21] Chronic inflammation occurring with inflammatory bowel disease (IBD) is a non-modifiable risk factor, accounting for <2% of total cases.[21,22]



Risk factors for the development of sporadic CRC in dogs are not established. However, a recent evaluation of the pathogenic pathways in canine CRC demonstrated similarities with human CRC, suggesting a similar mechanism of carcinogenesis.[23,24] A unique type of colorectal nonneoplastic inflammatory polyp has been described in a population of Japanese miniature dachshunds, termed inflammatory polyp of miniature dachshund (IPMD).[25]

In a recent study, 56% of dogs initially diagnosed with IPMD were later diagnosed with adenoma or ACA when biopsied.[25] The authors concluded that similar to human CRC, IPMD is a progressive disease with the potential to develop into adenomas or ACAs. Previously, these authors demonstrated a significantly altered fecal microbiome in miniature dachshunds with IPMD compared to those without, suggesting intestinal dysbiosis to play a role in the progression of IPMD to adenomas or ACAs.[25,26]

Microbiota profiles of humans with CRC differ from those without CRC.[27,28] The contribution of the **intestinal microbiome** to tumorigenesis in human CRC and its potential as a therapeutic target is currently being evaluated. The fecal and intestinal mucosal microbiota in a small number of dogs with colorectal epithelial tumors was recently characterized and compared to a control population.[29] A difference in the fecal microbial community was identified, but the effect on tumorigenesis could not be adequately evaluated due to the small sample size.[29]

Isolation of enterohepatic *Helicobacter* spp. (EHS) in cats was significantly associated with the presence of non-hematopoietic intestinal carcinoma in the LI, particularly the mucinous ACA subtype.[30] This suggests that intestinal bacteria, particularly EHS, may play a role in the pathogenesis of LI carcinoma in cats. However, further work is needed to better characterize a cause and effect.[30]

In both dogs and cats, LI cancer develops in middle-aged to older animals.[1–4,8,11] Some studies indicate cats with LI adenocarcinoma to be significantly older than those with small intestinal (SI) adenocarcinoma, but the number of cases evaluated was small. Except for the miniature dachshund described above, there is no consistently identified breed predisposition in dogs.[1–4,8,11,12,23] The significance of breed size as a potential risk factor in some studies likely reflects different cultural preferences in certain dog breeds affecting the patient population evaluated rather than a true predisposition for the development of LI cancer.



In cats, multiple studies have identified the Siamese to be at increased risk (1.8–3.7 times) for developing intestinal neoplasia.[11,17,18]

Differences in cancer risk based on location in the SI vs. the LI have not been reported. In dogs, similar incidences of intestinal cancer are reported between males and females. However, a small number of studies have found an increased incidence in males. Male cats are more frequently reported to have LI ACA than females, aligning with what is seen in humans.[11,17,18,30]

### 8.3.7.3 Clinical presentation

The duration and severity of clinical signs can vary greatly. Most dogs and cats with LI neoplasia have reported clinical signs ≤12 weeks prior to initial presentation, but in some cases, onset may be acute.[4,7,11,12,31] As with SI neoplasia, clinical signs may include weight loss, diarrhea, vomiting, anorexia, melena, and/or anemia. Additionally, dogs and cats with LI neoplasia may present with hematochezia, tenesmus, and/or dyschezia. Severe hematochezia and hemorrhage can cause moderate to severe anemia requiring emergent treatment and stabilization. This is more likely with epithelial tumors but is also reported with mesenchymal tumors.[32] Although less common in the LI, tumors can cause rupture of the intestinal wall and localized peritonitis. These patients will likely have clinical signs indicating an acute abdomen. Dogs and cats with carcinomatosis or sarcomatosis may present with abdominal distention, peritoneal effusion, and pain. In addition to the paraneoplastic syndromes reported for SI neoplasia, alopecia has been reported in a cat with metastatic colonic carcinoma and neutrophilic leukocytosis in dogs with rectal tumors.[33,34]

#### 8.3.7.4 Diagnostic evaluation and staging

The diagnostics discussed for SI neoplasia are also relevant for neoplasia in the LI. Additionally, **proctoscopy and colonoscopy** (▶Chap. 1.5) can be useful in determining the extent of colorectal neoplasia. Data suggests that the presence of multiple lesions in dogs is rare, with a recent study reporting multiple lesions identified via colonoscopy in 6/82 dogs (7%) evaluated.[35] Despite the infrequency of multiple lesions, colonoscopy is the most valuable diagnostic tool to identify affected dogs. CT scanning is increasingly being used for surgical planning and assessment of distant and locoregional metastatic disease, but evaluation of the intestinal mucosa is often difficult and may require follow-up colonoscopy to characterize the significance of any abnormalities identified.[36] In cases where the integrity of the mucosa is visually questionable proximal and/or distal to the mass, biopsies can be obtained and submitted for histopathology prior to surgical excision. This information can be very valuable for surgical planning, but it is important to ensure that any biopsies obtained will not negatively impact a definitive surgical procedure.

**Fine-needle aspirates** of LI neoplasias can be difficult pending location and should be attempted with image guidance. The success of such aspirates will depend on the layer of the intestinal wall involved, the presence of an extraluminal component, and the type of mass being aspirated. Tumors in the distal colon and rectum can be very difficult to visualize with ultrasound due to artifacts created by the pelvis. These tumors should be biopsied via proctoscopy or colonoscopy and submitted for histopathology. Distal intraluminal masses are often friable, and tissues can be obtained for histopathology via digital palpation. Diagnosis of LI neoplasia should be verified prior to prescribing surgery. An exception to this would be a patient with LI perforation or uncontrollable hemorrhage, where surgery is required for stabilization. Abdominocentesis should be performed on any patient with free intraperitoneal fluid so it can be evaluated for septic peritonitis, carcinomatosis, and sarcomatosis. Diagnosis of carcinomatosis or sarcomatosis will change the treatment approach and prognosis.

If any local or regional lymphadenopathy is noted, attempts should be made to aspirate and evaluate cytology prior to surgery. If aspirates are not possible or cytology is nondiagnostic, surgical excision of local lymph nodes should be considered to complete tumor staging.

**Metastasis** of LI neoplasia is most likely to occur locoregionally in lymph nodes with epithelial tumors and in the liver for mesenchymal tumors.[11] Pulmonary metastasis is also possible. Other sites of metastasis may include mesentery, omentum, spleen, kidney, bone, and peritoneum. Tumor staging should include a physical examination, abdominal ultrasound, and three-view thoracic radiographs. As discussed above, CT scanning can also be utilized for both staging and surgical planning and can be particularly helpful in large dogs where abdominal ultrasound is more difficult.

#### 8.3.7.5 Treatment

**Surgery** is the primary treatment for LI neoplasia.[11] The extent of surgery will depend on the underlying pathology of the lesion, demonstrating the necessity for a preoperative diagnosis. Several surgical approaches can be implemented based on tumor characteristics, including size, depth of invasion into the muscularis, and location within the LI. Few tumors are candidates for colectomy, and in most dogs and cats, the procedure is subtotal, limited by the ileocolic junction and the distal colon located within the pelvic canal. There are many possible complications, and the procedure is technically challenging. It should be performed by a skilled surgeon after thorough education of the client.

For **benign rectal polyps**, mucosal eversion and submucosal resection are recommended and sufficient for local disease control.[11] Transrectal endoscopic removal of polyps is also described, improving the patient's quality of life but resulting in an incomplete removal. Local recurrence is common following mucosal eversion, with 41% of dogs experiencing a return of clinical signs.[11,37,38] Additionally, 18% of rectal polyps are reported to undergo malignant transformation.[38]

For **malignant rectal tumors**, full-thickness removal via a rectal pull-through is recommended.[11,39,40] This procedure can be performed via a perineal or a combined perineal-abdominal approach.[39,40] Possible complications include diarrhea, tenesmus, stricture formation, bleeding, wound dehiscence, and infection. Clients must be aware that fecal incontinence is reported in 57% of dogs postoperatively and becomes permanent in 40%.[39,40]

The role of **chemotherapy** in dogs following surgery is unknown. Doxorubicin or carboplatin are most commonly initiated if there are concerns about aggressive tumor behavior.



In cats, administration of doxorubicin following subtotal colectomy demonstrated a significant survival advantage. Median survival times (MST) were 280 days with and 56 days without doxorubicin.[19]

The role of chemotherapy in a gross disease setting for dogs and cats has not been investigated.

**Rectal stenting** has been reported to palliate neoplastic obstruction caused by a colorectal tumor in a dog and two cats.[41,42] All animals experienced an improvement in clinical signs but continued to have intermittent tenesmus and obstipation.[41,42]

The administration of **tyrosine kinase inhibitors** (TKI) such as toceranib phosphate has been used by the author for colorectal carcinoma in dogs and cats when surgery is not pursued. Experience suggests a clinical benefit in some dogs and cats, but this is based on a small number of patients and should be evaluated cautiously.

#### 8.3.7.6 Prognosis

Prognosis with LI neoplasia depends on the tumor type, presence of metastasis at diagnosis, type of therapy initiated, and completeness of excision.

In dogs with colorectal tumors, surgical excision significantly prolongs survival over palliation alone. MSTs for colorectal ACA following a rectal pull-through procedure range from 2–4 years, compared with dogs receiving stool softeners who survive approximately 15 months.[11,31,39,40]

While these survival times are encouraging, clients need to be appropriately educated about the long-term management and potential impact of postoperative complications on the quality of life.[39,40]

Prognosis in cats with colorectal ACA does not appear to be as durable as reported in dogs.

### References

The complete list of references for this chapter can be downloaded from vetline.de:
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## 8.4 Diseases of the anorectum

### 8.4.1 Proctitis and rectal prolapse

Lars F.H. Theyse, Romy M. Heilmann

#### 8.4.1.1 Proctitis

Proctitis, an inflammation of the rectum, is often not isolated but extends into the colon. The inflammation can be primary, or it can be secondary to an infectious disease (e.g., endoparasites such as *Trichuris vulpis* or *Tritrichomonas blagburni*, endemic fungal or algal infections such as *Histoplasma capsulatum* or *Phytium insidiosum*), diet, metabolic diseases, toxins, medications (e.g., NSAID enteropathy), or trauma.[1] Primary (idiopathic) proctitis is a diagnosis of exclusion. There is no sex or breed predisposition except for proctitis associated with granulomatous colitis (▶Chap. 8.3.1.2).

##### 8.4.1.1.1 Clinical presentation and diagnosis

Clinical signs of proctitis include large bowel signs (i.e., tenesmus, hematochezia, dyschezia, increased fecal mucus production), fecal reservoir incontinence, and signs of rectal discomfort or pain (e.g., scooting).[1] Rectal neoplasia and prostatic (male patients) or lower urinary tract disease are to be excluded as differentials. Physical examination is often unremarkable, but rectal palpation (whenever possible and tolerated by the patient) may reveal a thickened, irregular mucosa and hematochezia. Concurrent perianal fistulas can be seen in some dogs with primary proctitis or proctocolitis.

A minimum database (i.e., hematology, biochemistry profile, urinalysis) is often unremarkable. Nonspecific findings include neutrophilia due to inflammation, eosinophilia due to endoparasites or fungal disease, hyperglobulinemia resulting from an inflammatory process, or hypercalcemia that can be associated with some types of neoplasia or granulomatous disease. If indicated, routine fecal parasitology should be complemented by molecular diagnostics for specific enteropathogens. However, fecal bacterial cultures are of little diagnostic value. A rectal scrape for cytology can detect fungal or neoplastic diseases. Diagnostic imaging (e.g., abdominal radiographs, ultrasonography) can rule out other etiologies and evaluate the intestinal wall and the presence of lymphadenopathy. Definitive diagnosis may require endoscopy (after preparation of the colorectum) with a collection of tissue biopsies.

#### 8.4.1.1.2 Treatment and prognosis

**Dietary management** with a hypoallergenic diet and/or supplemental fermentable fiber (e.g., psyllium) should be initiated (▶Chap. 3.2.1). **Empirical anthelminthic therapy** (fenbendazole 50 mg/kg PO q24h for 5 days) is also recommended. **Pain control** may be needed in some patients. Specific medical treatment should address any underlying infections (e.g., ronidazole to eradicate *T. blagburni*, itraconazole for *H. capsulatum*), primary inflammation (sulfasalazine 25–40 mg/kg PO q12h for 3 weeks, then taper, prednisone/prednisolone 1–2 mg/kg PO q12h for 1–4 weeks then taper, cyclosporine 5 mg/kg PO q12–24h or other immunomodulatory drugs), or neoplasia (various chemotherapeutic protocols). Antibiotics are usually not indicated.

Prognosis depends on the underlying cause. Complications of proctitis include stricture formation and rectal prolapse, and both require surgical intervention.

**KEY FACTS**

- Proctitis is often not isolated but extends into the colon. Clinical signs include large bowel signs, fecal incontinence, and signs of rectal discomfort or pain.
- Dietary management and empirical anthelminthic therapy are recommended. Pain control may be needed in some patients. Specific medical treatment should address any underlying infections.

### 8.4.1.2 Rectal prolapse

A prolapse through the anal orifice can be either partial or complete. In patients with a partial rectal (anal) prolapse, only the anal mucosa protrudes. This can occur at any point of the anal circumference or include the complete circumference. In a complete (rectal) prolapse, all layers of the rectum, including the entire circumference, protrude from the anal orifice. A rectal prolapse should be distinguished from a prolapsed intussusception, in which part of the colon invaginates on itself and protrudes through the anal orifice.[2]

#### 8.4.1.2.1 Etiology

The pathogenesis of **rectal prolapse** and **prolapsed intussusception** is not fully understood, but abnormal intestinal motility in combination with increased abdominal and intrapelvic pressure seem to play a critical role. Many factors contribute to tenesmus, including colitis, proctitis, GI parasitism, colonic duplication, and tumors of the colon, rectum, and anus (▶Chap. 8.3.4, ▶Chap. 8.4.4).[3,4] Factors not primarily related to the colon, rectum, and anus can include cystitis, prostatic disease, perineal hernia, and urogenital, intrapelvic, and perineal tumors.[5–7] All of these factors have the potential to affect neurogenic motility and proprioception.



**Fig. 8-11** Acute phase of rectal prolapse in a dog

Notice the swollen red mucosa protruding through the anus and the base of the prolapse localized to the level of the anus.

#### 8.4.1.2.2 Clinical presentation and diagnosis

The presentation of rectal prolapse or a prolapsed intussusception is similar, with a cylindrical elongated mass protruding through the anus. Differentiation is by identifying the base of a rectal prolapse at the level of the anus (▶Fig. 8-11), whereas the base of the intussusception is located more cranially within the abdomen. Consequently, with an intussusception there is a space between the intussusception and rectal wall, which remains in its normal position. By probing this space with a blunt instrument, intussusception can be confirmed. As a rectal prolapse starts immediately at the level of the anus, the probing of any space at the periphery of the protruding mass will be negative.

**NOTE**

Rectal polyps can present as intermittent protrusions through the anal orifice.



**Fig. 8-12** Advanced rectal prolapse in a cat
Notice the prolapsed tissue showing evidence of venous congestion with impending tissue necrosis.

The prolapsed tissue rapidly develops congestion primarily due to a decreased venous and lymphatic return. In the acute phase, this results in a swollen red mucosa. Depending on the duration, ulceration of the mucosa, laceration of deeper wall structures, and extensive **necrosis can develop** (▶Fig. 8-12). Although the diagnosis is straightforward, a complete set of clinical and laboratory diagnostics focusing on the gastrointestinal and urogenital system should be performed. Abdominal ultrasound, in combination with abdominal and pelvic CT imaging, is essential for evaluating any predisposing factors.[8]

#### 8.4.1.2.3 Treatment and prognosis

Treatment depends on the viability of the tissue and the potential to reduce the prolapse. General anesthesia, in combination with an epidural, will facilitate the evaluation and reduce the prolapsed tissue. An anal or rectal prolapse can initially be treated with a monofilament **purse-string suture** narrowing the anal orifice to such an extent that recurrence is prevented, but soft feces can still pass. The purse-string suture is typically left in place for 3–5 days, during which swelling will diminish, and definitive treatment of the underlying cause can be pursued. With a severely damaged or devitalized rectal prolapse or prolapsed intussusception, **resection** of the necrotic tissue and an end-to-end anastomosis are necessary. Resection of rectal prolapse is performed 1–2 cm caudal of the anus, and the anastomosis is reduced cranially.[9] In a prolapsed intussusception, the resection and end-to-end anastomosis is performed within healthy colonic wall tissue, but reduction and evaluation of the intussusception through an abdominal approach are still required. To reduce the risk of recurrence, a colopexy can be performed, permanently attaching the descending colon to the ventrolateral left abdominal wall cranial of the pubic bone.[10,11] Colopexy can also be performed endoscopically.[12,13]

Complications of rectal resection and anastomosis include fecal incontinence, recurrence, and anorectal stricture formation.

**KEY FACTS**

- Although the diagnosis of rectal prolapse is straightforward, a complete set of clinical and laboratory diagnostics focusing on the gastrointestinal and urogenital system should be performed to evaluate the patient for any predisposing factors.
- Surgical treatment is often needed.

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
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## 8.4.2 Rectoanal malformations

Anna-Lena Ziese, Stefan Unterer

### 8.4.2.1 Introduction

The rectoanal area includes the internal and external anal sphincter muscles, the anal canal, rectum, and associated surrounding structures, including the muscles of the pelvic diaphragm and the anal sacs and circumanal glands.[1] Rectoanal malformations, in general, are rare conditions in companion animals and can be accompanied by urogenital malformations such as rectovaginal or urethrorectal fistulas because of the common origin of the embryonic cloaca. During embryonic development, the cloaca divides into the dorsal rectum and the ventral urogenital sinus. After ectodermal ingrowth of the perineum, the anus is formed and separated from the rectum by the anal membrane, which then ruptures to form a continuous anal canal.[2]

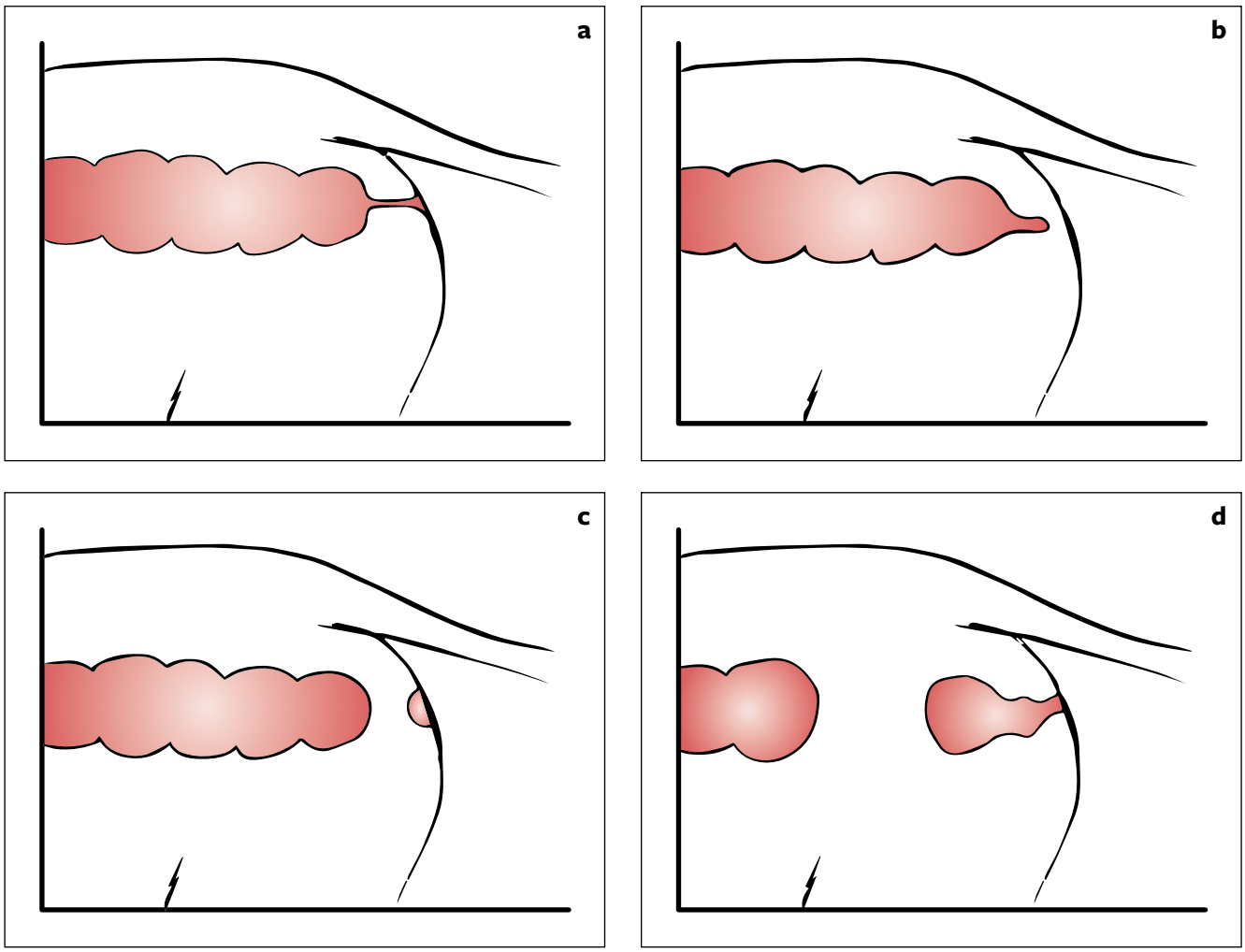



**Fig. 8-13** Types of atresia ani

**a** Type 1: anal stenosis with a fibrous ring at the anal opening

**b** Type 2: imperforate anus with a thin anal membrane

**c** Type 3: imperforate anus with the more cranial rectum terminating as a blind pouch

**d** Type 4: normal anus and distal rectum end in a blind pouch that is discontinuous with the proximal rectum

(Redrawn from Vianna ML et al., 2005[3])

*Atresia ani* (AA) is the most commonly described rectoanal malformation in cats and dogs. Although the exact incidence of AA in companion animals is unknown, because most affected puppies and kittens are euthanized shortly after birth, an incidence of 0.007% has been reported in dogs. Females are overrepresented in both dogs and cats. Finnish spitz, Boston terrier, Maltese, chow chow, German shorthair pointer, toy poodle, and miniature schnauzer are breeds predisposed for AA.[3] This malformation is defined as a congenital defect of the anorectum, resulting in anal canal closure and/or abnormal routing of feces.[2] Other congenital abnormalities, including sacrocaudal dysgenesis, tail agenesis, or open fontanel, may be concurrent malformations in patients with AA.[4]

Different types of AA are described based on the severity of the condition (▶ Fig. 8-13):

**Type 1** = anal stenosis with a fibrous ring at the anal opening

**Type 2** = imperforate anus with a thin anal membrane (most commonly occurs together with a recto-vaginal fistula[5])

**Type 3** = imperforate anus with the more cranial rectum terminating as a blind pouch

**Type 4** = normal anus and distal rectum ending in a blind pouch, which is discontinuous with the proximal rectum

#### 8.4.2.2 Clinical signs and diagnosis

Clinical signs vary depending on the type of AA. While patients with AA type 1 or 2 with concurrent rectovaginal fistula can appear asymptomatic until switched to solid foods, other types of AA usually become apparent shortly after birth. Aside from absent defecation, patients show tenesmus, abdominal distention, and nonspecific clinical signs such as anorexia and lethargy due to the accumulating fecal contents. On physical examination, perianal swelling, perineal bulging, or absence of the anus may be detected. Secondary to colonic distention, patients can develop colonic atony and megacolon (▶Chap. 8.3.6).[4] In female patients with concurrent rectovaginal fistula, vaginal defecation may be observed.[6] The patient's history, clinical signs, and findings on physical examination may suggest a diagnosis of AA. Abdominal radiographs can help to characterize the type of AA and diagnose secondary megacolon. A blunt probe can be carefully used to confirm a "blind-ending" anal tract.[7]

#### 8.4.2.3 Treatment and prognosis

Prompt surgical correction is the treatment of choice in patients with AA, with the technique depending on the underlying type. Type 1 anal stenosis cases are treated minimally-invasively with balloon dilation, whereas other types of AA require individual anoplasty. Postoperative care consists of analgesia and dietary management to ease defecation. The prognosis depends on the type of AA and concurrent malformations. Common post-surgical complications are rectal or rectoanal strictures and transient or permanent fecal incontinence.[2] Type 1 and 2 AA offer the best long-term survival rate and the possibility for sufficient fecal continence.[7]

**KEY FACTS**

- *Atresia ani* (AA) is the most commonly described rectoanal malformation in cats and dogs.
- Prompt surgical correction is the treatment of choice in patients with AA, with the technique depending on the underlying type.

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
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### 8.4.3 Perianal fistula

Adam P. Patterson

Perianal fistula(s), also known as anal furunculosis, is a chronic, progressive, painful ulcerative disease of the perianal skin with or without clinical colitis.[1] German shepherd dogs (GSD) are predisposed, but other dogs of pure and mixed-breed lineages are also affected. Although a definitive pathogenesis has not been fully elucidated, perianal fistula is an immune-mediated disease that is medically managed with immunomodulatory therapy. Perianal fistula in dogs shares some similarities with Crohn's disease in people.[2]

#### 8.4.3.1 Pathophysiology

The initial hypotheses for the development of canine perianal fistula centered on the anatomic conformation of the perianal region and tail of affected GSDs. Specifically, it was thought that a broad-based tail with low carriage encouraged fecal retention resulting in infection and abscessation. However, the lack of resolution with systemic antibiotic therapy and occurrence in other breeds of dogs negated this theory. Incrementally, with the scientific techniques available at the time, an immune-mediated pathogenesis emerged based on blunted lymphocyte proliferation response tests to phytomitogens,[3] presence of $CD3^+$ T-lymphocytes and their cytokines in affected lesional skin,[4,5] increased expression of matrix metalloproteinases in affected lesional skin,[6] and a decrease of T-cell mediated cytokine expression after cyclosporine A (CsA) treatment.[7] A definitive cutaneous or intestinal bacterial dysbiosis has not been documented in canine perianal fistula, but with today's next-generation sequencing methodologies, this should be explored.[8] Lastly, the predisposition for GSDs to develop perianal fistulas may be explained by genetic differences between affected and non-affected dogs – such as the DLA-DRB1*00101 allele and the *ADAMTS16* and *CTNND2* gene regions.[9]

#### 8.4.3.2 Clinical presentation

Perianal fistula usually affects middle-aged dogs of either sex. Dogs with perianal fistula have single or multiple malodorous ulcerative sinus tracts that often interconnect and dissect circumferentially through perianal tissue (▶Fig. 8-14). Ulcers are well-delineated, but vary in shape, size, and depth and may have an accompanying mucopurulent discharge. True fistulas, between the skin and anus/rectum, as can occur in Crohn's disease, are rare in dogs.[1,10] Lesion location and discomfort are associated with perianal licking, rubbing of the anus on the ground, hematochezia, and dyschezia. Dogs with



**Fig. 8-14** Perianal skin of a German shepherd dog with perianal fistula

The tail is extended, and perianal skin is shaved. Multiple ulcerating hemorrhagic sinus tracts are circumferential to the anal ring. Some tracts are coalescing to form large crater-like defects.

concurrent colitis may also present with soft mucoid stools, diarrhea, tenesmus, and increased defecation frequency.[1,8] However, clinical signs alone cannot be used as an indicator of colitis in cases of perianal fistula because the clinical signs can be identical.[11]

### 8.4.3.3 Diagnosis

Perianal fistula is usually a clinical diagnosis based on clinical presentation alone in GSDs. A ruptured anal sac, failed anal sacculectomy, mucocutaneous lupus erythematosus, and perianal neoplasia are the main differentials to consider. GSDs are also predisposed to mucocutaneous lupus erythematosus. However, this autoimmune dermatosis is represented by coalescing erosions and ulcers, erythema, crusting, and periulcer reticular hyperpigmentation on mucocutaneous regions not limited to the anus.[12]

**Rectal examination** should be performed with the degree of pain, determining the sedation protocol required. Digital rectal examination may reveal concurrent anal sac impaction or rupture, anorectal stenosis, and/or perineal hernia. When impacted, the anal sacs should be expressed. Difficulty expressing impacted anal sacs can occur when there is periductal inflammation and fibrosis.[1]

**Skin biopsy** is reserved for unusual presentations of perianal fistula, often in atypical small breed dogs. Histopathology shows mixed-cell periadnexal inflammation, hidradenitis, fibrosis, ulceration, and sinus tracts lined by epithelium.[13,14] Furunculosis and cellulitis may be present. When perianal fistula cannot be clinically differentiated from mucocutaneous lupus erythematosus, skin biopsy is warranted. Histopathologic features of mucocutaneous lupus erythematosus include lymphocyte-rich interface dermatitis with basal keratinocyte damage and superficial ulceration.[12] Malignant transformation has not been documented in canine perianal fistula but has been reported in people with Crohn's disease. Indeed, it would be prudent to biopsy dogs with chronic, acutely worsening, and/or medically unresponsive perianal fistula.

An association between perianal fistula and colitis has been observed, with one study reporting half the dogs with perianal fistula (9/18) having histopathologic lesions of varying severity consistent with colitis.[11,15] 13 of the 18 dogs were GSDs, with five of these GSDs (39%) having colitis.[11] The authors of this study recommended that colonic biopsies be performed on all dogs with perianal fistula to determine the presence of colitis. However, this procedure is not commonplace in everyday practice.

### 8.4.3.4 Therapy and monitoring

Corrective surgery–*en bloc* excision with bilateral anal sacculectomy, tail amputation, laser surgery, and/or cryosurgery — with or without medical therapy, was the norm for affected dogs with perianal fistula prior to accepting an immune-mediated process as the basis of disease. Surgery had varying success rates but was not without complications, such as recurrence, fecal incontinence, and stricture formation, which may contribute to an owner's decision to euthanize. **Medical immunomodulatory therapy** is now considered the standard-of-care, but surgical intervention may be needed for perianal lesions unresponsive to medical treatment options.

Prior to medical therapy, the goal, effectiveness, duration, and cost of care of a relapsing and remitting primary inflammatory disease that can be managed but not necessarily cured, should be discussed with the owner. If one drug protocol does not achieve the established goals, then another one should be attempted. The first goal is to alleviate clinical signs of pain or discomfort, such as dyschezia, tenesmus, hematochezia, constipation, and increased frequency of defecation.[1] The second goal is to reduce the extent, depth, and recurrence of sinus tracts. Multimodal therapy consisting of immunomodulation, antibiotic therapy for secondary infection, hygiene therapy (clipping fecal-stained hair away from the perineum), stool softeners, and dietary modification may all be required at some point during the course of treatment.[1,8]

Conventional immunosuppression with **glucocorticoids** (prednisone 2–4 mg/kg PO q24h until remission of clinical signs, then tapered to the lowest effective dose) may be initially required, often combined with other immunomodu-

lators, based on clinical signs associated with inflammation and pain/discomfort. However, this therapy is not ideal for long-term use, given unwanted side effects.[1,8]

**Calcineurin inhibitors** (systemic CsA and topical tacrolimus) are considered mainstay therapy provided by the best evidence of efficacy. Given the superior bioavailability, modified (microemulsified) CsA should be prescribed. A wide range of dosages of CsA (<1–10 mg/kg PO q12–24h for 8–16 weeks or longer) have been reported, but not all studies used the same formulation. Some included the co-administration of ketoconazole (5–10 mg/kg PO q24h), an inhibitor of CsA metabolism. Thus, direct comparisons cannot be drawn (▶Tab. 8-3). However, higher CsA dosages tended to have better outcomes.[16] Once perianal pain is relieved, a transition to topical tacrolimus (0.1% ointment q12h) can be attempted.[17] Topical tacrolimus monotherapy may suffice initially for mild presentations of perianal fistula. CsA blood monitoring is not routinely performed because blood concentrations of CsA do not reliably correlate with clinical efficacy.[16] Based on the literature and clinical experience, the author tends to use an initial dose of prednisone (2 mg/kg PO q24h) with CsA (2–5 mg/kg PO q24h) and ketoconazole (5–10 mg/kg PO q24h) or with sole CsA (>5 mg/kg PO q24h). Once clinical improvement is achieved, prednisone is tapered, then CsA is slowly withdrawn (same dose q48h), and a transition to topical tacrolimus is attempted.

A combination of metronidazole, with its immunomodulatory and antibiotic effects, and other immunomodulatory treatments (azathioprine, prednisone, and tacrolimus ointment) has been reported with varying success.[16,25] Mycophenolate mofetil was unable to improve perianal fistula lesions in a dog after 4 weeks of treatment.[26] Mesenchymal stem cell therapy has been reported, but there was recurrence post-therapy. Dietary modification (limited ingredient, novel, or hydrolyzed protein diet) may complement medical management. However, the true effect of dietary intervention or supplementation with pre- or probiotics, is largely unknown.[15] In the future, fluorescence light energy and extra-label oclacitinib may be alternative therapies for canine perianal fistula.[27,28]

**Tab. 8-3** Reports of cyclosporine A therapy for perianal fistulas in dogs

The target CsA blood trough concentration was usually 400–600 ng/mL. The associated signs (e.g., tenesmus, constipation, increased frequency of defecation, perianal licking, self-mutilation) varied with each study. Adjunctive surgical therapy was needed in several studies.

| Reference | Dosing (PO) | Summary of findings |
|---|---|---|
| Matthews et al. 1997[18] | • CsA (7.5–10 mg/kg q12h for 20 weeks)<br>• 80% of dogs required either trimethoprim-sulfamethoxazole (15 mg/kg q12h) or cephalexin (25 mg/kg q12h) for varying durations | • 100% of dogs showed progressive improvement in associated signs and lesions after 1 week.<br>• Total resolution occurred in 100% of dogs after 20 weeks.<br>• Remission lasted 6–18 months or more after treatment ended. |
| Matthews et al. 1997[19] | • CsA (5 mg/kg q12h for 16 weeks)<br>• 100% of dogs were treated with cephalexin (20 mg/kg q12h for 10 days) | • The study was randomized, blinded, and placebo-controlled during the initial 4 weeks.<br>• 100% of dogs improved with CsA therapy; 0% improved when administered a placebo.<br>• Several associated signs significantly improved within 4 weeks.<br>• There was a 78% surface area reduction and 62% depth reduction after 4 weeks of CsA therapy; these parameters worsened with administration of a placebo.<br>• After 16 weeks, 85% of dogs completely healed, and the remaining dogs showed improvement.<br>• The disease recurred in 41% of dogs after treatment ended.<br>• The authors acknowledged that CsA blood concentration and efficacy might not be related. |
| Griffiths et al. 1999[20]* | • CsA (7.5 mg/kg q12h for 10–20 weeks)<br>• No concomitant antibiotherapy was administered. | • The average lesion reduction was 75% in all dogs within 1 week.<br>• 100% of associated signs improved within 1 week.<br>• Lesions continued to resolve over 10–20 weeks.<br>• The recurrence rate was 17% during follow-up (mean: 7.7 months).<br>• There was a poor correlation between CsA blood concentration and efficacy (at least after the first week). |

**Tab. 8-3** Findings of Cyclosporine A therapy for perianal fistulas in dogs (Continuation)

The target CsA blood trough concentration was usually 400–600 ng/mL. The associated signs (e.g., tenesmus, constipation, increased frequency of defecation, perianal licking, self-mutilation) varied with each study. Adjunctive surgical therapy was needed in several studies.

| Reference | Dosing (PO) | Summary of findings |
|---|---|---|
| Hardie et al. 2000[21] | • CsA (4 mg/kg q12h until resolution [mean: 8.8 weeks])<br>• There was no mention of concurrent antibiotic therapy. | • 96% of dogs showed improvement; complete remission occurred in 72%.<br>• The recurrence rate was 36% during follow-up (mean: 6.8 months).<br>• Lesion recurrence averaged 10.6 weeks after treatment ended. |
| Mouatt 2002[22]* | • CsA did not exceed 1 mg/kg q12h for 16 weeks<br>• Ketoconazole (10 mg/kg q24h for 16 weeks)<br>• Antibiotic therapy was given for concurrent conditions | • 100% of dogs showed >50% reduction in surface area and depth within 2 weeks.<br>• 100% of associated signs improved within 2 weeks.<br>• Complete resolution occurred in 93% of dogs.<br>• 50% of dogs that had complete resolution were disease-free for >1 year.<br>• To maintain CsA at therapeutic blood levels, the dose of CsA was reduced 80%–90% when administered with ketoconazole.<br>• There was no consistent relationship between CsA blood concentration and efficacy. |
| Patricelli et al. 2002[23]* | • CsA (2.5 mg/kg q12h or 4 mg/kg q24h [duration not specified])<br>• Ketoconazole (~8 mg/kg q24h in all dogs)<br>• There was no mention of concurrent antibiotic therapy | • Resolution of associated clinical signs occurred within 9 weeks in all dogs.<br>• Significant lesion improvement occurred in all dogs (mean time to remission: 14 weeks).<br>• 63% of dogs that experienced remission had a mean time to recurrence of 12.4 weeks.<br>• All dogs that experienced recurrence had moderate to severe disease at the initial examination. |
| Doust et al. 2003[16]* | • CsA (1.5, 3, 5, or 7.5 mg/kg q24h for 13 weeks)<br>• If clinical signs continued after 13 weeks, owners could continue administering CsA<br>• There was no mention of concurrent antibiotic therapy | • Lesions and associated signs improved faster with the highest dose.<br>• The rate of complete resolution was higher in dogs administered the highest dose.<br>• A longer (>12 months) remission or controlled response occurred regardless of the dose when dogs were treated for >13 weeks.<br>• There was no consistent relationship between CsA blood concentration and efficacy. |
| O'Neill et al. 2004[24]* | • CsA (0.5, 0.75, 1, or 2 mg/kg q12h [duration not specified; estimated 3–10 weeks])<br>• Ketoconazole (5–9 mg/kg q24h)<br>• Amoxicillin-clavulanic acid (12.5 mg/kg) or cephalexin (15 mg/kg q12h) was administered for 7 days before CsA and ketoconazole | • Resolution of associated clinical signs began in 1–2 weeks.<br>• Lesions resolved in all dogs by 10 weeks, but dramatic improvement occurred in the initial 2 weeks.<br>• There was no correlation between the severity of lesions and duration of treatment.<br>• 63% of dogs remained in remission for 1–19 months.<br>• Most dogs had CsA levels that exceeded therapeutic blood levels regardless of the dose of CsA.<br>• Significant interindividual variation occurred in CsA blood levels with similar drug doses.<br>• There was a cost reduction of 70% compared with using CsA (5 mg/kg q12h) alone. |

**PO** = per os, **CsA** = cyclosporine A

(Table modified from Patterson and Campbell, 2005.[1])

***** The microemulsified form of cyclosporine was prescribed.

**KEY FACTS**

- Canine perianal fistula (anal furunculosis) is a spontaneous, relapsing and remitting, debilitating, immune-mediated disease causing painful ulcerative sinus tracts on the skin surrounding the anus.
- Calcineurin inhibitors (systemic cyclosporine A and topical tacrolimus) have become the mainstay therapy, but the time to effect may be long, and an initial course of systemic glucocorticoids may be required.
- The author uses an initial dose of prednisone (2 mg/kg PO q24h) with cyclosporine A (2–5 mg/kg PO q24h) and ketoconazole (5–10 mg/kg PO q24h) or with sole cyclosporine A (>5 mg/kg PO q24h). Once clinical improvement is achieved, prednisone is tapered, then cyclosporine A is slowly withdrawn (same dose q48h), and a transition to topical tacrolimus is attempted.
- Expense of long-term medical management, intolerance of treatment, recurrence, unrelenting pain, and anal stricture may be grounds for euthanasia.

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
svg.to/9842-08-04-03

8

## 8.4.4 Rectal and perianal neoplasia

Emma Warry

### 8.4.4.1 Introduction

Malignant rectal tumors have been discussed as part of a complex of neoplastic diseases of the large intestine referred to as colorectal tumors (▶Chap. 8.3.7). Adenomatous polyps are the most frequently reported benign tumors in the canine rectum, followed by carcinoma-in-situ.[1–4] Progression of carcinoma-in-situ to a malignant phenotype is reported in 17–50% of cases.[1–4]

In the dog, perianal sebaceous glands have a circular distribution around the anus and can also be found along the prepuce, tail, pelvic limbs, and trunk.[4,5] These glands are considered nonsecretory in the adult dog.

Tumors arising from perianal sebaceous glands are either benign sebaceous adenomas or malignant adenocarcinomas (ACA). Other tumors that can occur in this region but do not arise from the perianal glands include mast cell tumors, soft tissue sarcomas, melanomas, and plasmacytomas.

The anal sacs are surrounded by apocrine sweat glands.[4] Tumors arising from these glands are almost always malignant and referred to as apocrine gland anal sac adenocarcinomas (AGASACA). These tumors are reported to account for approximately 17% of perianal malignancies.[4,6,7] Other reported tumors involving the anal sacs include squamous cell carcinomas and malignant melanomas.[8–10]

Perianal tumors are not recognized in cats as they do not have sebaceous glands in the perianal region. AGASACA is uncommonly reported in the cat.[4,11–13]

### 8.4.4.2 Incidence

**Perianal adenomas** are the most common perianal tumor and account for 58–96% of tumors in this area.[4–6] These tumors present almost exclusively in intact male dogs because growth is stimulated by androgen production and suppressed by estrogen.[4,5,14,15] Perianal adenomas are also seen in ovariohysterectomized female dogs due to low estrogen levels with an inability to suppress growth.[4] Occasionally, these tumors can occur secondary to androgenic steroid secretion from an adrenal tumor or atypical hyperadrenocorticism.[4,16,17] Average age for disease onset is 10 years, with some reports suggesting cocker spaniels, beagles, bulldogs, and Samoyeds are predisposed.[5,6,14]

**Malignant perianal ACA** is rare, accounting for 3–21% of perianal tumors.[4,6] As opposed to their benign counterparts, these tumors do not appear hormone-driven and occur in castrated male, intact male, and female dogs.[14,18]

**AGASACA** is diagnosed in dogs at a mean age of 9–11 years. There is an equal distribution between male and female dogs.[19–22] Neutering has been suggested in some studies to increase tumor risk, but this has not been definitively established as a risk factor.[19] Breeds that appear to be overrepresented include English cocker spaniels, German shepherd dogs, Labrador retrievers, Alaskan malamutes, and dachshunds.[4,19–21,23–25]

In a recent evaluation of 30 cats with AGASACA, the median age of diagnosis was 13 years.[26] There was an equal distribution in males and females.[26] Domestic shorthair cats were most commonly reported, with Siamese cats being the next most commonly affected breed.[26]

### 8.4.4.3 Clinical presentation

**Perianal adenomas** are rarely associated with clinical signs and are often found incidentally.[4,5] They are slow-growing and can have a prolonged clinical course. These tumors may be noted as single, multiple, or in some cases, diffusely encircling the anus.[5] Reported size at presentation varies from 0.5–3 cm in diameter.[5] Some tumors will be ulcerated or infected at presentation, and the owner may incorrectly report the presence of blood streaking along the stool. Dogs that present with circumferential involvement of the perianal tissue may have a history of tenesmus, dyschezia, discomfort, or irritation.

Visually, **perianal ACAs** will appear very similar to adenomas but are often larger at presentation and more likely to be ulcerated.[18] ACAs have a faster growth rate than adenomas and are likely to have been present for a shorter period of time. On palpation, perianal ACAs are more likely to be fixed to surrounding tissue and may have less definable borders.[18] Dyschezia, tenesmus, pain, and rectal discomfort can be present depending on the location and size of the mass.[18]

Clinical signs associated with **AGASACA** vary depending on the size of the primary lesion, the presence of metastases, and paraneoplastic hypercalcemia. It is essential to be aware that 31–47% of AGASACAs are found incidentally on rectal examination, illustrating the importance of a rectal examination as part of the routine physical examination for all dogs.[21,25,27] Clinical signs associated with the primary tumor or presence of metastasis may include tenesmus, dyschezia, fecal obstipation, pain, scooting, bleeding, or an abnormal "ribbon" shaped stool.[4,20,21,25] Clinical signs associated with paraneoplastic hypercalcemia may include polyuria, polydipsia, hyporexia, lethargy, or vomiting.[4,20,21,25]

The most common clinical sign in cats with AGASACA is perineal ulceration or discharge reported in 85% of cats in a recent study.[26] Other clinical signs included tenesmus, constipation, and hyporexia.[26]

### 8.4.4.4 Diagnostics and staging

As with the diagnostic evaluation for all cancer cases, a thorough physical examination with rectal palpation and a minimum database, including complete blood count, biochemistry profile, and urinalysis should be performed.

Differentiation of perianal adenoma from perianal ACA can be difficult cytologically. The role of **cytology** in this instance is to rule out other types of cancer that could occur in this region, such as a mast cell tumor. Definitive diagnosis can only be achieved with an incisional biopsy and histopathology. Once a diagnosis is obtained, clinical staging can be appropriately selected. The reported metastatic rate for perianal ACA is 15%, with the most common sites being local lymph nodes and lungs. At a minimum, three-view thoracic radiographs and an abdominal ultrasound should be performed. However, as involved lymph nodes are likely located within the pelvic canal, an abdominal CT scan is likely superior to ultrasonography. If enlarged or abnormal lymph nodes are identified, fine-needle aspiration and submission for cytology are recommended.

The reported metastatic rate for dogs with AGASACA ranges from 26–96% at the time of diagnosis. **Metastasis** at diagnosis is most commonly found in the local lymph nodes, including the medial iliac, internal iliac, and sacral nodes. Distant metastasis to the lungs, liver, spleen, bone, heart, adrenal glands, stomach, omentum, pancreas, kidneys, urinary bladder, and mediastinum are reported. As mentioned above, it is essential to collect a minimum database, including an ionized calcium concentration. Paraneoplastic hypercalcemia is identified in 18–53% of dogs with AGASACA, with most recent studies reporting incidences <30%.[4,21,25,27]

Most AGASACAs are unilateral, with approximately 8–14% being bilateral.[23,27,28] A diagnosis of AGASACA is easily established via fine-needle aspiration and cytology. Neoplastic cells have a neuroendocrine appearance, and criteria for malignancy can be lacking.[4] All masses involving an anal sac should be aspirated and submitted for cytological evaluation.

Evaluation of the abdomen and thorax for metastatic disease is imperative prior to initiating treatment of the primary tumor. Historically, this has been done with three-view thoracic radiographs and abdominal ultrasound. However, as many lymph nodes most likely to be metastatic are located within the pelvic canal, evaluation with advanced imaging such as **CT or MRI scan** is becoming more routine.[29–31] Detection of abdominal lymphadenomegaly in dogs with AGASACA is more sensitive with CT or MRI than ultrasound.[29–31] One study demonstrated ultrasound to identify enlarged and ultimately metastatic lymph nodes in only 31% of the cases evaluated.[30] In addition, CT and MRI allow for evaluation of tumor extension and invasion into surrounding tissues. At the author's institution, a CT scan of the abdomen extending through to the anus is routine for the staging of AGASAC. If enlarged or abnormal lymph nodes are detected with imaging, attempts to collect a fine-needle aspirate for cytology should be made. If location and size of the lymph

nodes do not allow for safe fine-needle aspiration, surgical excision and histopathology should be discussed to complete tumor staging.

The metastatic potential of feline AGASACA is not as well established as in dogs but is likely lower at the time of diagnosis. Paraneoplastic hypercalcemia is also reported to occur less frequently than in dogs. Although ionized calcium concentration was not available for all cats, a recent study found 89% of cats with AGASACA to have a normal serum total calcium concentration.[26] As with the dog, complete staging with thoracic radiographs, abdominal ultrasound, or CT scan is recommended.

### 8.4.4.5 Treatment

For **perianal adenoma**, surgical excision along with castration of intact male dogs is recommended. Only a small margin is required. For **perianal ACA**, a larger surgery with at least a 1 cm margin is recommended. Without appropriate margins, local tumor recurrence is common. Given the location, size of the tumor, and number of tumors at the time of surgery, a staged procedure may be required. If surgical margins are incomplete, radiation therapy can be considered. If enlarged lymph nodes are identified, surgical excision is recommended. Dogs with metastatic disease may benefit from chemotherapy or the use of tyrosine kinase inhibitors (TKI), but there is no data available to support this recommendation.

Treatment for **AGASACA** in dogs needs to involve both local and systemic treatment. Local therapy should include surgical removal of the primary tumor via a closed anal sacculectomy. Complication rates are reported between 5–24% and include wound dehiscence, rectal perforation, incisional infection, and transient fecal incontinence.[32–35] Lymph nodes that are concerning for metastasis based on size, appearance on CT scan, or confirmed via cytology to be metastatic should be removed via lymphadenectomy at the same time. This has been shown to improve outcomes, and if the lymph nodes are large, it will also aid in improving quality of life by alleviating obstruction within the pelvic canal.[4,22]

**Chemotherapy** postoperatively is generally recommended. The most commonly used chemotherapy drug is carboplatin. Others that have been used include cisplatin, doxorubicin, mitoxantrone, and melphalan.[4,36,37] Whether or not all dogs with AGASACA benefit from additional chemotherapy postoperatively is not known. Some studies suggest no improvement in outcome with adjuvant chemotherapy, while others have demonstrated significant benefit. Unfortunately, there is currently no validated assessment scheme to identify dogs that benefit from adjuvant chemotherapy and those that do not. At this time, the author recommends chemotherapy for most patients with AGASACA with the knowledge that some dogs may be getting overtreated.

**Radiation therapy** is described as adjuvant therapy following surgery and in a palliative setting.[37–39] Similar to chemotherapy, the role of definitive radiation therapy postoperatively in a microscopic disease setting is not well defined. Some studies have suggested a benefit, while others have not. Unfortunately, most published data relating to this are from small populations with no standardized treatment prescription.[4] Given that most AGASACAs are narrowly or incompletely excised with local recurrence rates between 5–44%, there is likely a role for radiation therapy in a subset of patients.[21,23,25,32,34,35] However, similar to the situation with chemotherapy, there is no validated system to identify those patients that would benefit.

In a gross disease setting, response rates to hypofractionated radiation therapy range from 38–75%, with improvement in clinical signs reported being 63%.[38,39] When indicated, hypofractionated radiation therapy can be useful in controlling hypercalcemia in some dogs or be used concurrently with prednisone and bisphosphonates.[39] The median progression-free survival is 10–11 months, with median survival times (MST) reported to be 8–15 months.[38,39]

**Toceranib**, a TKI, has been evaluated for the treatment of dogs with gross disease. A clinical benefit was seen in 69% of patients and was positively associated with overall survival and progression-free survival.[24] This suggests that toceranib offers a reasonable and durable treatment option for dogs with gross disease, who have failed more traditional therapies, or for clients not wanting to pursue surgery and radiation therapy.



For cats with AGASACA, surgical excision of the primary tumor and any metastatic lymph nodes is recommended, similarly to what is recommended for dogs.[26] Even less is known about the role of chemotherapy or radiation therapy in cats. Adjuvant use of chemotherapy should be considered on a case-by-case basis, with consideration of any comorbidities.

#### 8.4.4.6 Prognosis

Dogs with AGASACA can have prolonged survival times despite the presence of metastasis at diagnosis or the development of metastasis following initial treatment. The presence of lymph node metastasis at the time of diagnosis is associated with a shorter median disease-free interval (134–197 days vs. 529–760 days for dogs without lymph node metastasis at diagnosis).[27,33,37] The development of metastatic disease following an initial round of therapy can be successfully treated with additional surgery or radiation therapy for a more durable response. In one study evaluating treatment for metastatic disease, dogs that received additional treatment had an MST of 374 days from the time of metastasis or recurrence, compared to 47 days for dogs that did not receive any additional therapy.[33] This finding supports the above recommendation that even with the development of metastatic disease, dogs with AGASACA can be managed successfully with additional therapy.

Regardless of therapy, 1- and 2-year survival rates for dogs with AGASACA are 65% and 29%, respectively.[21]

**KEY FACTS**

- Adenomatous polyps are the most frequently reported benign tumor in the canine rectum, followed by *carcinoma-in-situ*.
- Evaluation of the abdomen and thorax for metastatic disease with diagnostic imaging is imperative prior to initiating treatment of the primary tumor.
- For perianal adenoma and adenocarcinoma, surgical excision along with castration of intact male dogs is recommended. Treatment for apocrine gland anal sac adenocarcinoma (AGASACA) needs to involve both local and systemic treatment. Chemotherapy postoperatively is generally recommended. Radiation therapy is described as adjuvant therapy following surgery. Toceranib offers a reasonable and durable treatment option for dogs with gross disease.

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
svg.to/9842-08-04-04

# 9 Liver and biliary tract

## 9.1 Anatomy

Randi Gold

### 9.1.1 Liver structure

The liver lies within the cranial abdomen. Its parietal surface is adjacent to the diaphragm, the visceral surface is to the left of the stomach and spleen, on the right are the pancreas, right kidney, duodenum, and on the ventral surface are the omentum and small intestine.[1] The liver is divided into six lobes (▶Fig. 9-1). In both dogs and cats, the lateral parts of the right and left liver lobes can be seen on lateral abdominal radiographs as the caudoventral edge of the liver shadow under the costal arch.

The liver is organized into hepatic lobules that are arranged into irregular polygons composed of hepatocytes that radiate out from a central vein to several portal triads (▶Fig. 9-2a). Each portal triad is composed of a portal vein, hepatic artery, and bile duct. In larger triads, lymphatics and autonomic nerve fibers may also be observed. The portal vein supplies 70–80% of the total afferent hepatic blood flow and ~50% of the oxygen supply, while the remainder is supplied by the hepatic artery.[2] As blood enters a hepatic lobule, it travels from a portal triad through the hepatic sinusoids to the central vein (▶Fig. 9-2b). Hepatic sinusoids are lined by fenestrated endothelial cells that control fluid, solute, and particulate exchange between the blood and perisinusoidal space.[2] Once blood reaches the central veins, it flows into the caudal vena cava via the hepatic veins, where it is transported back to the heart for recirculation.

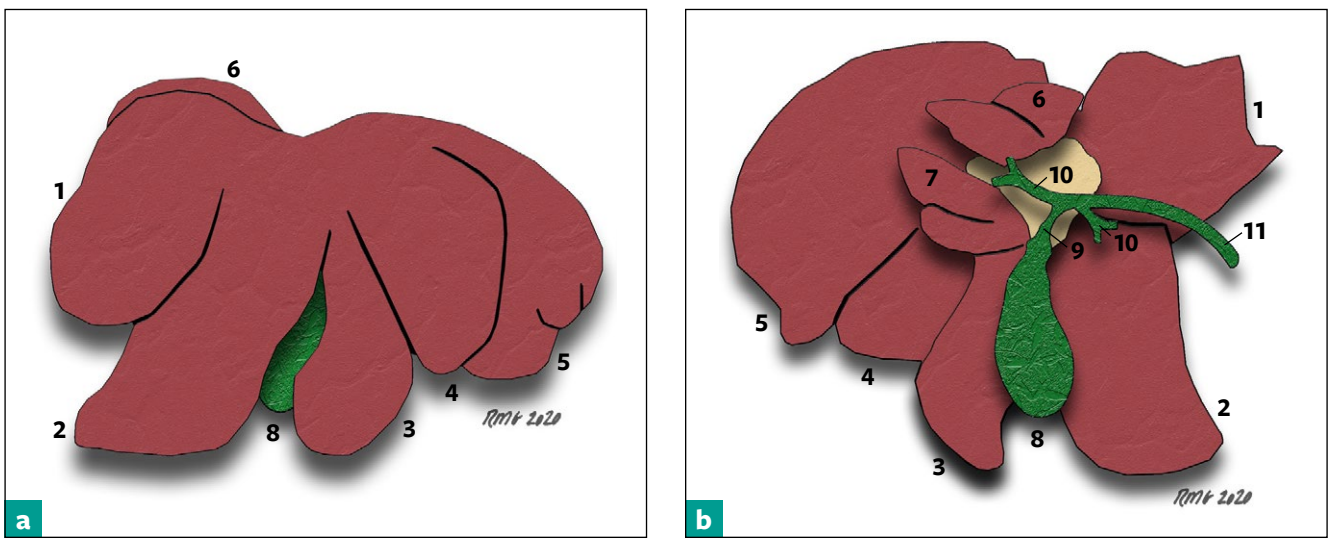



**Fig. 9-1** Graphic representation of the visceral and parietal views of the canine and feline liver

**a** Parietal surface

**b** Visceral surface

**1** = right lateral; **2** = right medial; **3** = quadrate; **4** = left medial; **5** = left lateral; **6** = caudate process; **7** = papillary process; **8** = gallbladder; **9** = cystic duct; **10** = hepatic duct; **11** = common bile duct

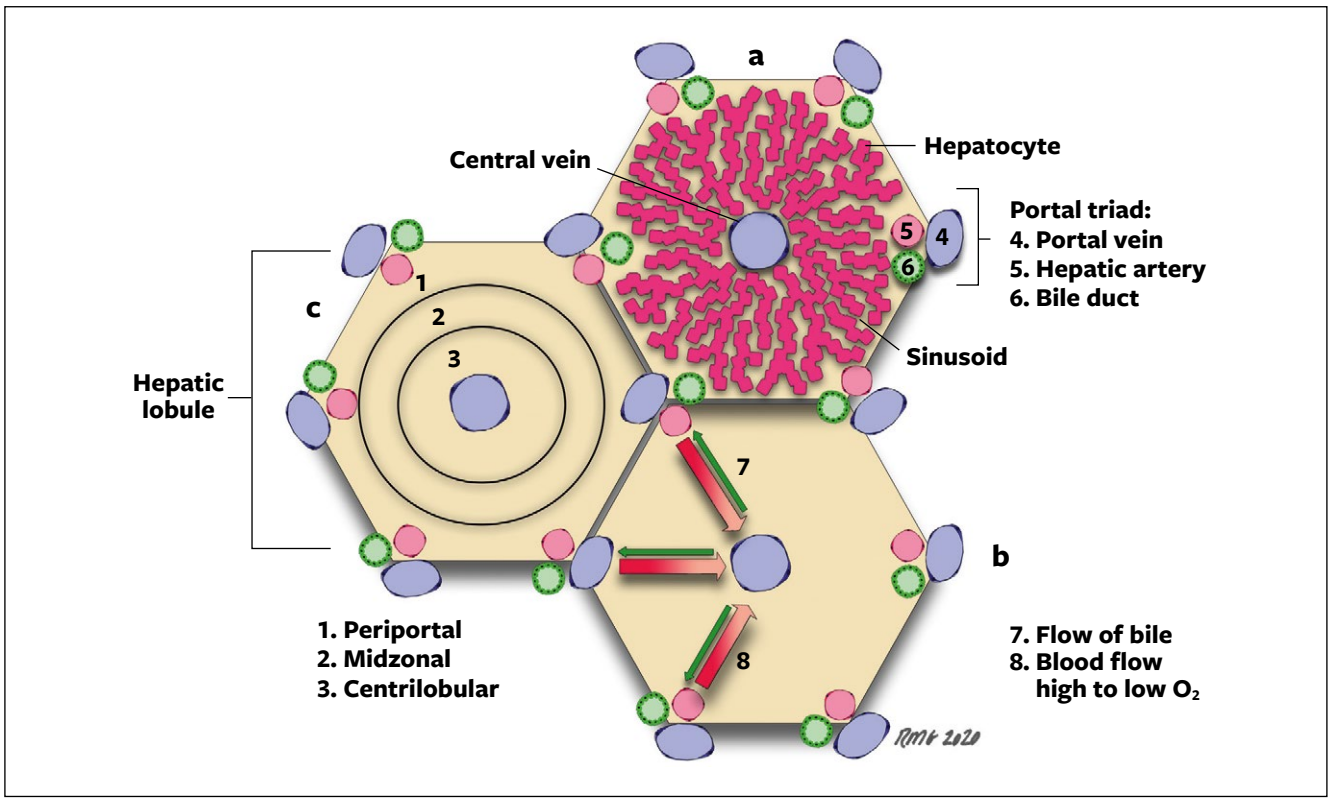



**Fig. 9-2** The classic hepatic lobule

**a** The hepatic lobules are arranged into 6-sided polygons of portal triads centered around a central vein. Hepatocytes create a sinusoidal network, allowing for the flow of blood, bile, and nutrients between the different regions.

**b Arrows** depict the flow of blood from high to low oxygen and nutrient concentration (**red**) and the direction of bile flow (**green**)

**c** The hepatic lobules are divided into three regions in relation to the blood supply. The blood of greatest oxygenation and nutrient concentration is furthest from the central vein at **1** (periportal region), while the lowest concentration is at **3** (centrilobular region).

Hepatocytes are divided into functional zones (▶Fig. 9-2c):

- Zone 1 (periportal zone) is nearest to the portal triads and the first to receive nutrient-rich arterial and portal inflow.[2] It is also the first region to be damaged by hepatotoxins arriving through the portal blood from the gastrointestinal tract.[3]
- Zone 2 (midzonal zone) is the transitional midzone.
- Zone 3 (centrilobular zone) is positioned around the central vein. It is the first region to be damaged by hypoxia due to reduced nutrient and oxygen levels because of the distance from the source of these.[3] Within the centrilobular areas, glycolysis, lipogenesis, and biotransformational activities, such as cytochrome P450 expression, are more active. Zone 3 hepatocytes are, therefore, more susceptible to toxic substances that are metabolically activated by cytochrome P450 enzymes.[2]

## 9.1.2 Cells of the liver

### 9.1.2.1 Hepatocytes

Hepatocytes account for 60–80% of the liver cell mass.[4] Around 30–40 µm in diameter, these polygonal epithelial cells are arranged in anastomosing plates of a single layer of cells that are separated by hepatic sinusoids.[2] The first row of hepatocytes adjacent to the portal tract connective tissue is referred to as the limiting plate. Most hepatocytes have a single nucleus, although some mammals have some hepatocytes that show binucleation. The number of hepatocyte nuclei increases in response to various stimuli and injuries that induce or affect regeneration.[2] Hepatocytes are organized into plates and separated by sinusoids. The sinusoids are separated from adjacent hepatocellular plates by an extracellular space called the space of Disse, which contains hepatic stellate cells, reticulin fibers, and nerves.[2]

#### 9.1.2.2 Cholangiocytes

Cholangiocytes, also known as biliary epithelial cells, account for 3–10% of the liver cell mass. They are composed of a strong network of intermediate filaments, including cytokeratins 7 and 19.[2] During the physiologic state, they modify the composition of bile by altering levels of water, bicarbonate, and cations.[4] During disease states, they may participate in the immune response as antigen-presenting cells, secreting immunoglobulins IgA, IgM, but not IgG.[2]

#### 9.1.2.3 Kupffer cells

Kupffer cells are specialized macrophages of the mononuclear phagocyte system located within the lumen of sinusoids and represent 2–5% of the liver cell mass.[4] They can phagocytize a variety of gut-derived materials, including bacteria, various biologically active bacterial components (i.e., lipopolysaccharides and lipoteichoic acid), and peptidoglycans, all without stimulating inflammation.[2] Once activated, Kupffer cells can secrete tumor necrosis factor-α, cytokines, nitric oxide that contributes to peripheral vasodilation and hypotension, interleukin 1 (IL-1) and IL-6 to mediate the acute phase response, and IL-10 to suppress macrophage activation and cytokine secretion.[2]

#### 9.1.2.4 Stellate cells

These cells have previously been referred to as lipocytes, Ito cells, fat-storing cells, or vitamin A-storing cells.[2,4] They store 50–80% of whole-body vitamin A. During disease states, stellate cells lose vitamin A and synthesize large quantities of extracellular matrix components, including collagen, proteoglycan, glycosaminoglycan, and adhesive glycoproteins.[4] The morphology of these cells also changes from that of a star-shaped stellate cell to one resembling more of a fibroblast or myofibroblast.[4] Other functions of stellate cells include maintenance and remodeling of the sinusoidal extracellular matrix, production of growth factors and cytokines, and regulation of the sinusoidal diameter by contraction of cellular processes.[2]

#### 9.1.2.5 Hepatic immune cells

Natural killer cells, also known as large granular lymphocytes or pit cells, represent 1–5% of the liver cell mass and serve as part of the immune surveillance system, with greater emphasis on the innate immune response.[4] They can defend against foreign antigens released from the gut, viral infections, metastatic tumors, and hepatocellular carcinoma and aid in the modulation of hepatic fibrosis.[2] In addition, hepatic dendritic cells are thought to play a role in the regulation of the immune response. Hepatic dendritic cells are antigen-presenting cells found within the portal tracts. Considered to be functionally immature compared with dendritic cells of the spleen and bone marrow, hepatic dendritic cells may be involved with immune tolerance of the liver.[2]

### 9.1.3 Hepatic pigments

#### 9.1.3.1 Lipofuscin

Lipofuscin is composed of golden-brown granules commonly found within hepatocytes of the centrilobular region, especially in older cats (▶Fig. 9-3a). Commonly referred to as a "wear-and-tear" pigment, it becomes increasingly more common with age and progressively accumulates within the midzonal and periportal hepatocytes.[2] It can also be associated with atrophy or increased turnover of membrane lipids.

#### 9.1.3.2 Bile

Bile pigment is excreted by hepatocytes into the canaliculi, then transported to the portal tracts, and finally, it enters the canals of Hering.[3] Histologically, bile pigment is golden-brown and can distend bile canaliculi, appearing as linear streaks between hepatocytes (▶Fig. 9-3b). Bile secretion is controlled primarily by secretin (stimulatory) and somatostatin (inhibitory).

#### 9.1.3.3 Copper

Excess hepatic copper is the most well-characterized cause of chronic hepatitis in dogs. Hepatic copper accumulation can result from:

1. A primary metabolic defect in hepatic copper metabolism
2. Abnormal hepatic function with cholestasis and altered biliary copper excretion (although this may be less of a concern in dogs than in humans or rodents)
3. Excess dietary copper intake.[2]

Copper can be visualized in the liver of affected animals with the aid of special stains, such as rhodanine (▶Fig. 9-3c) and rubeanic acid.

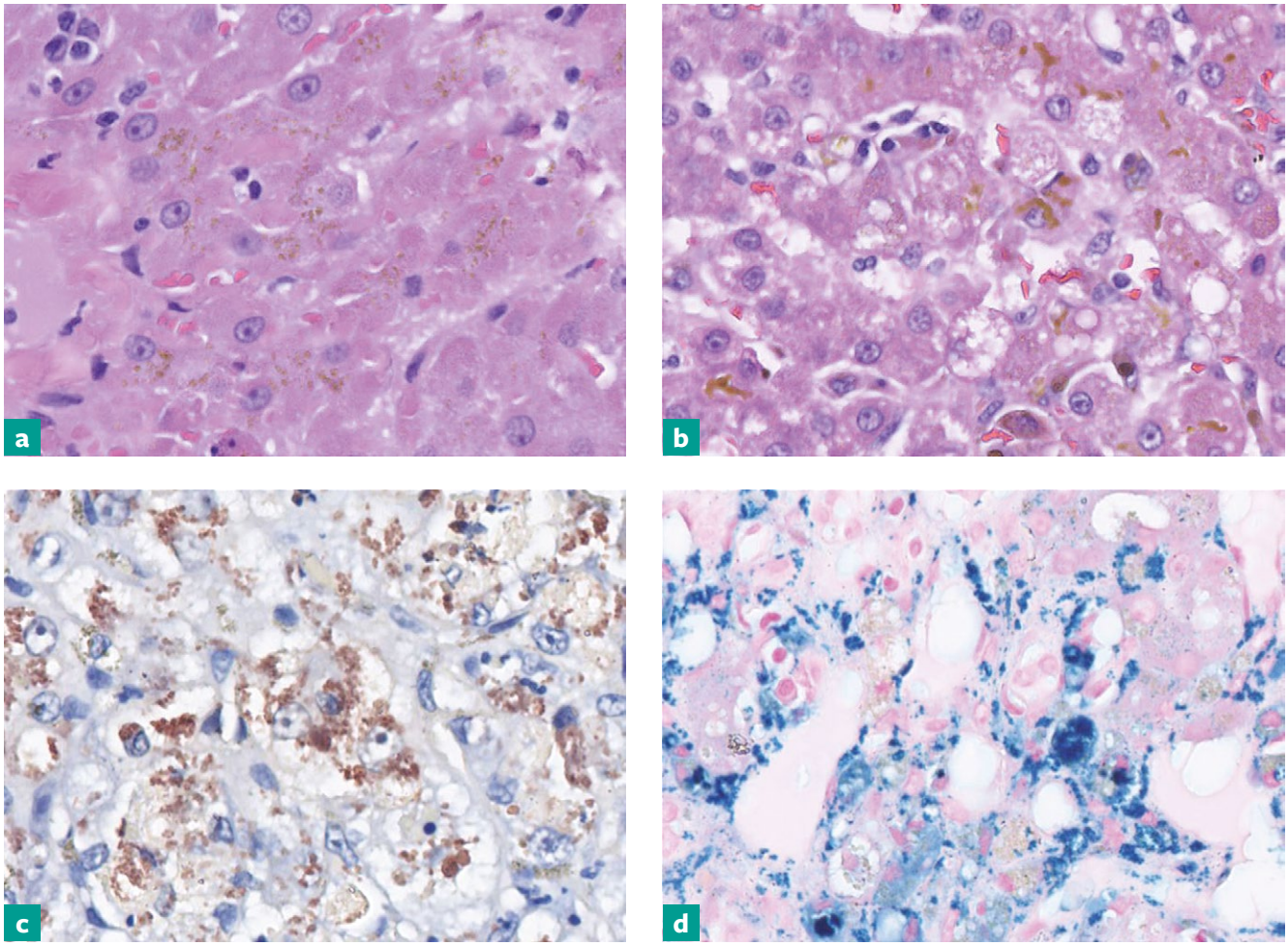



**Fig. 9-3** Hepatic pigments

**a** Lipofuscin is visible within the cytoplasm of centrilobular hepatocytes in a dog with lymphocytic cholangitis, H&E, 40x.

**b** Bile is expanding the hepatic canaliculi, resulting in cholestasis in a dog with a gallbladder mucocele, H&E, 40x.

**c** Copper granules are visible within the cytoplasm of centrilobular hepatocytes in a dog with chronic hepatitis, rhodanine, 40x.

**d** Iron is visible within the cytoplasm of hepatocytes in a dog with a gallbladder mucocele, Prussian blue, 40x.



#### 9.1.3.4 Iron

Iron is stored in the liver as ferritin or hemosiderin (▶Fig. 9-3d). Excess iron stores in the body are classified as either hemosiderosis, excess iron in Kupffer cells or hepatocytes with no apparent hepatocellular damage, or hemochromatosis, which leads to excess iron with resulting fibrosis, inflammation, and hepatic injury.[5] Hemochromatosis has been reported in mynah birds,[6] toucans,[7] rhinos,[8] Salers cattle,[9] and horses,[10] but it is rare in dogs and cats. Iron can be stored in the hepatic parenchyma and the biliary epithelium but can be predominantly found in lysosomes.[2] The pathogenesis for nutritional iron overload is unknown.

### 9.1.4 Biliary tract structure

The gallbladder is located within a fossa between the right medial lobe and the quadrate lobe (▶Fig. 9-1). Cats occasionally have divided or bi-lobed gallbladders.[2] The biliary system is a branched tree serving as a collecting system for bile from each individual hepatic cell, with the gallbladder being the primary site of storage. The neck of the gallbladder continues as the cystic duct, sending off hepatic branches before terminating as the bile duct and emptying into the major papilla of the duodenum.[1]

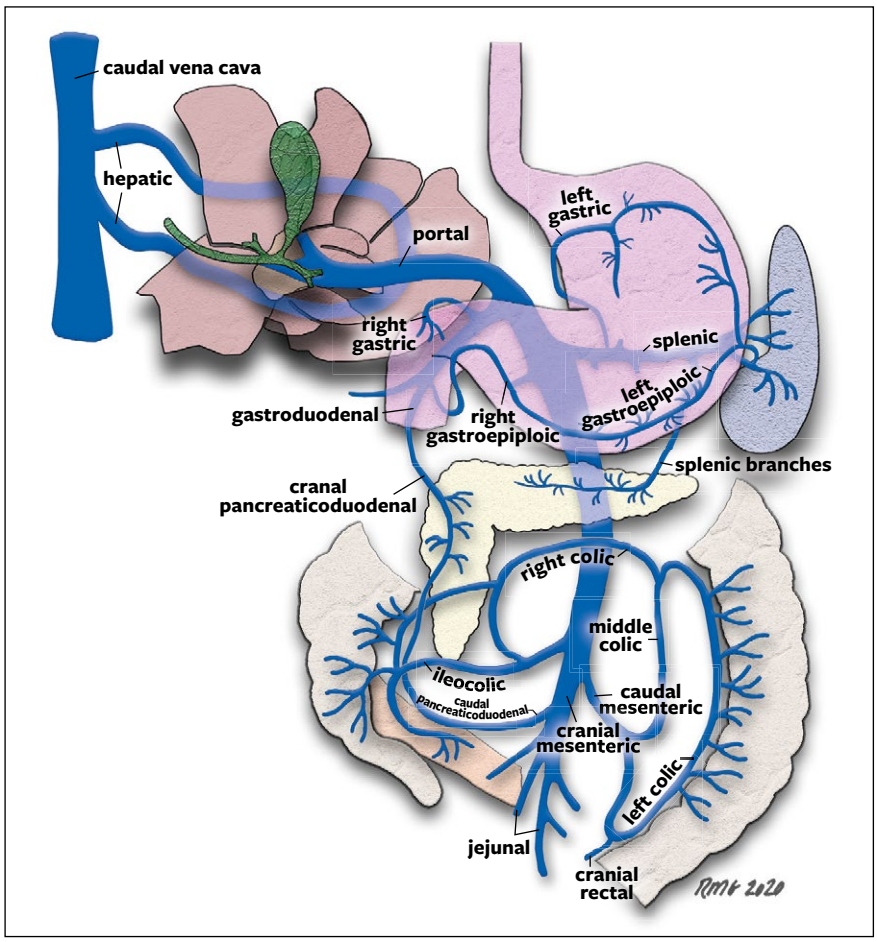



**Fig. 9-4** Venous hepatic circulation
The portal vein carries all the blood draining the stomach, intestines (sans rectum), pancreas, and spleen to the liver where it collects into branches of the hepatic veins, which terminate into the caudal vena cava for transport back to the heart.

Dogs have a separate opening for the bile duct and the pancreatic duct, which end on the major and minor duodenal papillae.

In cats, the pancreatic duct and common bile duct share a common entrance on the major duodenal papilla in about 80% of animals. The accessory pancreatic duct, which does not persist in about 80% of cats, opens into the minor duodenal papilla.

As mentioned above, blood flows in the opposite direction from the area of the central vein, while bile flows from the central vein to the portal area and the common bile duct.[3]

### 9.1.5 Portal circulation

The liver receives both venous and arterial blood. The arterial blood comes from the hepatic artery, while the venous blood is supplied from the portal vein. The portal vein accounts for 70% of the total blood flow to the liver and carries all the blood draining from the stomach, intestines (sans rectum), pancreas, and spleen (▶Fig. 9-4).[3] The portal vein is divided into a smaller right portal branch from which vessels to the caudate process and both right lobes arise and a more substantial left branch, which supplies the remaining portions of the liver.[11] All of the afferent blood arriving in both the portal vein and hepatic artery pass into the hepatic sinusoids, where they mix in close proximity to the hepatocytes before exiting into the hepatic veins.[3] The hepatic veins then drain into the caudal *vena cava* (▶Fig. 9-4).

**References**
The complete list of references for this chapter can be downloaded from vetline.de:
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## 9.2 Physiology

Randi Gold

### 9.2.1 Metabolism

The liver plays a central role in the body's metabolism. Most of the metabolic and detoxifying functions of the liver occur during the passage of blood along the sinusoids.[1]

#### 9.2.1.1 Carbohydrate metabolism

Glucose is the primary energy source for most mammals. Its metabolism is tightly regulated, and availability is dependent upon two sources: dietary absorption from the intestinal tract and release of glucose from the liver. The final products of carbohydrate digestion in the intestinal tract are almost entirely glucose, fructose, and galactose. After absorption from the intestinal lumen, much of the fructose and almost all of the galactose are rapidly converted to glucose in the liver by **glucose phosphatase**.[2] Once absorbed into a cell, glucose can either be used immediately or stored in the form of glycogen. Liver cells can store 5–8% of their weight as glycogen.[2] When the body's stores of carbohydrates fall below normal levels, glucose is generated from amino acids and the glycerol portion of triglycerides in a process called gluconeogenesis.[2]



Cats are obligate carnivores and show several differences in carbohydrate metabolism compared with dogs. For example, they have minimal to absent hepatic glucokinase, an enzyme that catalyzes the first step of glycolysis.[3]

#### 9.2.1.2 Lipid metabolism

Lipids are water-insoluble organic compounds. Of the many groups of lipids, the most important from a clinical standpoint are fatty acids, sterols, and acylglycerols (mainly triglycerides).[4] **Cholesterol** is the main sterol in animals, with dietary intake being the primary source (exogenous transport). However, the liver and other tissues can also synthesize it endogenously (▶Fig. 9-5).

##### 9.2.1.2.1 Exogenous transport

Dietary lipids that reach the duodenum undergo emulsification by bile salts followed by hydrolysis by pancreatic lipase supported by the actions of colipase.[5] Hydrolysis products are then transferred to intestinal microvilli at the epithelial brush border, where they undergo solubilization of fatty acids and monoglycerides into mixed micelles.[6] The mixed micelles then diffuse through the epithelial cell membranes into the intestinal mucosal cells. Within the epithelial cells, free fatty acids and monoglycerides reassemble to form triglycerides, which combine with phospholipids, cholesterol, and apolipoprotein (apo) B48, forming chylomicrons.[5,17] Chylomicrons are then released from enterocytes by way of exocytosis, traverse the interstitial space, and enter lacteals through gaps between endothelial cells. From there, they are transported into intestinal lymphatics and later the systemic circulation, where they acquire apo C and E from circulating high-density lipoproteins (HDLs).[4] Apolipoprotein C–II on the chylomicron surface then activates lipoprotein lipase on the capillary surface, allowing hydrolysis of free fatty acids, which in turn can enter muscle and fat cells to be utilized for energy generation.[4] The chylomicron remnants with attached cholesterol can then be taken up by the liver to be stored or used to create very low-density lipoproteins (VLDLs).

##### 9.2.1.2.2 Endogenous transport

VLDLs, intermediate-density lipoproteins, low-density lipoproteins (LDLs), and HDLs are involved in the metabolism of endogenously produced lipids.[5] VLDLs are secreted from the hepatocytes and acquire apo C and E from HDLs in the bloodstream. Apo C-II on the VLDL surface activates lipoprotein lipase on the capillary surface allowing hydrolysis of free fatty acids, which then can enter muscle and fat cells to be utilized for energy generation.[4] The VLDLs are then either removed from circulation by the liver or undergo further transformation by lipoprotein lipase and/or hepatic lipase into intermediate-density lipoproteins and LDLs.[4] LDLs circulate until they are absorbed by the liver or other peripheral tissues, where they are hydrolyzed within lysosomes, releasing cholesterol.[5]

#### 9.2.1.3 Protein metabolism

The liver deaminates amino acids and converts them to carbohydrates and lipids. This occurs mainly by transamination, which is the transfer of one amino group to some acceptor substance.[8] An example of amino transamination is:

**α-ketoglutaric acid + alanine → glutamic acid + pyruvic acid**

Also, the liver is an important site for ammonia removal. In the liver, ammonia is converted to urea by the enzymes of the urea cycle or is used during the conversion of glutamate to glutamine. Urea leaves the liver through the venous blood

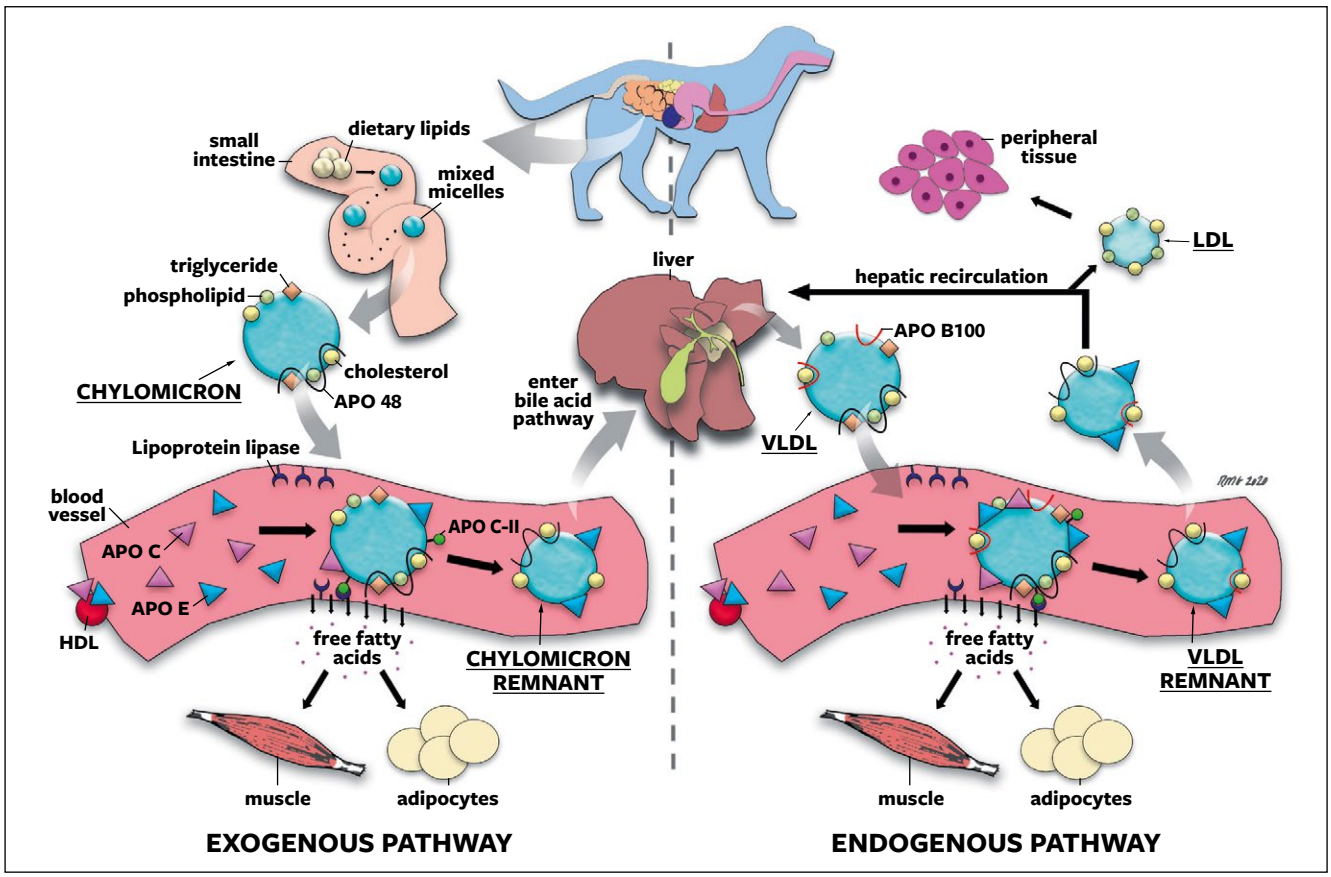



**Fig. 9-5** Lipid metabolism

**Left panel:** In the exogenous pathway, dietary lipids undergo conversion into mixed micelles within the small intestine. They diffuse into the epithelial cells, where they combine with triglycerides, phospholipids, cholesterol, and apo B48, forming chylomicrons. Once they reach the lacteals, they are transported via the lymphatic system to the systemic circulation, where they acquire apo C and E from circulating high-density lipoproteins (HDLs). Apoprotein (Apo) C-II on the chylomicron surface then activates lipoprotein lipase on the capillary surface, allowing hydrolysis of free fatty acids that muscle cells and adipocytes utilize for energy. Chylomicron remnants with attached cholesterol can then be stored or used to create VLDLs.

**Right panel:** In the endogenous pathway, very low-density lipoproteins (VLDLs) are secreted from the liver and acquire apo C and E from HDLs in the bloodstream. Apo C-II on the VLDL surface activates lipoprotein lipase on the capillary surface, allowing hydrolysis of free fatty acids that muscle and fat cells utilize for energy. VLDLs are then either removed from circulation by the liver or undergo further transformation by lipoprotein lipase and/or hepatic lipase into intermediate-density lipoproteins and low-density lipoproteins (LDLs). LDLs circulate until they are absorbed by the liver or other peripheral tissues.

**Apo** = apolipoprotein; **HDL** = high-density lipoprotein; **VLDL** = very-low density lipoproteins; **LDL** = low-density lipoprotein

and is excreted by the body via the kidneys. Any ammonia not removed by the liver enters into the systemic circulation.[9,10] The liver also synthesizes many proteins, including albumin and fibrinogen, most α-globulins and some β-globulins, prothrombin, and a variety of clotting factors, including factors V, VII, VIII, IX, and X.[5]

### 9.2.2 Bile secretion

The primary secretory product of the liver is bile, which serves as a means for the excretion of waste products into the small intestines. Bile acids are an important component of bile and are important for:

- Helping to emulsify large fat particles from the diet into smaller particles, which can then be hydrolyzed by pancreatic lipase
- Aiding in the absorption of digested fat end products through the intestinal mucosal membrane[20]

More recently, bile acids have been shown to also have an endocrine function and thus play an important role in regulating metabolism.[12] To produce bile acids, cholesterol is

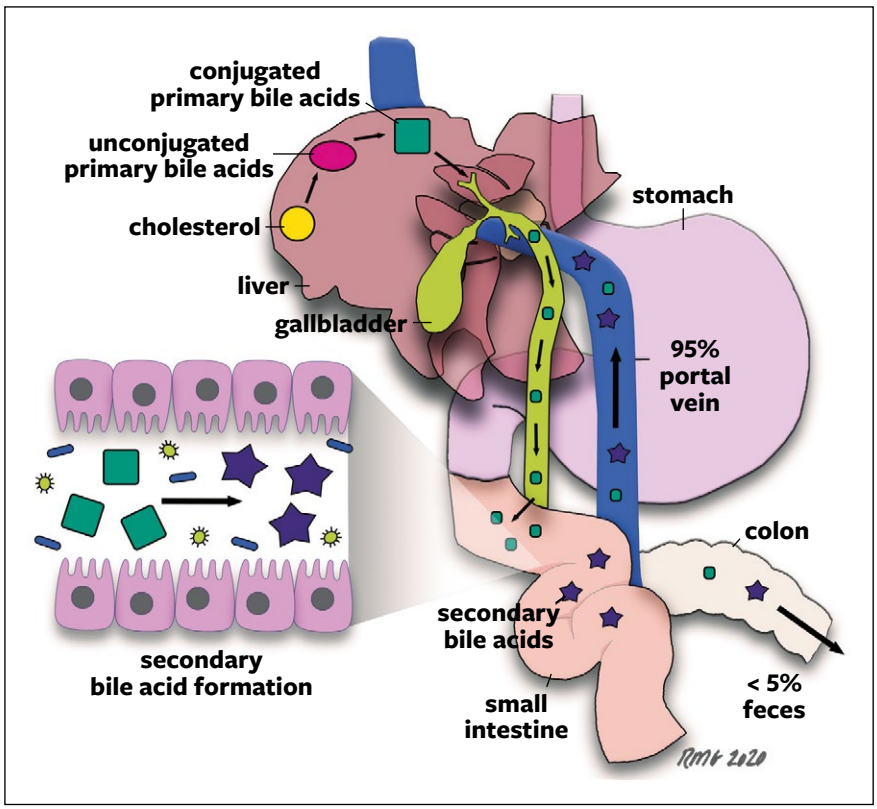



**Fig. 9-6** Bile acid metabolism and enterohepatic circulation

Hepatocytes produce primary bile acids (**pink ovals**) from cholesterol. These primary bile acids are then conjugated (**green squares**) by hepatocytes and secreted into the bile. The majority are reabsorbed in the intestine and transported back to the liver, but ~5% are lost in the feces. Some bile acids are deconjugated in the lumen of the distal small intestine. Also, within the distal intestinal tract, a small percentage of primary bile acids (both conjugated and deconjugated bile acids) are converted to secondary bile acids (**purple stars**) by bacterial enzymes.

first metabolized to a "primary" bile acid (i.e., cholic acid or chenodeoxycholic acid) via hydroxylase enzymes (▶Fig. 9-6). The primary bile acids are then conjugated to amino acids.

In dogs and cats conjugation is primarily to taurine, but dogs may also conjugate to glycine.

In contrast to dogs, even taurine depleted cats conjugate their bile acids almost exclusively to taurine.[13]

The salts of these acids are then excreted into the bile canaliculi. From there they empty into terminal bile ducts, the hepatic ducts, and ultimately the common bile duct before being stored in the gallbladder. After ingestion of a meal, gallbladder contraction is stimulated by the release of cholecystokinin (CCK), and bile is released into the intestinal lumen.[11] As described above, bile acids facilitate the absorption of dietary lipids. A portion of the conjugated bile acids are deconjugated, which are mostly reabsorbed in the ileum or lost in the feces. Also, some bile acids (both conjugated and deconjugated bile acids) remaining in the intestinal lumen are converted to "secondary" bile acids (e.g., deoxycholic acid, lithocholic acid, taurolithocholic acid, and others) by bacterial enzymes.[14]

However, the vast majority of bile acids are reabsorbed, either by an active transport system in the terminal ileum or by ionic and nonionic diffusion across the intestinal and colonic epithelium.[14,15] Enterohepatic circulation allows for roughly 95% of bile acids to be reabsorbed from the intestinal tract and be transported back to the liver via portal circulation, while <5% are lost in the feces.[12]

### 9.2.3 Vitamin storage

Fat-soluble vitamins (i.e., vitamins A, D, E, and K) are absorbed from the intestines together with dietary fats. Approximately 95% of the total body vitamin A is stored in hepatic stellate cells and hepatocytes.[5] Liver and plasma vitamin A concentrations decrease in cases of malnutrition, liver disease, and intestinal malabsorption, but clinical signs go unnoticed until the deficiency is severe.[5] Water-soluble vitamins are absorbed from the small intestines and used primarily as coenzymes in metabolic processes.[5] Large amounts of water-soluble vitamins, except vitamin C, are also stored in the liver.

### 9.2.4 Hemostasis

Coagulation factors are plasma proteins produced primarily by the liver and can be divided into:

1. A structurally related but functionally independent contact group (i.e., prekallikrein, high-molecular-weight kininogen [HMWK], and factors XI and XII)
2. A vitamin K-dependent group (factors II, VII, IX, and X)
3. A highly labile fibrinogen group (factors I, V, VIII, and XIII)[16]

The liver also produces anticoagulant factors (i.e., antithrombin, protein C, and protein S), thrombopoietin, and it also reactivates vitamin K. Because the liver produces both coagulant and anticoagulant factors, severe liver disease can result in either bleeding diathesis or thrombosis.

### 9.2.5 Detoxification

The liver is the major site of biotransformation, whereby drugs and other substances are converted into non-reactive compounds that can be safely excreted from the body via urine or bile. These reactions take two pathways:

1. Phase I reactions (aka modification reactions)
2. Phase II reactions (aka conjugation reactions)

The **phase I system** is composed mainly of cytochrome P450 enzymes. These enzymes represent a large superfamily of membrane-bound heme-containing monooxygenases that catalyze the oxidation of a variety of chemicals, drugs, carcinogens, sterols, fatty acids, and others, using oxygen and a cofactor to add a reactive group, such as a hydroxyl radical.[17,18] Cytochrome P450 can also facilitate reactions that include N-, O-, and S-dealkylation; aromatic, aliphatic, or N-hydroxylation; N-oxidation; sulfoxidation; deamination; and dehalogenation.[5] As a result, reactive intermediate compounds, many of which are often more toxic than the parent compound, are produced and can damage proteins, RNA, and DNA within the cell.[17] **Phase II reactions** transform the reactive intermediates into water-soluble compounds via glucuronidation, sulfation, or glutathione and amino acid conjugation so that they can be excreted in the urine or bile.[17]



Cats have a lower glucuronidation capacity compared with dogs, which has important pharmacokinetic consequences.

### 9.2.6 Hematologic and immunologic functions

In the fetus, hematopoiesis occurs mainly in the perisinusoidal compartment of the liver sinusoids. After birth, this function declines but can return as extramedullary hematopoiesis in conditions of increased demand.[19] The liver contains many cells that are characteristic of the innate immune response, including natural killer T-lymphocytes and Kupffer cells, as well as some that are characteristic of the acquired immune response, such as $CD8^+$ T-cells.[19] Many of these cells help protect the body against foreign antigens released from the gastrointestinal tract, viral infections, metastatic tumors, and hepatocellular carcinoma, as well as modulating hepatic fibrosis.[5,19]

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
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## 9.3 Diagnostic approach to liver disease

Adrian Tinoco-Najera, Jonathan Lidbury

### 9.3.1 Introduction

The liver is paramount for maintaining homeostasis. This is accomplished through an array of approximately 1,500 essential biochemical functions that help support metabolism (e.g., of carbohydrates, protein, or fats), synthesis of vital substances (e.g., albumin, coagulation factors, and hormones), immunity, digestion (e.g., conjugation and excretion of bile acids), detoxification (i.e., drugs, exogenous and endogenous toxins; ▶Chap. 9.5.1), vitamin (e.g., cobalamin, vitamin A) and mineral storage (e.g., copper, iron) amongst other functions.[1] Despite these essential attributes, early detection of hepatobiliary diseases is commonly impaired due to nonspecific clinical semiology. This often necessitates a multi-step approach composed of a physical examination, routine laboratory and liver function test analysis, and diagnostic imaging, followed by histological evaluation to obtain an accurate diagnosis.

### 9.3.2 Prevalence and breed predispositions

Given that the etiology and pathogenesis of most clinical signs associated with hepatic diseases are nonspecific, the clinician needs to be aware of the prevalence and breed predispositions for hepatobiliary disorders.[2] Common congenital breed-related liver diseases encompass abnormalities related to the hepatic vasculature and ductal plate development, of which congenital portosystemic shunts (CPSS) are the most common in dogs and cats (▶Chap. 9.5.3.2).[2,3] Intrahepatic CPSS predominate in large breed dogs, whereas extrahepatic CPSS predominate in small and toy breed dogs. Although these disorders have been reported in numerous breeds worldwide, an inherited component has only been proven in Irish wolfhounds,[4] cairn terriers,[5] Yorkshire terriers,[6] and Maltese.[7] In cats, it appears that mixed breeds, Persians, and Himalayans are overrepresented for developing CPSS.[8] The prevalence of CPPS is estimated to be 1–4%, and they are usually diagnosed in young dogs and cats.[3]

Chronic hepatitis (CH) is the most common liver disorder in dogs, with an estimated prevalence of 12%, and in most cases, is categorized as being idiopathic[9] (▶Chap. 9.5.5.4). Predispositions for CH have been recognized in several breeds with an increased prevalence in Doberman pinschers,[10] Labrador retrievers,[11] Dalmatians,[12] American cocker spaniels,[13] English springer spaniels,[14] and West Highland white terriers.[15] Chronic hepatitis may develop as early as 2 years of age, with an overall mean of 7.2 years.[16] Copper-associated chronic hepatitis (▶Chap. 9.5.5.4.1) is a form of CH characterized by abnormal hepatic copper accumulation due to inadequate biliary excretion, increased dietary intake, or a combination of both.[17] Copper-associated CH can manifest in many predisposed breeds. Specific gene mutations (*COMMD1*) associated with this disorder have been recognized in the Bedlington terrier.[18] Recently, mutations in Wilson's disease gene (*ATP7B*) have been characterized in Labrador retrievers with abnormal hepatic copper accumulation.[19] Abnormal copper accumulation can start at an early age, but clinical signs usually manifest in older individuals (>6 years).

Given the current information available, it was estimated that hepatobiliary diseases represent an incidence of 1–2% for all clinical cases presented to a referral hospital.[20] Therefore, the clinician needs to keep in mind these aspects when formulating differential diagnoses for a given patient.

### 9.3.3 Clinical presentation

It is usually impossible to distinguish a hepatic disease from other disorders based on clinical semiology alone.[21]

**CLINICAL PEARLS**

The liver has a tremendous (~80%) reserve and regenerative capacity, and clinical signs usually only manifest when these are exhausted. This means that hepatic disorders can remain subclinical for lengthy periods of time or initially manifest in a mild fashion.[22]

Additionally, it is very difficult to definitively diagnose specific liver disorders based on clinical signs, as these are often very similar and tend to overlap. Regardless, certain clinical signs such as lethargy, vomiting, mild polyuria/polydipsia, and acholic feces may alert the clinician that a hepatobiliary disease could be present or developing.[23] Disturbances in liver function may influence other organ systems, and this could raise the suspicion of a disease process of that organ system rather than the liver. Examples of this situation include hepatic encephalopathy or polyuria/polydipsia, suggesting a disease process of the central nervous (CNS) or renal/endocrine systems.[24] On the other hand, pathologic events originating in major organs, such as the GI tract, often secondarily affect the liver. Examples of this situation can be seen in cats suffering from hepatic lipidosis due to chronic enteropathies (▶Chap. 11.2) or pancreatitis (▶Chap. 10.3.1), or in patients with acute centrilobular hepatic necrosis due to severe anemia.[23] Other clinical signs or symptoms that can be observed in varying degrees or combinations in hepatic disorders include weight loss, icterus, ascites, coagulopathies, dysuria, abdominal pain, dull mentation, and listlessness. Although hepatic disorders possess a wide spectrum of clinical signs, it is still not possible to relate them to a specific disease process. Therefore, further diagnostic tools should be pursued to confirm or exclude any hepatopathy.[24]

### 9.3.4 Approach to a patient with suspected liver disease

A rational approach is necessary for the accurate diagnosis of primary hepatobiliary disorders in dogs and cats. This includes incorporating key case aspects, including accurate patient history, a thorough physical examination, clinicopathologic testing, diagnostic imaging, and, often finally, histologic examination of the liver (▶Chap. 1.8.2).[20] A properly taken history contains relevant information that includes current and past medications (including potentially hepatoxic drugs, supplements, nutraceuticals, or anesthetic agents), environmental exposure to toxins or infectious agents, travel history, preventive medicine status, household habits, interaction with other pets, and dietary history.[25]

Although the physical examination may be unremarkable, some distinct signs may raise suspicion of a hepatobiliary disorder. Icterus is one of the most common manifestations of hepatobiliary disease and is often observed on mucus membranes, sclera, third eyelid, soft palate, and below the tongue.[21] ▶Fig. 9-7 illustrates an approach to the icteric patient. Abdominal palpation may reveal abnormalities, such as hepatomegaly or ascites. Ascites can occur with hepatic diseases that cause portal hypertension, such as advanced chronic hepatitis, cirrhosis, portal vein hypoplasia, or lobular dissecting hepatitis.[23]



Hepatomegaly in dogs can occur with primary hepatic tumors or secondary hepatic involvement with venous congestion or glycogen accumulation.



In cats, hepatomegaly is common and is suggestive of hepatic steatosis.

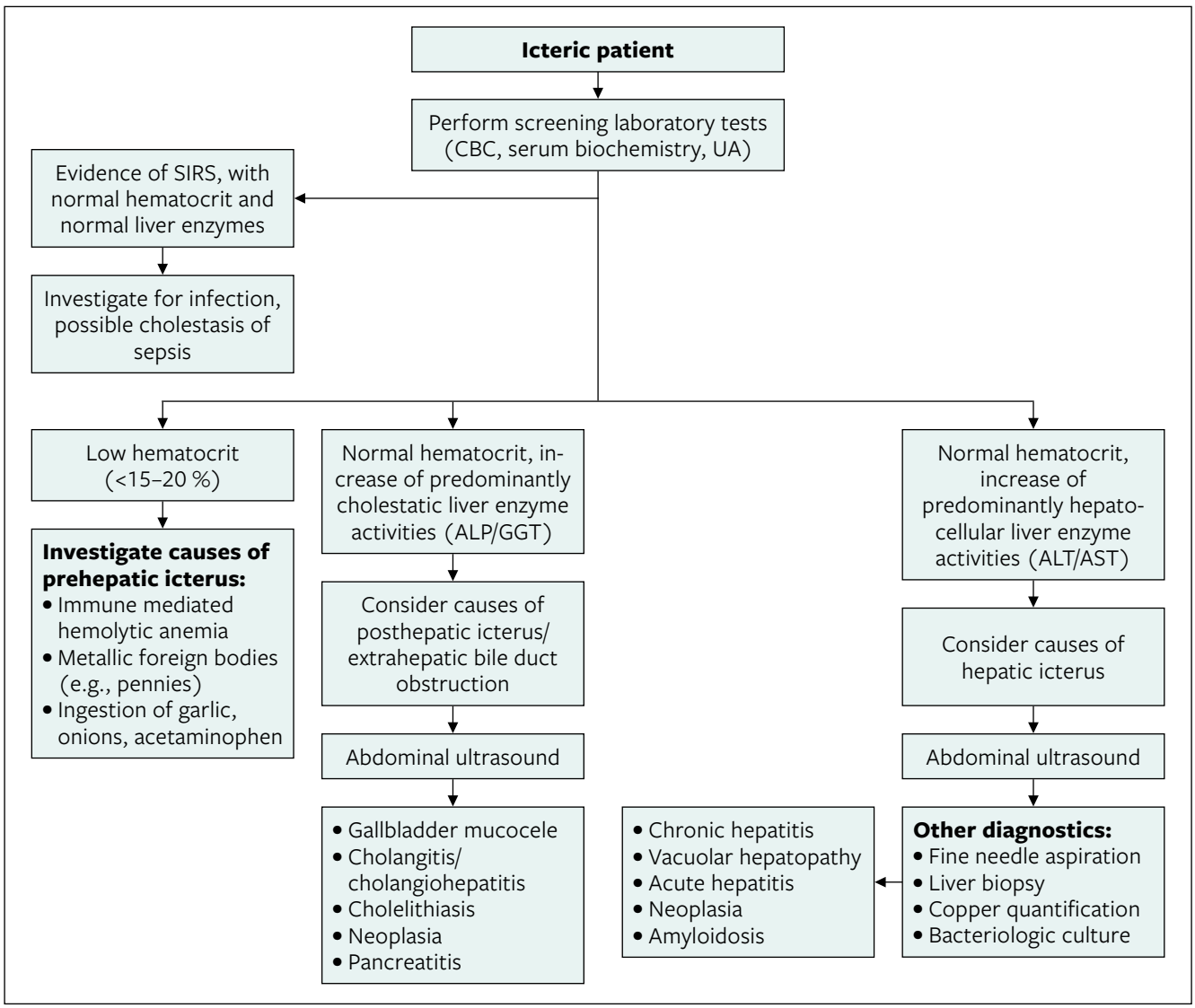



**Fig. 9-7** Approach to an icteric patient

**CBC** = complete blood count; **UA** = urinalysis; **SIRS** = systemic inflammatory response; **ALP** = serum alkaline phosphatase; **GGT** = γ-glutamyl transferase; **ALT** = serum alanine transaminase; **AST** = serum aspartate transaminase

Clinicopathologic testing has several objectives:[26]

1. Determining whether hepatobiliary disease is present
2. Determining if it is primary or secondary
3. Obtaining a definitive diagnosis (for some diseases)
4. Assessing disease progression
5. Evaluating therapeutic response

A detailed discussion of these diagnostic tests can be found in ▶Chap. 1.3.3. In general, evaluation of serum enzyme activities is sensitive for hepatocellular damage (ALT and AST) or cholestasis (ALP and GGT) but is not specific for primary hepatobiliary disease. It is important to state that some hepatobiliary disorders are characterized by relatively mild changes in these enzyme activities and that such abnormalities do not necessarily reflect hepatic dysfunction or a poor prognosis.[27] ▶Fig. 9-8 illustrates a rational approach to a patient with increased liver enzyme activities. If such screening tests strongly suggest the presence of a hepatobiliary disorder, further diagnostic modalities, such as diagnostic imaging, cytology, and/or histological examination of a liver biopsy, can be pursued. Once the diagnosis is confirmed, it is prudent to determine the stage of the disease, establish a prognosis, and choose the most appropriate treatment plan for a given patient.[24]

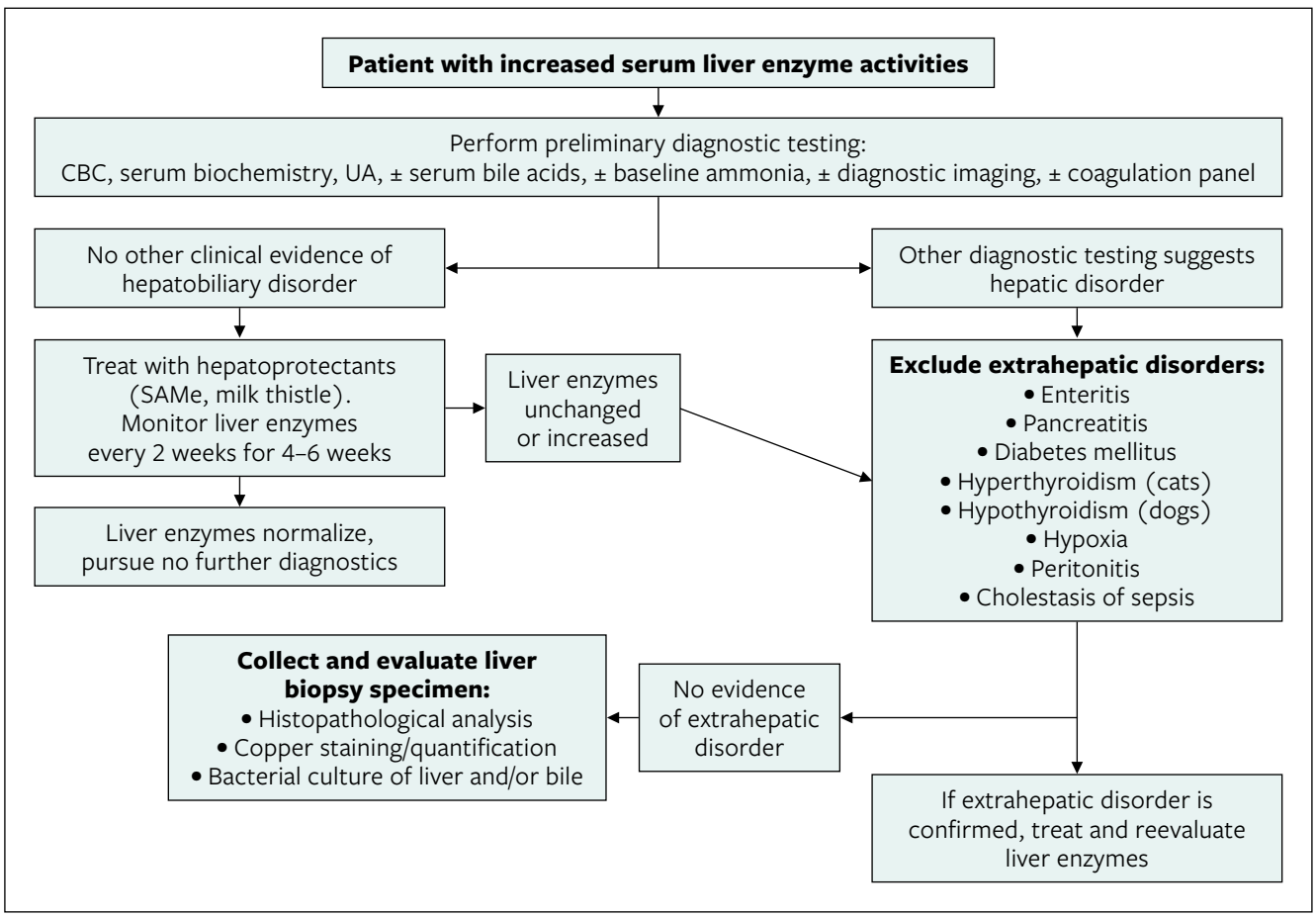



**Fig. 9-8** Approach to a patient with increased serum liver enzyme activities

**CBC** = complete blood count; **UA** = urinalysis; **SAMe** = S-adenosylmethionine

**KEY FACTS**

- Clinical signs and symptoms of liver diseases are usually nonspecific and hepatic disorders can remain subclinical for lengthy periods of time or initially manifest in a mild fashion.
- Diagnostic evaluation aspects include an accurate patient history, thorough physical examination, clinicopathologic testing, diagnostic imaging, and, often finally, histologic examination of the liver.
- Evaluation of serum enzyme activities is sensitive for hepatocellular damage (ALT and AST) or cholestasis (ALP and GGT), but is not specific for primary hepatobiliary disease. Some hepatobiliary disorders are characterized by relatively mild changes in these enzyme activities, which do not necessarily reflect hepatic dysfunction or a poor prognosis. If such screening tests strongly suggest the presence of a hepatobiliary disorder, further diagnostic modalities, such as diagnostic imaging, cytology, and/or histological examination of a liver biopsy, can be pursued.

## 9.4 Complications of liver disease

Adrian Tinoco-Najera, Jonathan Lidbury

### 9.4.1 Icterus

Icterus is a common abnormality encountered upon physical examination of patients with hepatobiliary disease. It can be observed in approximately 20% of dogs and 30–40% of cats with hepatobiliary disorders. Alterations in bilirubin metabolism (increased production, impaired conjugation, reduced clearance, or impaired bile flow) can lead to excessive accumulation in the extravascular space and tissues, causing the patient to become icteric. Icterus can typically be detected when serum bilirubin concentrations are >3 mg/dL (▶Chap. 1.3.3).[21] Cholestasis (intra- or extrahepatic) is a predominant cause of icterus in small animals. Extrahepatic cholestasis usually occurs because of obstruction of the common bile duct (▶Chap. 9.6.1).[28]



Hepatic lipidosis is a common cause of icterus in cats.[29]

When a severe hemolytic disease is present, the increased bilirubin production, in combination with reduced liver function due to hypoxia, may lead to icterus.[30]

### 9.4.2 Polyuria and polydipsia

Polyuria/polydipsia can be observed in up to 50% of dogs with liver disease. This is commonly seen in dogs and cats with congenital or acquired portosystemic shunts (▶Chap. 9.5.6.2) that suffer from hepatic encephalopathy (HE). Several potential mechanisms have been proposed. Firstly, the abnormal neurotransmitter disturbances generated during HE may result in increased secretion of adrenocorticotropic hormone (ACTH), leading to increased levels of free cortisol, which will generate a higher threshold for the release of arginine vasopressin, triggering thirst that will induce affected dogs to drink.[23] Additionally, increased plasma levels of bile acids in animals with hepatobiliary disorders may also cause polyuria/polydipsia due to 11β-hydroxyl steroid dehydrogenase activity inhibition.[31] Finally, reduced conversion of ammonia to urea is common in liver disease. It is theorized that in urea-deficient states, the kidney lacks the ability to generate an adequate osmotic gradient in the medulla, leading to polyuria/polydipsia.[23]

### 9.4.3 Portal hypertension and ascites

Portal hypertension (PH) is defined as an abnormal increase of pressure (>5 mmHg) in the portal circulation and is classified as prehepatic, intrahepatic, and posthepatic. The main causes of PH include excessive blood delivery to the portal system or increased resistance to the passage of portal blood. Increased delivery of blood to the portal circulation can be seen in animals with hepatic arteriovenous shunts in the splanchnic circulation.[30] In most cases, PH is caused by increased resistance to blood flow in the portal bloodstream. Common causes include collagen deposition in the hepatic parenchyma (fibrosis/cirrhosis), infiltration of inflammatory cells (chronic hepatitis [CH]), portal vein hypoplasia, or portal vein thrombosis.[32]

Ascites is the accumulation of free fluid within the peritoneal cavity. Ascites in liver disease may result from severe PH or a combination of moderately increased portal pressure and low plasma oncotic pressure due to hypoalbuminemia. With sustained increases in blood pressure in the portal system, fluid is driven into the interstitial space, eventually overwhelming the resorptive capacity of regional lymphatics and leading to ascites. As liver disease progresses, other compensatory mechanisms start to fail, leading to activation of the renin-angiotensin-aldosterone system, causing further

volume expansion and increasing hydrostatic pressure in the portal vasculature.[32] Dogs and cats with ascites may present with a distended abdomen and have a ballotable fluid wave noted on abdominal palpation. The presence of ascites in liver disease is considered to be a negative prognostic factor.[33]

### 9.4.4 Hepatic encephalopathy

Hepatic encephalopathy (HE) is a syndrome of neurocognitive impairment caused by hepatic disease, portosystemic shunting, and/or arginine deficiency (most common in cats). The pathogenesis of HE is multifactorial and incompletely understood. Toxins derived from the GI tract bypass hepatic metabolism, gaining entry into the peripheral and cerebral circulation.[34] Ammonia, derived from enterocyte conversion of glutamine to glutamate and bacterial degradation of urea and proteins, is considered the most important toxin implicated in HE. The effects of ammonia on the CNS are inhibitory due to glutamate depletion, blockade of GABA receptors, inhibition of Na/K-dependent ATPase, and impaired cerebral energy metabolism. Other substances and/or factors contributing to HE include inflammatory mediators, manganese, neurosteroids, oxidative stress, and amino acid imbalance.[35] There are two types of HE: acute and chronic.

- **Acute HE** is mainly seen in acute liver failure and is characterized by neurologic derangements, such as stupor or coma caused by cerebral edema and increased intracranial pressure.
- **The chronic form of HE** occurs more commonly and can be seen in patients with portosystemic shunts or in cats with arginine deficiency due to hepatic lipidosis. Typical clinical signs include behavioral changes (head pressing, ataxia, circling), mental dullness, anorexia, lethargy, and salivation, but can progress to more severe symptoms.[34]

### 9.4.5 Dermatologic signs

Hepatocutaneous syndrome (now called hepatocutaneous-associated hepatopathy) is a form of superficial necrolytic dermatitis that has been reported in dogs and cats with liver disease.[36] Typical signs in dogs include paw soreness caused by the presence of crusts, erosions, erythema, serous to purulent discharge, and varying degrees of hyperkeratosis. Other affected areas include perioral, perianal, perivulvar, preputial, and scrotal skin. In cats with hepatocutaneous syndrome, it is common to see ulceration and crusting of oral mucocutaneous junctions and ulceration of the pinnae, periocular areas, interdigital areas, ventral abdomen, and inguinal areas with or without crust formation.[21]

### 9.4.6 Gastrointestinal signs

Vomiting is a common clinical sign in all conditions that result in portosystemic shunting and liver dysfunction and occurs when toxins from the GI system bypass the liver, causing direct stimulation of the vomiting center via the chemoreceptor trigger zone in the fourth ventricle. Hepatic disorders that alter liver shape (e.g. carcinomas, contralateral hypertrophy) can induce nausea and vomiting by vagal stimulation. Bile duct dilation is another suspected cause of vomiting due to sympathetic innervation.[23]

Diarrhea in dogs with hepatic disease can occur by two primary mechanisms: cholestatic disease that disrupts the normal enterohepatic cycle of bile acids, causing decreased fat absorption, leading to hyperosmotic diarrhea, and splanchnic and intestinal vasculature congestion due to PH, resulting in decreased intestinal water resorption, vascular fragility, and hemorrhage. The latter is observed with end-stage CH, lobular dissecting hepatitis, portal vein hypoplasia, or portal vein thrombosis.[23] Gastroduodenal ulceration is common in humans with PH, and although histological evidence of this syndrome has yet to be reported in veterinary medicine, it is considered that dogs and cats with PH due to liver disease may be at increased risk.[32]

### 9.4.7 Bleeding disorders

All coagulation factors apart from von Willebrand subtype of Factor VIII are synthesized within hepatocytes. Additionally, vitamin K-dependent activation of Factors II, VII, IX, X, protein C, and protein S occurs in the liver. With hepatobiliary disease, coagulation homeostasis is disrupted, leading to hypocoagulable, hypercoagulable, and/or hyperfibrinolytic states, increasing the propensity to bleed and/or clot.[37] Portal vein thrombosis is a potentially serious complication of liver disease. The decision as to whether it is safe to perform a liver biopsy in a patient with hepatobiliary disease should be based on bleeding risk assessment, including assessment of packed cell volume, coagulation times, platelet count, and ideally, measurement of plasma fibrinogen concentration and buccal mucosal bleeding time.[38]

### 9.4.8 Management of main complications of liver disease

Many clinicians face a challenging task when formulating an adequate therapeutic plan for dogs and cats with liver disease. This can be attributed to two main factors:

1. Many of the complications and syndromes associated with liver disease tend to overtly manifest only with advanced disease, making treatment strategies less effective.
2. Limited information regarding the efficacy and optimal use of most of the drugs used in liver disease in veterinary medicine.[21,39,40]

▶Tab. 9-1 shows the most common drugs used to manage the main complications of liver disease in dogs and cats. Liver transplantation, the treatment of choice with end-stage hepatic disease in humans, is currently not available for companion animals.

## References

The complete list of references for this chapter can be downloaded from vetline.de:
svg.to/9842-09-03-04

**Tab. 9-1** Common drugs used to manage the most important complications of liver disease

| Agent | Mechanism of action | Dosage | Side effects |
|---|---|---|---|
| **Ascites**[16,21,32,41,42] | | | |
| Spironolactone (first choice) | Aldosterone receptor antagonist | 2–4 mg/kg PO q24h | Hyperkalemia and hyponatremia |
| Furosemide | Loop diuretic, inhibits the $Na^+/K^+/Cl^-$ cotransporter | 1–2 mg/kg PO q12h | Hypovolemia, hypokalemia, metabolic alkalosis, potential worsening of HE |
| Moderate sodium diet | Reduces sodium and therefore circulating volume | NA | Low sodium diets have reduced palatability |
| **Hepatic encephalopathy (HE)**[20,35,43] | | | |
| Lactulose | Leads to synthesis of low molecular weight organic acids that trap ammonia in the GI tract | 1–3 ml/10 kg PO q6–8h<br>2–10 ml/kg as retention enema | Flatulence, diarrhea, cramping, dehydration, mild hypercalcemia (cats) |
| Metronidazole | Synthetic nitroimidazole that binds to DNA and causes cell death | 7.5 mg/kg PO q8–12h | At higher doses can cause neurotoxicity |
| Ampicillin | Time-dependent bactericidal that acts on bacterial cell walls | 20 mg/kg PO q6–8h | Nausea, diarrhea, rarely skin rashes |
| **Hemostatic disorders**[37,38,44] | | | |
| Vitamin $K_1$ (for cholestatic liver disease) | Involved in the formation of active coagulation factors II, VII, IX, and X | 0.5–1.5 mg/kg SC or PO q12h for three doses | Anaphylactic reactions, hemolytic anemia when given IV |
| LMW heparin (for acute portal vein thrombosis) | Anticoagulant that inhibits Factor Xa and thrombin | Dalteparin:<br>• Dogs: 150–175 IU/kg SC q8h<br>• Cats: 75 IU/kg SC q6h<br>Enoxaparin:<br>0.8–1.0 mg/kg SC q6–8h | Hematoma formation, spontaneous bleeding, thrombocytopenia |
| Rivaroxaban (an alternative to LMW heparin for treating acute portal vein thrombosis) | Anticoagulant that inhibits factor Xa | 1–2 mg/kg PO q24h | Spontaneous bleeding, thrombocytopenia |

▶▶

**Tab. 9-1** Common drugs used to manage the most important complications of liver disease (Continuation)

| Agent | Mechanism of action | Dosage | Side effects |
|---|---|---|---|
| **Gastrointestinal signs**[16,23,45] | | | |
| Omeprazole (suspected or proven gastroduodenal erosion/ulceration) | Proton pump inhibitor | 0.5–1.5 mg/kg PO q12h | Diarrhea, dysbiosis |
| Sucralfate (suspected or proven gastroduodenal erosion/ulceration) | Forms stable complexes with proteins in damaged mucosa | 250–2000 mg total PO q8–12h | Aluminum intoxication, constipation, interference with absorption of other PO drugs if given concurrently |
| Maropitant | Antiemetic ($NK_1$ receptors antagonist) | 1 mg/kg SC q24h or 2 mg/kg PO q24h | Transient pain reaction, hemolysis at high doses, use with caution in dogs with hepatic dysfunction |
| Ondansetron | Antiemetic effects through the GI tract and chemoreceptor trigger zone | 0.5–1 mg/kg PO or SC q12–24h | Hypersensitivity reactions, fecal incontinence |

**PO** = per os; **SC** = subcutaneous; **IV** = intravenous, **HE** = hepatic encephalopathy; **LMW** = low-molecular-weight; **GI** = gastrointestinal

## 9.5 Diseases of the liver

### 9.5.1 Hepatotoxins and drug-induced liver injury

Adam Gow

#### 9.5.1.1 Introduction

Whether a compound is hepatotoxic depends on various factors, such as dose or individual susceptibility. However, many hepatotoxicities are idiosyncratic and thus not dose-dependent. The majority of hepatotoxicities seen in dogs and cats either by medication (drug-induced liver injury) or ingested substances are acute, although chronic toxicity is possible when comparatively lower doses are ingested over a period.[1]

One of the many functions of the liver is as a "first responder" in the detoxification of compounds from the gastrointestinal (GI) tract arriving via the portal vasculature. To improve contact, the sinusoidal vasculature is fenestrated, and the abutting hepatocyte membranes are villous, increasing the surface area.[2] The hepatocyte membrane contains a superfamily of solute carriers to facilitate uptake. Therefore, hepatocytes are at high risk when potential toxins are ingested. The majority of compounds taken up are detoxified via a three-step process. All three phases, or a combination of them, may be used.[3]

**Phase 1:** An array of cytochrome P450 (CYP) enzymes are bound to the membrane of the smooth endoplasmic reticulum. These can transform almost all xenobiotics by oxidation, reduction, or hydrolysis. The net result is to make them more water soluble to facilitate biliary or renal excretion. This process generally modifies the activity of compounds, often decreasing their activity or even inactivating them, but, in some instances, increasing biological activity or producing reactive metabolites. Enzymes may act on a wide variety of substrates, and this is clinically relevant when two or more drugs utilize the same pathway.[4] These compete for the same enzyme (competitive inhibition). As well as direct competition, compounds or their metabolites may bind elsewhere on the enzyme and reduce affinity for the substrate (non-competitive inhibition) or covalently bond to the enzyme and prevent activity (mechanism inhibition). These interactions can considerably alter the pharmacokinetics and potential for toxicity. Compounds may induce an increase in CYP enzyme activity, increasing the rate of biotransformation of themselves and other compounds using the same pathway. Although all hepatocytes have CYP activity, hepatocytes within each unit of the liver are not identical in terms of function, with CYP activity concentrated within the centrilobular areas. If toxic metabolites form during CYP transformation, then these hepatocytes are at the highest risk for toxic damage. Cytochrome P450 activities are known to vary between species, breeds, and individuals, which also accounts for variation in toxicity.[5]

**Phase 2:** Many compounds are then bound to substances to further inactivate them and facilitate excretion through the biliary or urinary tract. There are a variety of pathways resulting in glucuronidation, sulfurylation, the addition of glutathione or amino acids, acetylation, or methylation of the substrate. There are species and individual variations in these pathways. This may mean that substrates are cleared much more slowly or that alternative routes are utilized.



Dogs have relatively low hepatic glutathione stores. Hepatocyte glutathione deficiency not only reduces the capacity of this pathway but also removes one of the defense mechanisms against free-radical damage from oxidized compounds produced in phase 1.



Cats have specific enzyme deficiencies involved in glucuronidation compared with other species, which affects their ability to remove phenolic-based compounds.[6]

**Phase 3:** Further modification may be carried out before compounds are transported out of hepatocytes, utilizing the ATP-binding cassette transport proteins (ABC transporters), either into the biliary canaliculi for excretion via the biliary system or into the vascular system for renal excretion.

### 9.5.1.2 Mechanisms of hepatotoxicity

Pharmacological (or intrinsic) hepatotoxins (Type A) produce predictable, dose-dependent damage due to either the parent compound or metabolites produced during processing.[2] Idiosyncratic hepatotoxins (Type B) cause toxicity that does not appear to be dose-dependent in susceptible individuals, and toxicity onset can be variable.[7] These are unpredictable, and toxicity rarely occurs during use in a population. Idiosyncratic hepatotoxicities can be due to the compound or metabolite binding to proteins and triggering immune-mediated hypersensitivity or due to an individual idiosyncrasy in the metabolization pathway producing toxic metabolites.[6] Immune-mediated hypersensitivity takes time to develop, leading to delayed reaction at first exposure but developing more rapidly upon subsequent exposure.

Direct toxins that do not need metabolization to exert their effects cause damage to all encountered hepatocytes, whereas if the toxin is a phase 1 metabolite, damage occurs in hepatocytes with the greatest CYP activity, in the centrilobular areas.[2] A cholestatic pattern is seen with some compounds where phase 3 concentrates these in the biliary canaliculi or where the toxin affects bile transport.

Many factors affect how sensitive the liver is to toxin damage. Concurrent drugs metabolized by the same pathways may cause toxicity at a lower dose than expected. Extrahepatic effects may enhance hepatotoxicity. For example, concurrent GI toxicity may result in hemorrhagic diarrhea, reducing oxygen delivery to the highly metabolically active liver by hypovolemia and anemia, as well as increased delivery of endotoxin and translocated bacteria through the portal vein.

### 9.5.1.3 Diagnosis of hepatotoxicity

Any animal presenting with liver disease should have the clinical history and records reviewed with regard to toxins or potential drug-induced liver injury. The spectrum of clinical signs varies dependent on the severity of the hepatic injury and if the toxin has been ingested as a one-off or chronically. Clinical signs and clinical pathology can be identical to that seen in acute hepatic injury, hepatic failure, or chronic hepatopathy. The area of the liver affected can vary depending on the mechanism of action of the toxin. Some toxins affect other body systems, either concurrently, or at a different time course, which may help increase the index of suspicion if ingestion is not known.

A wide variety of substances have the potential to be hepatotoxic, including metals, compounds in plants, bacteria, fungi, and, not least, pharmaceutical agents, both prescribed for an animal or ingested accidentally. No list can be exhaustive, and commonly reported hepatotoxins are detailed below. Veterinarians should also be aware that food supplements and alternative medicines have the potential to be hepatotoxic and may not be readily volunteered by the owner.[8] As many toxins can affect multiple body systems, management of specific toxicities is beyond the scope of this chapter, and readers are advised to consult specific texts. General supportive treatment for the type of hepatopathy as detailed in ▶ Chap. 9.4.8 and ▶ Tab. 9-12 is also generally required.

### 9.5.1.4 Common drug-induced hepatotoxicities

**Acetaminophen** A pharmacological hepatotoxin in dogs and cats. Toxicity occurs due to the saturation of glucuronidation (hence the sensitivity in cats) and sulphation pathways. Metabolism occurs via CYP enzymes, producing the toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI). This metabolite is detoxified by glutathione, but glutathione depletion occurs. NAPQI binds to cell membranes and

proteins, resulting in hepatocyte death. Prior to hepatic necrosis occurring, oxidation of hemoglobin occurs, producing methemoglobinemia. Hypoxia may potentiate hepatotoxicity. Administration of n-acetylcysteine, a glutathione precursor, allows detoxification of NAPQI to continue by this route. Silimarin has also been shown to be protective.[9]



Acetaminophen toxicity in cats occurs at approximately 10% of the toxic canine dose.[6]

**Azathioprine** Hepatotoxicosis appears common in the dog, with a report of around 15% developing a 2-fold increase in hepatobiliary enzymes at around 2 weeks of treatment, although clinical signs of hepatotoxicity have not been reported.[10] German shepherd dogs are suspected to be at higher risk.

**Diazepam** Toxicosis has not been reported in dogs. However, cats are highly sensitive to intoxication. This marked species difference appears to be due to the production of different metabolites during phase 1 metabolism.[12]



Oral preparations of diazepam can cause centrilobular acute hepatic necrosis in cats within approximately 1 week with a grave prognosis.[11]

**Imidazoles (e.g., ketoconazole and itraconazole)** These inhibit CYP3A12, which may potentiate the toxicity of other substances that utilize this pathway. This class of drugs increases hepatocellular enzymes and has the potential to cause hepatotoxicity.[13] Anecdotally, cats appear more sensitive to side effects than dogs.[14]

**Lomustine** Bone marrow suppression is the most common dose-limiting effect; however, biochemical evidence of hepatotoxicity is also frequent, reported in just under 50% of dogs.[15] A cumulative dose development of chronic hepatic disease has also been recognized in the dog.[16] Smaller numbers of studies are reported in the cat, with apparently fewer cases having dose-limiting hepatotoxicity.[17–19]

**Non-steroidal anti-inflammatory drugs (NSAIDs)** As well as dose-dependent side-effects, idiosyncratic hepatotoxicity with a large increase in serum alanine transaminase (ALT) activity can be noted after 1–2 weeks of treatment. Initial reports centered around carprofen; however, hepatotoxicity has also been recognized with other NSAIDs, such as robenacoxib.[20] Labradors were thought to be at increased risk initially, and idiosyncratic hematological and dermatological abnormalities are also occasionally concurrently reported.



Many NSAIDs have a longer half-life in cats, potentially because their metabolism utilizes the glucuronidation pathway.

**Phenobarbital** Chronic use induces CYP as well as ALT and ALP activities in dogs.[21] This drug has also been recognized to precipitate chronic liver injury.[22] Differentiation between induction and damage requires other parameters, such as the measurement of serum bilirubin and bile acids, as well as imaging. Other anti-epileptic drugs, such as phenytoin and primidone (which is partially converted to phenobarbital), are used less commonly but are also recognized to cause chronic drug-induced liver disease.

**Trimethoprim-sulphonamides** These cause an idiosyncratic hypersensitivity hepatotoxicity where mortality is reported to be 21% due to hepatocyte necrosis and cholestasis.[23] A genetic predisposition is suggested as Dobermans appear to be at increased risk. A variation in one CYP gene has been associated with an increased risk, although some drug-tolerant individuals also are homozygous for this mutation, and the function of this enzyme in sulphonamide metabolism is not apparent.[24]

**Thioureylenes (methimazole and carbimazole)** These occasionally cause idiosyncratic reactions with increases in hepatocellular enzyme activities and jaundice.[25] Hepatotoxicity appears less common than cutaneous and hematological adverse effects. The mechanism of hepatotoxicity is not known and resolves by discontinuing the drug.

**Xylitol** This is a sugar substitute used to sweeten foods for human consumption.



Xylitol is safe in all species apart from the dog, where it potently stimulates insulin release at low doses (>50 mg/kg), leading to life threatening hypoglycemia within an hour of ingestion.[26] At higher doses (500 mg/kg), hepatotoxicity due to hepatocellular necrosis is also seen subsequent to hypoglycemia.

The mechanism has not been identified, and treatment is supportive. Some authors recommend the use of hepatoprotectants and n-acetylcysteine in xylitol hepatotoxicity, although these have not yet been proven to be beneficial.

#### 9.5.1.5 Common environmental hepatotoxins

**Aflatoxins** These are produced by *Aspergillus flavus* and *Aspergillus parasiticus*, which grow on grains and seeds in conditions of high moisture and temperature. The toxin is stable and survives processing. A low level is accepted as inevitable in commercial pet foods.[27] Toxicosis associated with commercial dog food are well documented, as well as ingestion of contaminated material.[28] Although aflatoxins are present in cat foods, there are no documented cases of toxicosis. Phase 1 metabolism activates the toxin, and dogs are thought to be more sensitive to the effects as the major detoxification is by phase 2 glutathione conjugation before biliary excretion. The active metabolite covalently binds to multiple structural and enzymatic proteins as well as DNA and RNA. Aflatoxins can cause acute or chronic hepatotoxicity, depending on the dose and duration of exposure. Chronic low-grade aflatoxin exposure is known to potentiate the development of hepatocellular carcinoma (▶Chap. 9.5.7). Acute hepatic toxicity and fulminant failure are most commonly reported in the dog, with treatment being supportive as no specific antidotes are known. Laboratory testing of food for aflatoxins is widely available.

**Amatoxins** This group of toxins is found in some fungal species, including *Amanita, Conocybe, Galerina*, and *Lepiota*. Of these, the death cap mushroom (*Amanita phalloides*) is most prevalent worldwide.[29] Amatoxins are potent direct toxins, inhibiting mRNA synthesis with small quantities of mushroom, producing toxicity in both dogs and cats.[29,30] Clinical signs are phasic with initial severe GI signs, apparent improvement of up to 24 hours during which hepatotoxicity is developing, generally resulting in acute fulminant failure and high mortality. The toxin undergoes biliary excretion and enterohepatic recirculation. It is excreted in the urine unchanged. Urine, serum, and tissues, particularly the kidney and liver, can be tested for their presence. Other therapies commonly employed in human medicine are benzylpenicillin, which is thought to reduce hepatocyte toxin uptake (due to entero-hepatic recirculation, there may be a benefit for some time after ingestion), acetylcysteine to reduce free radicals, cimetidine that has some evidence experimentally of reducing necrosis, and silibinin, which was shown to be beneficial in a large retrospective study.[31] Several intravenous (IV) human-licensed products containing silibinin are available. One experimental study in beagles demonstrated a hepatoprotective effect of silibinin administered at a dose of 50 mg/kg IV, although the initial dose was given within 5 hours of toxin ingestion, which may not always be feasible clinically.[32]



**Fig. 9-9** Typical example of a blue-green algal (i.e., cyanobacteria) bloom in a lake, forming a green to turquoise surface scum

Such algae blooms most commonly form in still or slow-flowing water, in warm weather. From a distance, blooms can be mistaken for duckweed. Cyanobacteria produce microcystins that are hepatotoxic as well as separate neurotoxins. (Courtesy of Laurence Carvalho.)

**Blue-green algae (BGA)** These are cyanobacteria occurring worldwide, mainly in still or slow-flowing freshwater, but variants can occur in saltwater areas (▶Fig. 9-9). They appear to be more prevalent due to nutrient run-off from agricultural land, stimulating growth. BGA contains hepatotoxins termed microcystins.

Microcystins are extremely potent toxins in all species; however, dogs appear to be at a high risk, possibly due to high exposure to blue-green algae environments.[33]

Microcystins are actively transported into hepatocytes and are direct toxins, affecting multiple cell pathways within hepatocytes. They also undergo phase 1 metabolism, producing toxic products. Many BGA also contain neurotoxins that cause an onset of clinical signs within minutes, causing muscle tremors that progress to flaccid paralysis. Renal damage is also reported. Diagnosis is by history and clinical suspicion; however, colonies of the organism may be identified in vomit, or the water source, and high-performance liquid chromatography can be used to specifically identify these toxins.[34]

**Sago (Cycad) palm** These are popular ornamental plants, both outdoors and as houseplants (▶Fig. 9-10). They contain various toxins, particularly concentrated in the seeds, including cycasin, which is metabolized by intestinal bacteria, to methylazoxymethanol, which is neuro- and hepatotoxic.[35] Acute toxicity is reported in the dog most commonly, but long-term low-grade toxicity can cause chronic hepatopathy. In acute toxicity, gastrointestinal and neurological signs predominate with evidence of acute hepatic injury to failure biochemically. Centrilobular necrosis is seen on histopathology. Prognosis depends on the severity of the hepatic insult based on clinical pathology, with hepatic failure having a poor prognosis.[36] Cycads are toxic to a wide range of animals anecdotally, including the cat, although there are no published cases.



**Fig. 9-10** Sago palm (*Cycd* spp.)
These ornamental plants can be found outdoors in warm climates, but also as houseplants worldwide. They have spiny evergreen leaves and can reach 3 m in height outside, but they are also popular as indoor bonsai plants. All parts of the plant are toxic, but the seeds contain the highest concentrations of the toxin cycasin.
(Africa Studio - stock.adobe.com)

### KEY FACTS

- Most hepatotoxicities are acute, although chronic toxicity is possible when comparatively lower doses are ingested over a longer period .
- Cats have specific enzyme deficiencies of enzymes involved in glucuronidation, which affect their ability to remove phenolic-based compounds.
- Any animal presenting with liver disease should have the clinical history and records reviewed with regard to toxins or potential drug-induced liver injury.
- A wide variety of substances have the potential to be hepatotoxic, including metals, compounds in plants, bacteria, fungi, and pharmaceutical agents.
- Many toxins can affect multiple body systems, which needs to be addressed in the management of specific toxicities. General supportive treatment for the type of hepatopathy is generally required.

### References

The complete list of references for this chapter can be downloaded from vetline.de:
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## 9.5.2 Infectious diseases of the liver

Penny Watson

### 9.5.2.1 Introduction

Serious infectious diseases of the liver are relatively uncommon in vaccinated dogs and cats. Canine adenovirus type 1 is an important cause of acute hepatitis in non-vaccinated dog populations, and acute and chronic leptospirosis is recognized in both vaccinated and unvaccinated individuals. Feline infectious peritonitis (FIP) causes hepatitis in cats, which can be difficult to distinguish from chronic non-infectious cholangitis.

The Hepatic Kupffer cells (i.e., tissue macrophages; ▶Chap. 9.1.2.3) play an important role in clearing infectious organisms from the circulation, particularly disseminated infections and those of gut origin arriving through the portal vein. As in other organs, there is a balance between the number and pathogenicity of the organisms involved and host factors that increase susceptibility. The risk that transient bacteria and other organisms are not cleared from the liver, but become established, is increased by immunosuppression, portosystemic shunting, hepatic hypoxia, and preexisting compromise. Once established in the liver, an infectious organism may cause acute or chronic liver disease.

**Tab. 9-2** Hepatic infections in dogs

| Common infections predominantly affecting the liver in immunocompetent individuals |
|---|
| • Leptospirosis (acute or chronic)<br>• Canine Adenovirus type 1 infection (acute)<br>• Canine acidophil cell hepatitis (historic reports; current importance unknown) |
| **Rare/sporadic primary liver infections or disseminated infections often associated with immunocompromise** |
| • Neonatal canine herpes virus (acute disseminated disease in 1–2-week-old puppies with no maternal immunity)<br>• *Bartonella henselae* and *clarridgeiae* (peliosis hepatitis most commonly; granulomatous hepatitis has also been reported)<br>• Salmonellosis (acute)<br>• *Yersinia enterocolitica*<br>• Tyzzer's disease (*Clostridium piliforme* infection, leading to acute hepatic necrosis)<br>• *Rhodococcus equi*<br>• *Francisella tularensis* (tularemia, leading to granulomatous lesions in puppies)<br>• Biliary tract infection leading to acute cholangitis (usually with organisms of gut origin; less common than in cats)<br>• Hepatic abscesses (usually more than one organism)<br>• *Helicobacter* spp.<br>• Mycobacteria (particularly non-tuberculous, mycobacterium avium complex)<br>• Ehrlichia, rickettsia, borrelia, and anaplasma infection<br>• Sarcocystic organisms (e.g., neospora, hammondia, toxoplasma)<br>• *Babesia canis* and *Babesia gibsoni*<br>• Visceral larva migrans (*Toxocara* spp.)<br>• Disseminated fungal infections (e.g., histoplasma, blastomyces, aspergillus, cryptococcus, coccidioides) (usually granulomatous disease; geographical variation; German shepherd dogs may be predisposed to disseminated aspergillosis)<br>• Disseminated protothecosis<br>• *Leishmania infantum* (the liver is not the primary organ involved, but leishmaniosis can cause chronic hepatitis)<br>• Disseminated toxoplasmosis<br>• *Hepatozoon canis*<br>• Liver fluke – *Heterobilharzia americana* |

**Tab. 9-3** Hepatic infections in cats

| Common infections predominantly affecting the liver in immunocompetent individuals |
|---|
| • Biliary tract infection leading to acute cholangitis (usually organisms of gut origin)<br>• Feline infectious peritonitis (FIP)<br>• Liver fluke in endemic areas (*Platynosomum* spp., *Amphimerus pseudofelineus* and *Metametorchis intermedius*) |
| **Rare/sporadic primary liver infections or disseminated infections often associated with immunocompromise** |
| • Domestic cat hepadnavirus<br>• Disseminated toxoplasmosis<br>• *Francisella tularensis* (granulomatous lesions in young cats)<br>• Tyzzer's disease (*Clostridium piliiforme*, leading to acute hepatic necrosis)<br>• Mycobacteria (particularly non-tuberculous, mycobacterium avium complex)<br>• Disseminated fungal infections, usually leading to granulomatous disease (e.g., histoplasma, blastomyces, aspergillus, cryptococcus, coccidioides, sporothrix; geographical variation)<br>• *Cytauxzoon felis* (endemic areas only) |

A large number of organisms have been reported to cause liver disease in individual animals or small numbers of animals, particularly in dogs.[1] Infectious diseases of the liver of dogs are summarized in ▶Tab. 9-2 and those in cats in ▶Tab. 9-3. The diseases are divided into those that primarily affect the liver in immunocompetent individuals and those which are rare, or part of a more disseminated disease often associated with immunocompromise. The most important ones are discussed in more detail in the text.

In a dog presenting with acute hepatitis, infectious or toxic causes should be at the top of the list of differential diagnoses. However, the clinician should also remember to rule out infectious causes in dogs and cats with more chronic and low-grade liver disease. Granulomatous hepatitis, in particular, often has an infectious cause in either species, so a liver biopsy is mandatory before reaching for immunosuppressive treatment.

### 9.5.2.2 Important causes of infectious hepatitis in dogs

#### 9.5.2.2.1 Canine Adenovirus Type 1

##### Etiology

Canine adenovirus type 1 (CAV-1) is an important cause of often fatal acute hepatitis in unvaccinated dogs. In Western Europe, widespread vaccination has resulted in a marked reduction in the prevalence of the disease, which means that clinicians tend to forget to consider it as a differential diagnosis. However, recent outbreaks reported in Italy[2] and Switzerland[3] have stressed the potential for this disease to re-emerge at any time in a susceptible dog population, either because of failure to vaccinate or because of the illegal import of susceptible unvaccinated dogs. Vaccination using

a modified live CAV-2 vaccine produces a robust response in dogs, provided the initial course is completed after maternal antibodies have waned. Studies have shown that dogs are immune for at least 3 years after their initial puppy course of vaccination and, in some cases, up to 14 years.[4] Long-term immunity in these animals may partly be due to "auto vaccination" by exposure to virus particles in the environment, which is also the likely source of outbreaks in unvaccinated dogs. There is widespread carriage of CAV-1 in wild carnivores, in particular in red foxes in Europe, where the infection is usually asymptomatic. A recent study using polymerase chain reaction (PCR) to look for virus in the kidneys and liver at post-mortem examination of 86 wild foxes found a prevalence of 38% in the UK, 28% in Italy, and 3% in Germany.[5]

Infectious canine hepatitis caused by CAV-1 is mainly diagnosed in unvaccinated dogs less than one year of age and can be seen in coinfections with canine coronavirus, parvovirus, and/or distemper virus. The virus has a tropism for hepatocytes and the vascular endothelium. Transmission from infected animals is through saliva, feces, urine, or respiratory secretions and prolonged excretion in the urine is possible after infection.

### Clinical presentation

The fever is biphasic: an initial pyrexia of >40°C lasts for 1–2 days, after which the dog either recovers or goes on to develop a second pyrexia associated with depression, anorexia, vomiting, and diarrhea. Affected dogs usually have abdominal pain and often ascites, which is serosanguinous or hemorrhagic. Bleeding diathesis is also common. Occasionally, neurological signs or respiratory distress are seen due to intracranial or pulmonary vasculitis. Mortality is 10–30%, and dogs that recover often develop corneal opacities (a.k.a., blue eye) and/or interstitial nephritis 1–3 weeks later due to immune-complex disease and persistence of virus in the kidneys.

### Diagnosis and treatment

Typical changes in routine clinical pathology reports include leukopenia due to neutropenia, marked elevations in hepatocellular enzyme activities (i.e., ALT and AST), thrombocytopenia, and/or prolonged clotting times. The major differential diagnoses for acute infectious hepatitis in an unvaccinated dog are CAV-1 and leptospirosis. Specific diagnostic tests can differentiate between them, but until such results can be obtained, clinical pathology findings can be suggestive for either disease, with leukopenia and elevated ALT activities being more common with CAV-1 and leukocytosis and marked elevations in ALP activity being more common with leptospirosis. However, coagulopathies can be seen with either disease. An abdominal ultrasound will show changes typical of acute hepatitis with mild to moderate hepatomegaly, with a diffuse change in hepatic echogenicity often present. Edema of the gallbladder wall also is a common finding with CAV-1 infections.

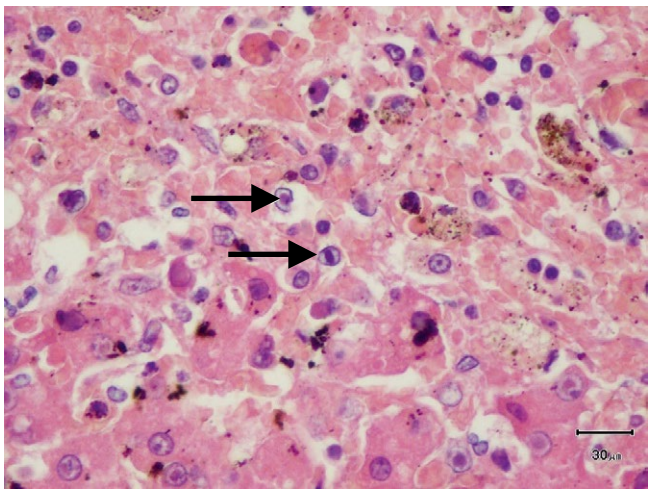



**Fig. 9-11** Histopathological section of liver from a dog with acute necrotizing hepatitis due to adenovirus type 1 infection. Intranuclear inclusion bodies are present in hepatocytes (**arrows**).
(Hematoxylin & Eosin stain, Courtesy of Dr. Nick Bexfield, Queen's Veterinary School Hospital, University of Cambridge UK).

Diagnosis relies on PCR or virus isolation in histological sections or secretions: ocular swabs, feces, and urine should be submitted for PCR testing. Histological examination of liver biopsies or post-mortem examination is usually diagnostic with typical acute centrilobular hepatic necrosis and nuclear inclusions in dogs with CAV-1 infections (▶Fig. 9-11). Immunofluorescence and PCR performed on tissue are confirmatory.

There is no effective treatment for CAV-1 apart from intensive supportive and symptomatic care of acute hepatic dysfunction, as detailed in ▶Chap. 9.5.5.3.2.

## 9.5.2.2.2 Bacterial causes of liver disease

### Leptospirosis

**Etiology** Leptospirosis is another potential cause of acute hepatic failure in dogs. The acute disease is most often seen in unvaccinated dogs, but unlike CAV-1, leptospirosis vaccinations are not universally effective both because of a relatively short duration of immunity and because of the involvement of a number of pathogenic serovars in causing the disease. Leptospirosis is a gram-negative motile spiro-

chete with over 250 pathogenic serovars as well as non-pathogenic serovars. Most organisms infecting the dog belong to *Leptospira interrogans*, including serogroups Icterohaemorrhagiae, Canicola, Pomona, Australis, Sejroe, and Autumnalis, but also the *Leptospira kirschneri* serogroup, Grippotyphosa. There are two types of leptospirosis vaccinations available for dogs: the older L2 vaccine contains inactivated *Leptospira interrogans* serogroups Icterohaemorrhagiae and Canicola, which are most often involved in acute disease. The new L4 vaccine also contains *L. interrogans* serogroup Australis and the *L. kirschneri* serogroup, Grippotyphosa.

*Leptospira* organisms have a number of reservoirs, including domestic animals and wildlife (particularly rodents), which shed chronically in the urine. The bacteria can survive for months in water or moist soil. Studies show an increased prevalence of disease after wet and moist conditions. Anecdotally, leptospirosis is increasingly recognized in both Europe and North America, and clinicians should increase their index of suspicion to avoid missing cases. The disease can vary from mild to severe, depending on host immunity and whether the animal infected is a reservoir or incidental host of that serovar.

Leptospirosis can affect any age or breed of dog, and the European consensus panel recommends clinicians consider the disease regardless of signalment.[6] However, there may be an increased index of suspicion in dogs that have access to water or those that like to swim. Male hunting dogs have an increased prevalence in some studies. The "classical" manifestation in affected dogs is an acute presentation with renal and hepatic involvement. Acute lung disease, generalized vasculitis, and hemorrhagic diathesis are also common, and the pancreas and heart can also be affected. The pathogenesis of organ damage remains poorly understood but is associated with vasculitis in some but not all cases. At least in experimental infections, the incubation period is approximately 7 days. After entering the body across mucous membranes or open wounds, the organism circulates in the bloodstream, during which time, unlike many other infections, the infection is asymptomatic.

**Clinical presentation** Clinical signs ensue after the immune response has attempted to clear the organism, and it becomes concentrated in immune-privileged sites. Clinical signs vary from severe acute disease to mild or even subclinical infections.

Typical acute hepatic signs are hepatocellular necrosis and cholestasis. Liver enzyme activities are usually elevated, but ALP activity and bilirubin are elevated more often than ALT activity. Dogs with acute disease also often show neutrophilia and thrombocytopenia (another finding that should trigger a reminder to check for leptospirosis). About half of acute cases are also anemic. Acute renal injury is also very common in acute canine leptospirosis and is often combined with evidence of hepatic involvement. Dogs can be mildly to severely azotemic with a variety of electrolyte abnormalities. Isosthenuria is common, although dogs can also be hyposthenuric. Proteinuria is common, but normoglycemic glycosuria is less common, though is a finding that should trigger a search for leptospirosis.

**Diagnosis** is initially presumptive based on the clinical and clinicopathological findings and can be confirmed in the acute phase by PCR testing of blood and urine for the presence of organism DNA. The organism is usually present in the blood for the first 10 days after infection and then in the urine, but since the exact date of infection is often unknown in dogs, it is best to both blood and urine. The microscopic agglutination test (MAT) can be used to demonstrate seroconversion to a variety of serovars, but sensitivity and specificity vary with different laboratories and stages of disease and are increased by showing a rising titer on two tests taken 1–2 weeks apart. Dogs can also show high titers for at least 15 weeks post-vaccination.

**Treatment** usually involves intensive symptomatic care with careful infection control. Urine output should be maintained with adequate fluid therapy. Some dogs develop acute renal shutdown and require dialysis. Initial antibiotic therapy is commenced with potentiated amoxicillin, preferably intravenously (20–25 mg/kg q8h). However, amoxicillin is not bactericidal to the leptospiral organism, and treatment with doxycycline needs to commence after treatment with amoxicillin. Some clinicians prefer treatment with doxycycline from the beginning of therapy. Doxycycline should be given orally with food at 5 mg/kg q12h or 10 mg/kg q24h for 14 days.[5]



**NOTE**

Owners must be warned of the zoonotic potential of leptospirosis and should be encouraged to consult with their physician.

**Leptospirosis as a cause of chronic hepatitis** There is also increasing evidence that leptospiral organisms may cause chronic granulomatous hepatitis in some dogs. There has been a suspicion that leptospirosis might be involved in

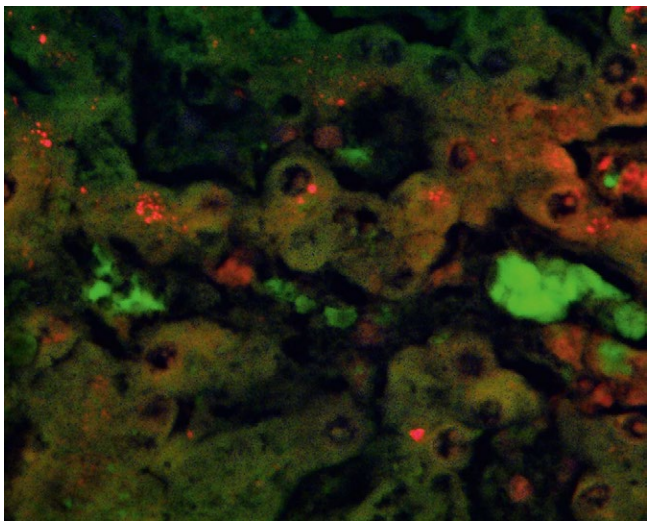


**Fig. 9-12** Fluorescent in situ hybridization (FISH) of a liver section from a dog with granulomatous hepatitis showing clusters of *Leptospira* (**red**) within hepatocytes

The green background areas represent cells in the liver

(Courtesy of Dr. Tristan Cogan, School of Veterinary Sciences, University of Bristol.)

chronic hepatitis for a number of years: Bishop et al. reported infection with the serovar grippotyphosa, and Adamus et al. reported infection with the serovar australis in dogs with chronic hepatitis.[7,8] A recent report from the UK describes ten dogs with chronic hepatitis without prominent renal involvement associated with *leptospiral* organisms identified by fluorescence in-situ hybridization (FISH; ▶ Fig. 9-12) and confirmed by PCR speciation to be *Leptospira interrogans* or *kirschneri*.[9] Clinical signs were generally typical of chronic liver disease, but three of the dogs were asymptomatic but showed elevated liver enzyme activities. The histology in all cases showed chronic granulomatous hepatitis. Eight dogs were treated with doxycycline, but in spite of treatment, two of three dogs that underwent repeat liver biopsies were still positive for *Leptospira* DNA by FISH. It should be noted that this study raised more questions than it answered: it remains unclear whether the *Leptospira* organisms were primary or secondary to chronic hepatitis. It is also unclear why some dogs showed persistent infection in spite of treatment – in fact, it is not known if these infections were persistent or recurrent due to repeat environmental exposure. However, it is very unlikely that these dogs were chronic shedders, as there was no evidence of renal involvement.

## Other potential bacterial causes of canine liver disease

Canine chronic hepatitis can be associated with certain other bacterial infections, although reports are uncommon, and disease association cannot always be proven.

**NOTE**

A diseased liver is likely at increased susceptibility to secondary bacterial infections. Thus, cause and effect may be difficult to prove. Nonetheless, it is important to treat any primary or secondary bacterial infection before considering immunosuppression in these dogs.

Granulomatous forms of chronic hepatitis (i.e., an infection that is associated with a large number of macrophages on histopathology) are more likely to be bacterial or fungal, and a search for infectious organisms should be instigated in these cases. Another possible rule-out would be copper storage disease, which can also cause granulomas in the areas of copper accumulation, and a copper stain should be undertaken. If the copper stain is negative, the biopsy should ideally be submitted for bacterial culture (including a bile culture if possible) and eubacterial FISH, followed by identification of the species. Finding occasional individual bacteria on FISH is not diagnostic of active infection since the organisms may have been cleared from the liver by Kupffer cells, but finding clusters of bacteria suggests active infection and bacterial proliferation and warrants treatment. There are case reports of dogs with *E. coli, Enterococcus,* and other bacteria of intestinal origin that have been discovered by FISH of liver tissue from dogs with hepatitis that responded to antibiotic treatment.[10] Also, *Salmonella* spp. have been reported in hepatic abscesses and dogs with acute hepatic necrosis.[11,12] These reports are sporadic, but there is a suspicion of an increased risk in dogs that are being fed raw diets,[13] emphasizing the importance of taking a complete dietary history.

*Bartonella* spp. are sporadically reported to cause liver disease in dogs. Typically, this organism causes peliosis hepatitis in humans where the liver has multiple cystic vascular spaces, and this has also been reported in a dog with *Bartonella henselae*.[14] *Bartonella henselae* and *Bartonella clarridgeiae* were identified by PCR in two dogs with chronic granulomatous hepatitis, but it was unclear if these organisms were the primary cause, or if opportunistic infections secondary to another underlying disease were present.[15]

#### 9.5.2.2.3 Canine liver fluke – *Heterobilharzia americana*

Another potential cause of granulomatous hepatitis in endemic areas is *Heterobilharzia americana*.[16,17] This trematode with a freshwater snail intermediate host is found in the Southeastern United States. The natural definitive hosts are predominantly raccoons but also other wild mammals.

Affected dogs present with lethargy, weight loss, anorexia, vomiting, diarrhea, and occasionally ascites, although some are asymptomatic. Lesions are caused by fluke eggs, which cause a granulomatous reaction and dystrophic mineralization in multiple organs, particularly the gut wall, liver, and pancreas. Liver enzyme activities are elevated in about a third of cases, and hypercalcemia secondary to granulomatous inflammation has also been reported. Only a small number of dogs show azotemia or eosinophilia. On ultrasound, the liver may appear normal, but it is usually diffusely mottled and hyperechoic with nodules. There is often splenomegaly. Mineralization may be visible in the gut wall, liver, and pancreas.[18] Diagnosis is made on histology or fecal saline sedimentation.

Treatment with a combination of high-dose praziquantel (25 mg/kg PO q8h for 2 days) and fenbendazole (50 mg/kg PO q24h for 10 days; repeat in 3 weeks) can be effective.

#### 9.5.2.2.4 Other viral causes of chronic hepatitis

Non-granulomatous canine chronic hepatitis is usually idiopathic, as detailed in ▶Chap. 9.5.5.4. For many years, researchers have looked for a potential viral cause to explain the high prevalence and histopathological and clinical appearance that are often very similar to chronic viral hepatitis in humans, but to date, no convincing causative viruses have been identified. In the 1980s, a transmissible agent was identified in dogs with chronic hepatitis, which was called **"acidophil cell hepatitis."**[19,20] However, more recent studies have failed to repeat the original successful transmission studies, and no evidence of a novel virus in dogs with chronic hepatitis has been found.[21,22]

Meanwhile, a hepatitis B-like virus (hepadnavirus) has been identified in cats (▶Chap. 9.5.2.2.4) but not dogs. A hepatitis C-like virus (hepacivirus) has been identified in dogs with respiratory disease,[23] but studies in both the UK and Netherlands have failed to determine any association with liver disease in dogs.[24,25] Hepatitis E virus is a zoonotic infection in humans largely associated with pigs. There is a high seroprevalence in dogs in endemic regions of the developing world, prompting recent concerns that dogs may also be a source of human infections. However, although an 18% and 2% seroprevalence have been reported in the Netherlands and UK, respectively, no evidence of viral RNA has been found in large numbers of canine liver or stool samples.[26,27]

### 9.5.2.3 Infectious causes of feline liver disease

#### 9.5.2.3.1 Bacterial infections

Bacterial infections are commonly identified as the primary cause of acute biliary tract disease in cats (i.e., suppurative, neutrophilic cholangitis). More details are found in ▶Chap. 9.6.3. The involvement of bacteria in chronic biliary tract disease is more controversial. Some authors suggest that chronic neutrophilic cholangitis may be caused by chronic persistent bacterial infection. However, a study of eubacterial FISH in cats with liver disease showed that bacteria were most often localized under the liver capsule, in the parenchyma, or perivascularly, with only one cat showing a peribiliary localization, suggesting that these bacteria may occur secondary to hematogenous spread rather than due to chronic biliary tract infection.

#### 9.5.2.3.2 Parasitic infections

Liver fluke infestation is commonly found in cats in endemic areas. Flukes all belong to the family Opisthorchiidae, with the most common species, *Platynosomum fastosum*, found in up to 70% of cats in endemic regions of the USA (i.e., Florida and Hawaii). Cats are infected by eating the second intermediate host (i.e., lizards, amphibians, geckos, or fish depending on the species). The fluke causes peribiliary fibrosis and inflammation, which can be severe.

#### 9.5.2.3.3 Viral causes

##### Feline infectious peritonitis

Feline infectious peritonitis (FIP) due to feline coronavirus is the most important infectious cause of feline liver disease and an important differential diagnosis for inflammatory liver disease, particularly in old and young cats. Both effusive and non-effusive forms of FIP can involve the liver, with high protein ascites seen in about half of the cases. Hepatic ultrasound can be normal or show diffusely hypoechoic or hyperechoic parenchyma.[28]

Definitive diagnosis and differentiation from chronic hepatitis or lymphocytic cholangitis usually require liver biopsy or cytologic evaluation of a fine needle aspirate. Fibrinous and pyogranulomatous hepatitis with vasculitis is found on liver biopsy, which is usually diagnostic (▶Fig. 9-13). Feline

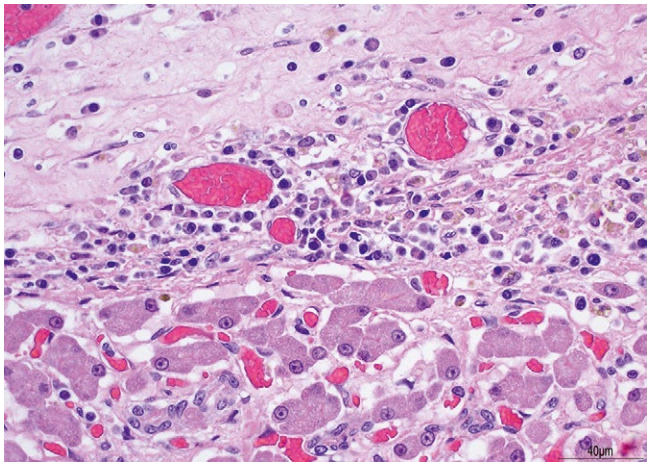



**Fig. 9-13** Histopathological section of liver from a cat with feline infectious peritonitis showing typical vasocentric lesions with infiltration of plasma cells, lymphocytes, and macrophages in the liver subcapsular area

(Hematoxylin & Eosin stain, Courtesy of Dr. Fernando Constantino-Casas, Pathology Department, Queen's Veterinary School Hospital, University of Cambridge UK).

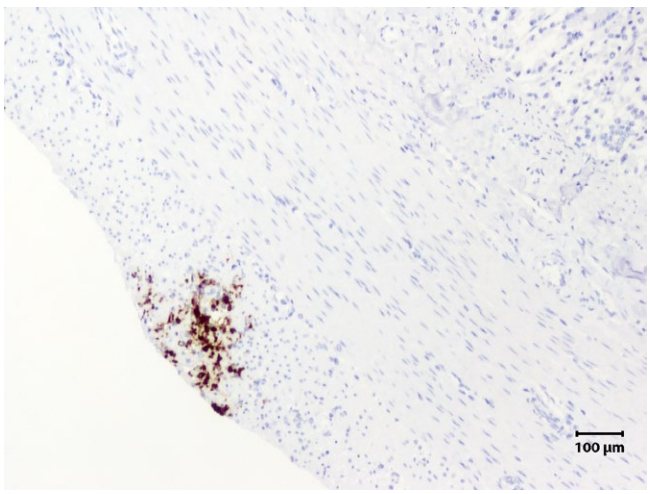



**Fig. 9-14** Histopathological section of small intestine of a cat with feline infectious peritonitis

There are clusters of inflammatory cells staining for feline coronavirus in the gut serosa. (Immunohistochemistry, anti-coronavirus antibody FIPV, 3,3'-Diaminobenzidine, Courtesy of Dr. Fernando Constantino-Casas, Pathology Department, Queen's Veterinary School Hospital, University of Cambridge UK).

coronavirus immunohistochemistry on histopathological sections is confirmatory (▶ Fig. 9-14). One study suggested that histopathologic evaluation of liver biopsies or cytologic evaluation of live aspirates have a higher sensitivity for diagnosis than evaluation of kidney samples.[29]

### Hepadnavirus

Recently, a novel hepatitis B-like virus (hepadnavirus) has been identified in domestic cats. A study in 71 cats found virus by PCR in 43% of cats with chronic hepatitis and 28% of cats with hepatocellular carcinoma, but not in cats with biliary tract disease.[30] This study suggests that this virus may be involved in chronic parenchymal liver disease in cats, but more studies are needed to investigate this virus further.

### KEY FACTS

- Infectious hepatitis, particularly due to canine adenovirus type 1 (CAV-1) and leptospirosis, is an important differential diagnosis for acute hepatic necrosis in dogs.
- Vaccination provides robust and long-term protection against CAV-1, but only partial and short-term protection against leptospirosis.
- Infectious causes of canine chronic hepatitis are uncommon, but should be considered, particularly where there is granulomatous inflammation on histopathological evaluation.
- Feline infectious peritonitis is an important differential diagnosis for both acute and chronic liver disease in cats.
- Hepadnavirus is an emerging potential cause of chronic parenchymal hepatitis in cats, which merits further investigation.
- Both cats and dogs are susceptible to hepatic involvement in a wide variety of systemic bacterial, fungal, and parasitic infections

### References

The complete list of references for this chapter can be downloaded from vetline.de:
svg.to/9842-09-05-02

## 9.5.3 Hepatic vascular anomalies

M. S. Tivers

### 9.5.3.1 Introduction

There are several forms of hepatic vascular anomalies seen in dogs and cats, but the most common and best categorized are congenital portosystemic shunts (CPSS). Other congenital anomalies include hepatic arteriovenous malformations (HAVM, ▶Chap. 9.5.3.3) and primary portal vein hypoplasia (PPVH, ▶Chap. 9.5.6.2.2) and microvascular dysplasia (MVD). Multiple acquired portosystemic shunts (MAS) can be seen secondary to underlying liver disease.

### 9.5.3.2 Congenital portosystemic shunts

#### 9.5.3.2.1 Anatomy and physiology

Congenital portosystemic shunts (CPSS) are functional communications between the hepatic portal vein and the systemic circulation. In general, CPSS can be extrahepatic with the abnormal vessel outside of the liver or intrahepatic with the shunt originating from an intrahepatic portal vein branch and being located within the hepatic parenchyma.

**Extrahepatic shunts** have a wide range of different morphologies, although they can be easily characterized by their insertion into the systemic circulation (i.e., *vena cava*, azygous vein, or phrenic vein; ▶Chap. 9.1.5).



The most common canine CPSS are spleno-caval, left gastro-phrenic, right gastro-caval, and left gastro-azygous.[1]



The most common feline CPSS are spleno-caval, left gastro-phrenic, and left gastro-caval.[1]

**Intrahepatic shunts** are defined by their location within the liver and are divided into left, right, and central divisional shunts. Left divisional shunts are most common and typically are comprised of a patent ductus venosus.

A CPSS allows blood from the portal system to bypass the liver, resulting in a hypoplastic, underdeveloped liver and effective hepatic insufficiency. The amount of shunting is variable between animals, and this may, in part, reflect the marked variations in clinical signs seen.

#### 9.5.3.2.2 History and clinical presentation

Overall, CPSS are relatively common in dogs, but they are seen more frequently in certain pedigree breeds that appear to be predisposed. In a 2003 study of North American teaching hospitals, CPSS were diagnosed in 0.18% of all dogs but only 0.05% of mixed-breed dogs.[2] In the UK, the prevalence of CPSS in specific dog breeds was reported to vary from 0.1 to 2.9%.[3] CPSS are less common in cats, with a 1995 study reporting that 0.025% of cats seen in referral practice were diagnosed with shunts.[4] In dogs, CPSS are considered to be hereditary in Yorkshire terriers, cairn terriers, Maltese, Irish wolfhounds, and Australian cattle dogs. In cats, several breeds are suggested to be predisposed, including Persians, Himalayans, Siamese, and British shorthair cats. Extrahepatic CPSS are most common and are typically seen in small breed dogs, whereas intrahepatic CPSS usually affects large breed dogs. However, large breed dogs can have extrahepatic CPSS and vice versa.

As this is a congenital condition, the majority of animals show clinical signs early in life and are typically diagnosed between 6 weeks and 6 months of age. However, some animals are diagnosed later in life. Clinical signs are directly related to the shunting of blood past the liver and are characteristic of hepatic insufficiency. This can result in signs relating to the neurologic system, gastrointestinal system, and urinary tract. Neurologic signs are caused by hepatic encephalopathy (HE), and these are the most common signs seen in affected animals. Signs of HE can be intermittent and variable (▶Chap. 9.4.4). Urinary tract signs are primarily related to ammonium urate urolithiasis as a result of the excretion of excessive ammonia. Clinical signs can vary considerably in nature and severity between individuals (▶Tab. 9-4), but it has been suggested that the shunt morphology can directly affect the severity of clinical signs.[5,6] Shunts inserting cranial to the liver (i.e., porto-phrenic and porto-azygous shunts) may have reduced shunting due to intermittent compression of the shunt during normal movement of the diaphragm with respiration or distention of the stomach after a meal. This results in reduced severity of clinical signs with these morphologies, and animals are more likely to be older at the time of diagnosis.

Some animals can be presented as emergencies due to severe HE with seizures or even comatose or with dysuria secondary to urethral obstruction from ammonium urate stones. Emergency treatment of HE is covered in more detail in ▶Chap. 9.4.8.

**Tab. 9-4** Common clinical signs in dogs and cats with congenital portosystemic shunts

| Affected system | Clinical signs |
|---|---|
| Neurologic (hepatic encephalopathy) | • Reduced mentation<br>• Lethargy<br>• Abnormal behavior<br>• Ataxia<br>• Head pressing<br>• Wandering/circling<br>• Tremors<br>• Blindness<br>• Seizures<br>• Coma |
| Gastrointestinal | • Vomiting<br>• Diarrhea<br>• Pica<br>• Gastrointestinal bleeding: melena and hematemesis (more common in dogs) |
| Urinary tract (related to ammonium urate urolithiasis +/- secondary bacterial infection) | • Hematuria<br>• Dysuria<br>• Stranguria<br>• Pollakiuria |
| Other | • Polyuria/polydipsia (more common in dogs)<br>• Poor body condition/failure to gain weight<br>• Small stature<br>• Intolerance to sedative/anesthetic agents<br>• Hypersalivation (cats)<br>• Copper-colored irises (cats) |

**Tab. 9-5** Common abnormalities on routine complete blood count, biochemistry profile, and urinalysis in dogs and cats with congenital portosystemic shunts (CPSS).

| Diagnostic test | Finding | Note |
|---|---|---|
| Complete blood count | Microcytosis | - |
| | Anemia | Less common in cats |
| Biochemistry | Hypoalbuminemia | Less common in cats |
| | Decreased blood urea nitrogen | More common in cats |
| | Hypo-cholesterolemia | - |
| | Hypoglycemia | Less common in cats |
| | Increased liver enzyme activities (ALP and ALT) | - |
| Urinalysis | Decreased urine specific gravity | - |
| | Ammonium biurate crystalluria | - |

**ALP** = alkaline phosphatase; **ALT** = alanine aminotransferase

Although most animals show obvious clinical signs at an early age, a small proportion have relatively mild or no obvious signs. Occasionally, animals are diagnosed with a CPSS when mature, either as an incidental finding or due to the development of late-onset clinical signs. Decision-making for these animals can be challenging.

### 9.5.3.2.3 Diagnosis

#### Laboratory investigations

Routine biochemistry profile and complete blood count, as well as urinalysis, will often show characteristic changes suggestive of a CPSS (▶Tab. 9-5). However, the findings can be variable and are relatively nonspecific. Clotting times (activated partial thromboplastin time and prothrombin time) are often increased in dogs and cats with CPSS.[7,8] However, significant clinical coagulopathy is rare, and dogs are more likely to be hypercoagulable.[9]

Liver function tests (▶Chap. 1.3.3), including plasma ammonia and dynamic bile acid concentrations, are recommended. Bile acids are preferred as they are more accurate and more readily available. The sensitivity of serum bile acids for CPSS diagnosis is excellent (100% for paired pre- and post-prandial sample analysis), but they cannot be used alone to differentiate CPSS from other potential causes of hepatic dysfunction. Occasionally, animals may have normal pre-prandial serum bile acids concentrations, and thus a dynamic test is recommended.

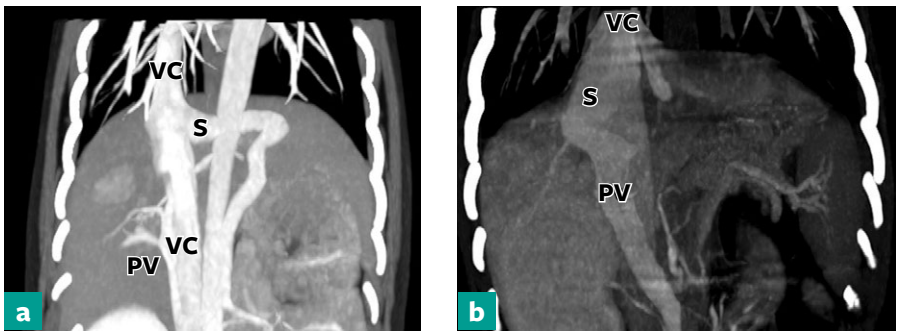



**Fig. 9-15** Reconstructed dorsal computed tomography angiography (CTA) images
**a** Gastrophrenic extrahepatic congenital portosystemic shunt in a dog
**b** Central divisional intrahepatic congenital portosystemic shunt in a dog
**S** = shunt, **PV** = portal vein, **VC** = vena cava

## Diagnostic imaging

Diagnostic imaging is necessary to identify the shunt in order to confirm the diagnosis and to rule out other causes of liver dysfunction. It also provides important information on the location and morphology of the shunt to allow appropriate treatment.

Abdominal ultrasonography is useful as a screening tool and may provide sufficient information on the nature of the shunt for surgical planning. Although convenient, ultrasound is very operator dependent, and the accuracy is therefore variable. Doppler ultrasound can show the blood flow in a CPSS (▶Fig. 9-20).

Computed tomography angiography (CTA) is recommended as the gold standard for imaging a CPSS and provides a wealth of information on the location and morphology of the shunt as well as the degree of portal vasculature development (▶Fig. 9-15). It is minimally invasive and can be performed safely prior to surgery but is relatively expensive and does require sedation or anesthesia.

Rectal, or more commonly, splenic portal scintigraphy with technetium pertechnetate ($^{99}Tc^{m}O_{4-}$), can be used to investigate a CPSS and has been associated with good sensitivity and specificity. However, scintigraphy is not widely available and is not useful to localize a portosystemic shunt and has been superseded by ultrasound and CTA in most instances.

Some surgeons use intra-operative mesenteric portovenography (IOMP) with fluoroscopy as an adjunct to surgery. This allows confirmation of the shunt during surgery, provides information on the morphology of the shunt, and rules out a second CPSS or MAS (▶Fig. 9-16 and ▶Fig. 9-17). It is particularly useful in animals that have not had pre-operative CTA. IOMP is used to confirm the correct identification of the shunt and its branches during surgery and thus facilitates optimal placement of any attenuation. In addition, IOMP during temporary complete shunt occlusion allows assessment of the degree of intrahepatic portal blood flow, which can help determine whether complete acute ligation can be tolerated.

In the author's experience, ultrasonography, performed by an experienced operator, is sufficient to diagnose a shunt and allow surgical planning in most animals with an extrahepatic CPSS. CTA is recommended when diagnosing and planning the treatment of an intrahepatic CPSS. The author routinely uses IOMP for the reasons described above.

## Differential diagnosis

CPSS must be differentiated from other causes of liver dysfunction. These would include other vascular disorders, such as hepatic arteriovenous malformation (HAVM), primary portal vein hypoplasia (PPVH), and primary liver disease with or without MAS (see sections in this and other chapters for further details). It should be pointed out that there can be considerable overlap between the history and clinical signs for these different conditions, as well as the results of laboratory investigations. Although certain variables may point specifically towards a CPSS or otherwise, the mainstay of diagnosis is the identification of a CPSS on imaging.

Another differential diagnosis in the cat is a splenosystemic shunt.[10] The etiology of this type of shunt is unclear, and it is uncertain whether they are congenital or acquired. They take the form of a relatively large vessel, connecting the splenic vein with the left gonadal or left renal vein, sometimes associated with MAS. The history, clinical signs, and biochemical abnormalities are very variable, and they are frequently seen as incidental findings.

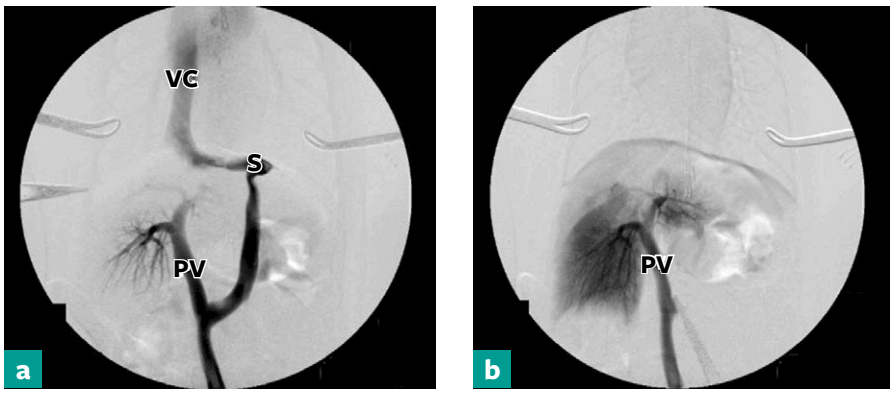



**Fig. 9-16** Intra-operative mesenteric portovenogram images from a dog with an extrahepatic congenital portosystemic shunt (CPSS)

This is the same dog as in ▶ Fig. 9-15a. The dog is in dorsal recumbency, with cranial being toward the top of the image. Contrast has been injected through a catheter in a jejunal vein under fluoroscopic guidance with digital subtraction.

**a** Pre-attenuation portovenogram showing a left gastrophrenic extrahepatic CPSS. The majority of blood flow is through the shunt, with some opacification of the portal vein and the intrahepatic vasculature.

**b** Repeat portovenogram following temporary complete occlusion of the shunt. There is increased opacification of the intrahepatic vasculature, and no contrast flow through the shunt.

**VC** = vena cava, **PV** = portal vein, **S** = shunt.

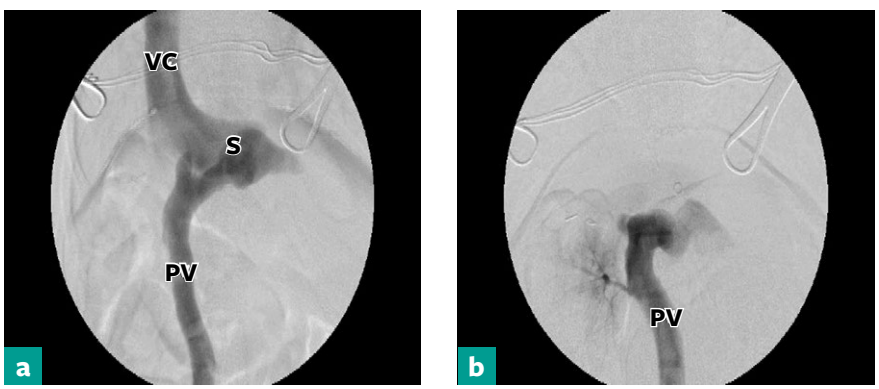



**Fig. 9-17** Intra-operative mesenteric portovenogram images from a dog with an intrahepatic congenital portosystemic shunt (CPSS)

The dog is in dorsal recumbency with cranial being to the top of the image. Contrast has been injected through a catheter in a jejunal vein under fluoroscopic guidance with digital subtraction.

**a** Pre-attenuation portovenogram showing a left divisional intrahepatic CPSS. There is no opacification of the intrahepatic vasculature.

**b** Repeat portovenogram following temporary complete occlusion of the shunt. There is some opacification of the intrahepatic vasculature and no contrast flow through the shunt.

**VC** = vena cava; **PV** = portal vein; **S** = shunt.

#### 9.5.3.2.4 Treatment

### Stabilization

The initial management for animals diagnosed with CPSS is medical. Medical management aims to treat the signs of HE and consists of a combination of lactulose, a low-protein diet, and antimicrobials. However, many animals may not need antibmicrobials,[11] and the author reserves their use for those animals that are refractory to treatment with lactulose and a low-protein diet alone. Animals with severe HE must be given emergency treatment (▶Chap. 9.4.8).

### Medical management

Medical management can be used as the sole treatment for dogs and cats with CPSS and can result in an acceptable long-term outcome. However, medical management does not address the underlying cause or improve liver function. Therefore, dogs are at risk of recurrent clinical signs, and their quality of life may not be normal. A recent study of 78 dogs with CPSS that were medically managed showed good improvement in clinical signs and owner-reported quality of life.[11] However, 54% of dogs died or were euthanized due to CPSS-related reasons. Also, a prospective study compared the outcome for 27 dogs managed medically with 97 dogs treated with surgical attenuation.[12] The long-term outcome for dogs managed surgically was significantly better than for those managed medically, both in terms of survival and the frequency of ongoing signs. There is very little published on medical management as the sole treatment in cats with CPSS.

In general, surgical management is recommended for dogs and cats with CPSS. However, surgery is not without risks, and this must be considered when determining the best treatment for an individual animal. Medical management can be used long-term for animals where surgery is not considered appropriate or when it is declined by the owner. Regardless, a period of 2–4 weeks of medical management is recommended to stabilize the animal prior to surgical shunt attenuation.

As mentioned previously, some animals with minimal or no clinical signs can be diagnosed with a CPSS, often when mature. Deciding between medical and surgical management (or even no treatment for animals without clinical signs) can be challenging. Surgical management is associated with a risk of mortality and the risk of significant complications, which are likely to be increased in older animals.[13] It can also be difficult to assess the cost/benefit of surgery for animals with no apparent clinical signs. However, the author believes that these animals are not normal, that they may have subclinical disease, and would ultimately benefit from surgical correction of the shunt. However, this benefit must be considered against the risk of serious complications and death, as well as the financial implications.

### Surgical management

The aim of surgical management is to close the shunt and restore normal portal blood flow to the liver and hence normal liver function. There are several approaches to shunt closure, including acute suture ligation, gradual attenuation devices, and endovascular coils.

The original technique for the closure of CPSS was suture ligation. Intra-operative objective and subjective assessment of portal pressure changes and portal blood flow on fluoroscopy are used to determine whether the shunt can tolerate complete ligation (▶Fig. 9-18).



**NOTE**

Acute complete shunt closure is not possible in a significant proportion of animals as the liver and portal venous system are hypoplastic and cannot tolerate normal portal flow, leading to portal hypertension. In these animals, partial ligation can be performed, but persistent flow through the shunt is expected and can result in persistent or recurrent clinical signs.

Overall, the outcome for animals treated with complete ligation is superior to those treated with partial ligation. A second surgery is recommended for animals treated with partial ligation in order to achieve complete closure.

Gradual attenuation devices are commonly used in animals with CPSS and include ameroid constrictors (AC), thin film bands (TFB), and polyacrylic acid-silicone gradual occlusion devices (PAS-OD) (▶Fig. 9-19). They are placed around the shunt and provide gradual closure over a period of weeks. These devices are preferred to suture ligation by many surgeons as they avoid concerns over the risk of portal hypertension and the inability to provide acute complete closure in some animals. They are also relatively easy to use and are associated with a favorable outcome. However, one disadvantage of these devices is that once they have been placed, there is no control over the rate or completeness of closure. This can lead to persistent shunting if the device fails to close the shunt completely. In contrast, the shunt may close too rapidly, resulting in MAS. Studies have shown a rate of persistent shunting of 24% after ARC compared with 30.6–37.5% after TFB.[14–16]

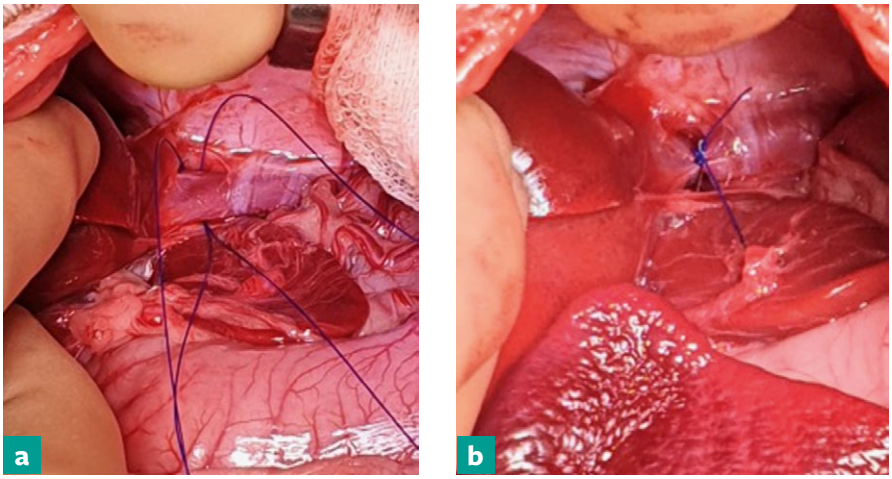



**Fig. 9-18** Intra-operative image of a dog with a left gastrophrenic extrahepatic congenital portosystemic shunt (CPSS)

This is the same dog as seen in ▶Fig. 9-14a and ▶Fig. 9-15a and b.

**a** The shunt has been dissected just prior to its entrance to the vena cava, and two loops of polypropylene suture (Prolene™; Ethicon) have been placed around it.

**b** The shunt has been completely ligated. This decision was based on a subjective and objective assessment of portal pressure and the degree of intrahepatic portal blood flow on portovenography before and after temporary complete attenuation.

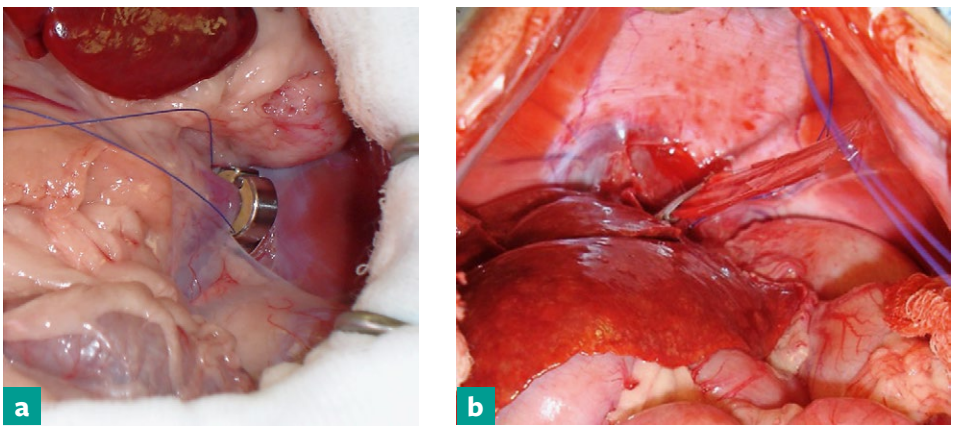



**Fig. 9-19** Intra-operative images from two congenital portosystemic shunts

**a** Intra-operative image of a cat with a portoazygous extrahepatic congenital portosystemic shunt (CPSS). An ameroid constrictor has been placed around the shunt at the point where it passes through the diaphragm. Note the length of loose polypropylene suture (Prolene™; Ethicon) around the shunt. This will be left in situ and can be used to facilitate further attenuation at revision surgery, if necessary.

**b** Intra-operative image of a dog with a left divisional intrahepatic congenital portosystemic shunt (CPSS). A thin film band had been placed around the left hepatic vein just before it enters the *vena cava*. The band has been secured with hemoclips. Note the length of a loose polypropylene suture (Prolene™; Ethicon) around the shunt as in ▶Fig. 9-19a.

Due to their location within the liver, intrahepatic CPSS are technically more challenging to treat surgically. Surgical management of intrahepatic CPSS is associated with a relatively high rate of complications compared with that of extrahepatic CPSS. Surgery involves placement of a suture, TFB, AC, or hydraulic occluder around the hepatic vein draining the shunt, the portal vein branch supplying the shunt, or the shunt itself. Coil embolization via interventional radiology has been recommended for the treatment of intrahepatic CPSS in dogs to reduce the morbidity and mortality associated with surgery.[17] This technique involves the placement of coils into the shunt via a jugular vein catheter. In dogs, a stent is placed in the *vena cava* to prevent the migration of coils into the systemic circulation. This technique provides acute partial closure of the vessel via thrombosis, although further closure may occur over time. Indeed, it has been suggested that complete closure is not necessarily the goal, and therefore continued shunting may be expected in some dogs.[17] However, some animals benefit from the placement of additional coils to provide further closure. Coil embolization can also be used in cats, although many individuals may be too small.[18,19] A hybrid surgical approach also has been described for use in cats.[19]

The different approaches to treatment all have their own advantages and disadvantages, and all can be associated with a good outcome. There are relatively few studies directly comparing one or more treatment options, and the evidence base for determining the best treatment for extrahepatic and intrahepatic shunts in dogs is weak.[20–22] A recent review suggested that ameroid constrictors are superior to TFBs in leading to the closure of extrahepatic CPSS, but the quality of evidence is still low.[22] The evidence base for the treatment of CPSS in cats is even weaker. Prospective comparison studies are needed to create a more robust evidence base, but obtaining sufficient numbers of dogs and cats remains challenging.

**CLINICAL PEARLS**

The author's approach to surgical management of both extrahepatic and intrahepatic CPSS is to perform complete ligation in dogs and cats that will tolerate it. For those animals that cannot, a gradual attenuation device (AC or TFB) is placed. When using a gradual attenuation device, the author routinely leaves a length of suture material loose around the shunt in order to facilitate further surgical attenuation if full shunt closure is not achieved with time. This approach is intended to maximize the number of animals that achieve complete closure of their shunt and to reduce the incidence of persistent shunting (▶Chap. 9.5.3.2.5).

## Complications of surgery

Attenuation of a CPSS has been associated with significant complications, including post-attenuation neurological signs portal hypertension, peri-operative hemorrhage, postoperative gastrointestinal hemorrhage, and hypoglycemia.

**Post-attenuation neurological signs (PANS)** are the most significant postoperative complications in animals with extrahepatic shunts. The cause of PANS is unclear, although it is thought to be related to changes in aberrant neurotransmitters associated with HE and is not directly related to HE or hypoglycemia. PANS vary in severity from mild tremors, ataxia, or changes in behavior to blindness or seizures. Signs typically manifest within 72 hours following surgery and can occur with any closure technique. The incidence of PANS varies considerably between studies but has been reported in 9.4–27.3% of dogs and 36.7–62.0% of cats undergoing surgical treatment of an extrahepatic CPSS. Seizures occur in 3.2–8.3% of dogs and 22.0–23.5% of cats. When severe, PANS can be challenging to treat, and they represent the most common cause of death in animals with an extrahepatic shunt. A recent study found that increasing age and the presence of signs of HE immediately prior to surgery were significant risk factors for the development of PANS.[13]

**Portal hypertension** can occur due to excessive attenuation of the shunt or by kinking of an ameroid constrictor. However, with the use of gradual attenuation devices or careful assessment when performing suture ligation, significant portal hypertension is rare.

**Other complications** Intra-operative hemorrhage from the shunt during dissection is very uncommon, particularly for extrahepatic CPSS. Postoperative GI hemorrhage associated with gastric ulceration is reported as a serious complication of intrahepatic shunt surgery and is a significant cause of mortality. Blood glucose should be monitored peri-operatively, and glucose should be supplemented when needed.

The mortality rate for shunt attenuation is variable (▶Tab. 9-6 for mortality rates in dogs). Studies of cats are smaller and fewer in number. The mortality rate for cats varies from 4.1 to 12.0% in the larger studies reporting suture ligation, ARC, and TFB for the treatment of predominantly extrahepatic CPSS.[23–26]

**Tab. 9-6** Reported peri-operative and postoperative mortality for surgical treatment of extrahepatic and intrahepatic congenital porto-systemic shunts (CPSS) in dogs. The data are taken from the largest and most recent studies. There is considerable variation in the data reported by the different studies.

| Technique | Mortality for extrahepatic CPSS closure | | Mortality for intrahepatic CPSS closure | |
|---|---|---|---|---|
| | Number of dogs in study | Percentage mortality | Number of dogs in study | Percentage mortality |
| Suture ligation | 49–66[27,28] | 2.0–28.8% | 17–55[28–31] | 5.9–22.6% |
| Ameroid constrictor | 23–206[14,15,32,33] | 2.6–7.3% | 9–11[30,34] | 0–9.1% |
| Thin film band | 23–95[15,32,33,35] | 0.0–11.8% | 11–31[35,36] | 3.2–27.3% |
| Intravascular coil | Only studies with <10 dogs | - | 25–95[17,36,37] | 0–7.4% |

#### 9.5.3.2.5 Prognosis and outcome

When successful, surgery results in an improvement in portal blood flow and liver volume, due to hepatic regeneration.[38,39] This results in an improvement in liver function and hence the resolution of clinical signs. A good clinical response should also be associated with significant improvements in hematological and biochemical parameters and dynamic bile acids concentrations. However, in some animals, there is a persistent mild increase in bile acids following complete attenuation, despite a good clinical outcome.[40] This could be due to persistent sub-clinical shunting or concurrent PPVH.

Significantly increased serum bile acids concentrations are not expected post-surgery and suggest significant **persistent shunting**. Animals can have persistent shunting due to incomplete closure of the CPSS or due to the development of MAS, which can cause ongoing or recurrent clinical signs. A study of the treatment of extrahepatic CPSS in dogs with placement of ARC found that 28/116 dogs (24.1%) had evidence of persistent shunting on scintigraphy at 4–14 weeks post-surgery.[14] Importantly, dogs without shunting on scintigraphy were 10.7 times more likely to have a good long-term outcome. This suggests that persistent shunting is an important factor, and the author believes that complete shunt closure should therefore be the aim of treatment whenever possible. Animals with clinical signs post-surgery should undergo further imaging to assess for persistent shunting. Animals with persistent flow through the CPSS are likely to benefit from repeat surgery to attempt further closure. Long-term medical management can be considered as an alternative, or for animals with MAS. Nevertheless, some animals can have a good clinical outcome despite significant persistent shunting.

Although several studies report the long-term outcome for animals with CPSS, there is considerable variation between how outcome was measured and reported, making a direct comparison of studies difficult. Studies rely on owner and veterinary assessment of clinical signs and quality of life, and the definition of an excellent or good outcome can be quite variable. Studies report a good to excellent outcome following surgery in 52.0–100% of dogs with extrahepatic shunts and 70.0–100% of dogs with intrahepatic shunts. The larger studies of cats with CPSS treated with suture ligation, AC, or TFB have reported an excellent or good outcome in 75.0–86.6%.[24–26]

### 9.5.3.3 Hepatic arteriovenous malformations

Hepatic arteriovenous malformations (HAVM) is a very rare congenital condition in dogs and cats and represents a communication between the high-pressure hepatic arterial system and the low-pressure portal system, resulting in portal hypertension due to hepatofugal flow in the portal vein. Typically, there are multiple vessels connecting a hepatic artery branch with the portal vein. MAS develops to compensate for portal hypertension.

Animals with HAVM normally show clinical signs when immature. Signs can be acute or chronic and include vomiting, diarrhea, lethargy, poor growth, ascites, neurologic signs of HE (although this may be less common than in animals with CPSS), or a combination thereof. A murmur may be present over the cranial abdomen (i.e., cranial abdominal bruit).

Routine blood tests show changes similar to those seen with a CPSS, with microcytic anemia, hypoalbuminemia, and increased liver enzyme activities. Plasma ammonia and dynamic bile acids concentrations are abnormal and consistent with hepatic dysfunction. HAVM are easily identified on ultrasonography with Doppler, but CTA is preferred to give detailed information on the precise location and nature of the abnormality. IOMP may also be used, particularly if surgical treatment is undertaken.

Treatments for HAVM include surgical removal of the affected liver lobe, ligation of the artery supplying the malformation, or embolization with either glue or an endovascular coil.[41–43] In dogs, glue embolization has been suggested to be safer, with a better long-term outcome than surgery.[41] Due to the nature of the condition and the presence of MAS, persistent shunting is likely, and some animals will benefit from ongoing medical management.

**KEY FACTS**

- Congenital portosystemic shunts (CPSS) are the most common form of hepatic vascular anomaly and are seen more frequently in dogs than in cats.
- Clinical signs of CPSS can be quite variable, but the most common signs are due to hepatic encephalopathy.
- While a CPSS may be suspected based on history, clinical signs, and characteristic changes on routine blood tests, liver function tests (dynamic bile acids), and diagnostic imaging are necessary to confirm the diagnosis.
- Medical management is recommended initially for animals with CPSS to treat signs of hepatic encephalopathy, and this consists of a combination of lactulose and low protein diet, with antimicrobials ideally reserved for animals that do not respond.
- Surgical attenuation to close the shunt and restore normal portal blood flow is the recommended treatment for dogs and cats with CPSS.
- Although most animals with CPSS are diagnosed when immature, shunts can be seen in mature animals, and deciding on the optimal treatment for these mature animals in the absence of clinical signs can be challenging.
- Surgical treatment results in a good response in most animals, leading to resolution of clinical signs. However, persistent shunting, either through the original shunt or via multiple acquired shunts, can result in ongoing or recurrent clinical signs.

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
svg.to/9842-09-05-03

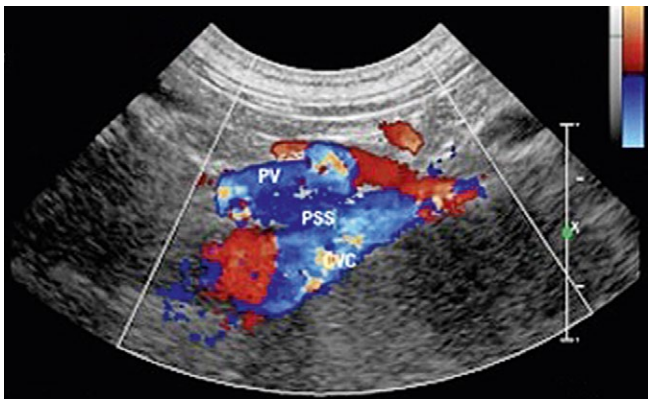



**Fig. 9-20** Doppler ultrasound image of an extrahepatic congenital portosystemic shunt in a dog

The shunt (**PSS**) can be seen connecting the portal vein (**PV**) with the caudal *vena cava* (**CVC**).

## 9.5.4 Metabolic diseases of the liver

Floris C Dröes and Jonathan A Lidbury

The liver plays a central role in the body's metabolism. Therefore, liver diseases can result in a wide array of metabolic consequences, including altered production, breakdown, or transport of proteins, lipids, carbohydrates, trace elements, or minerals. Metabolic liver diseases often result in multisystemic disease. Some metabolic diseases are acquired, whereas others are congenital and have a genetic etiology. This chapter focuses on liver diseases that occur due to altered metabolism (e.g., feline hepatic lipidosis), while the metabolic consequences of other liver diseases (e.g., chronic hepatitis) are discussed elsewhere.

### 9.5.4.1 Vacuolar hepatopathies

#### 9.5.4.1.1 Feline hepatic lipidosis

Feline hepatic lipidosis (FHL) is the most common hepatobiliary disease in cats in North America and Europe. In other countries, such as New Zealand, the UK, and Japan, this disease has been reported to be less common than cholangitis.[1] The reasons for these geographical differences remain unknown, although breed, dietary, and environmental variances have been suggested.

**Pathophysiology**

The exact pathophysiology of FHL remains unknown. Several pathways have been studied, elucidating parts of the pathophysiology (▶Fig. 9-21). A negative energy balance

due to a period of anorexia, typically ranging from 2–14 days in duration, is considered to initiate FHL.[2–5] Secondary hepatic lipidosis (HL), caused by an underlying disease (e.g., inflammatory bowel disease or diabetes mellitus), is the most common form, accounting for approximately 95% of cases.[2] However, primary FHL caused by decreased food availability, administration of non-palatable foods, or decreased food intake related to a stressful event has also been described.

Cats are strict carnivores whose lipid and protein metabolism depends on acquiring essential fatty acids (EFAs), amino acids, and vitamins directly from their food. Unlike other mammals, cats are unable to convert alpha-linoleic acid to eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA) and have a limited capacity for synthesizing long-chain polyunsaturated fatty acids, such as arachidonic acid.[6] Their protein metabolism has limited adaptability to conserve nitrogen, leading to the rapid development of essential amino acid deficiency and protein malnutrition after a period of anorexia.[2] Plasma concentrations of alanine, arginine, citrulline, taurine, and methionine become markedly reduced (by more than 50% of baseline) in cats with FHL.[2,5,7,8]

Decreased insulin concentration and sensitivity can be observed in cats with HL, especially when increased insulin resistance is associated with obesity.[5,9,10] Increased concen-

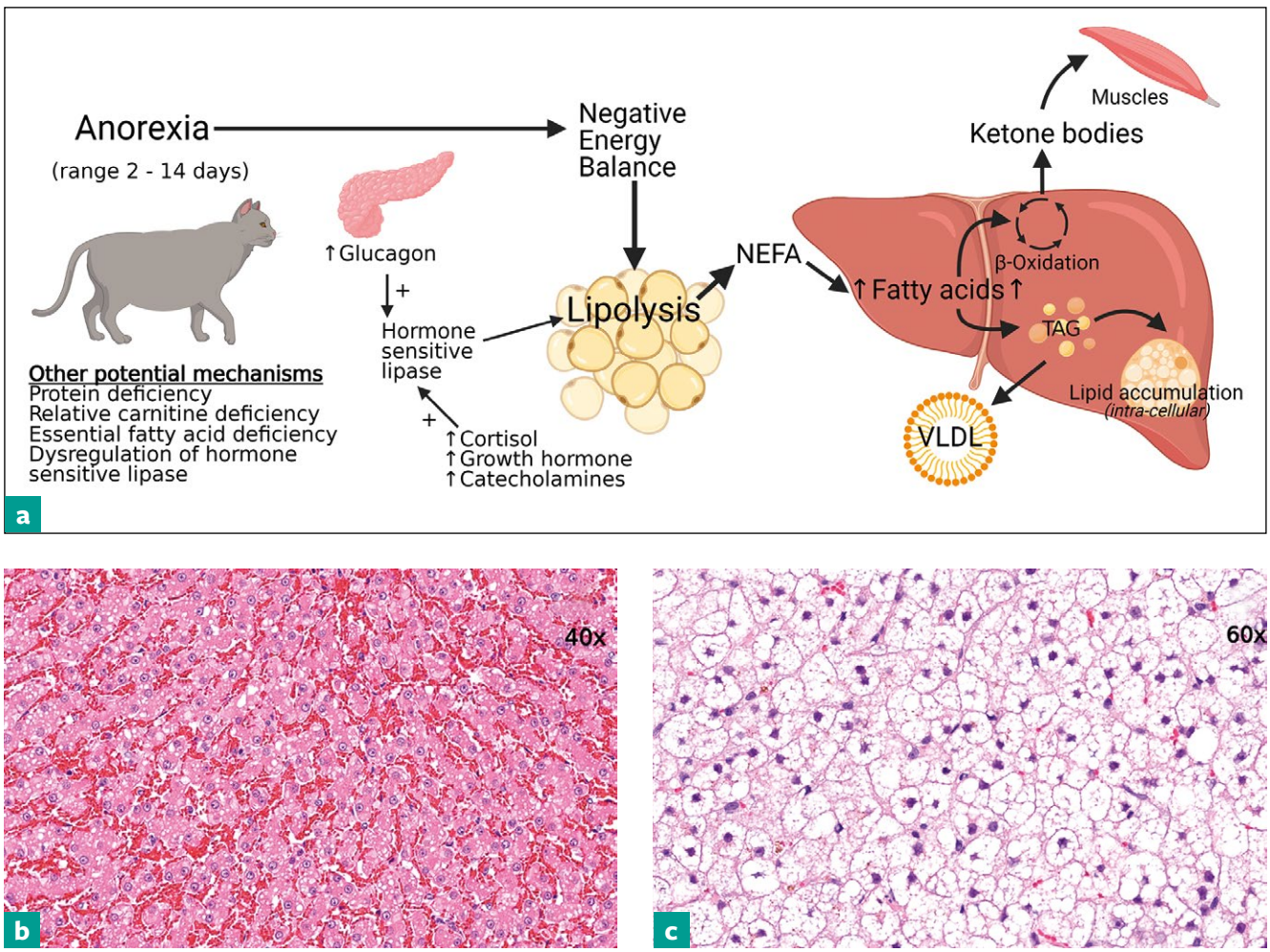



**Fig. 9-21** Feline hepatic lipidosis

A simplified schematic representation of the pathophysiology of feline hepatic lipidosis (**a**) and representative findings on hepatic histopathology (**b** and **c**).

Histologic preparation of a liver biopsy from a cat with mild to moderate feline hepatic lipidosis (HE staining, 40x, **b**) and severe feline hepatic lipidosis (HE staining, 60x, **c**), showing vesicular steatosis of hepatocytes.

**NEFA** = non-esterified fatty acids, **VLDL** = very low-density lipoproteins; **TAG** = triacylglceride

(Histopathology images courtesy of Dr. Randi Gold, Texas A&M Veterinary Medical Diagnostic Laboratory, College Station, Texas, USA; Panel created with Biorender.com.)

trations of glucostatic counter-regulatory hormones (i.e., glucagon, cortisol, growth hormone, and catecholamines) drive an increased activity of hormone-sensitive lipase, promoting lipolysis and mobilization of non-esterified fatty acids (NEFAs) from visceral adipose tissues.[2] The increase of NEFA's from peripheral adipose tissues reaches the liver, resulting in increased beta-oxidation of fatty acids, leading to increased ketogenesis and an increase of hepatic triglyceride excretion through very low-density lipoproteins (VLDLs).[2] However, this is not enough to remove the entire lipid load, and triglycerides accumulate in >80% of hepatocytes, increasing the hepatic weight by up to ~50%.[2] A recent study showed downregulation of sterol regulatory element-binding factor (SREBF-1), a liver enzyme, in cats with FHL. This finding does not support the role of *de novo* lipogenesis in hepatic accumulation of fatty acids.[11]

## Clinical presentation

FHL is mostly seen in middle-aged (median age, 7 years) overweight or obese cats without any breed or gender predilection.[2,3,5,12] Anorexia and weight loss are seen as hallmarks in the history of cats with HL. Other presenting complaints can be related to the underlying disease process and may include vomiting, nausea, constipation, diarrhea, or a poor hair coat.[3,5,12]

Icterus, dehydration, altered mentation, ventroflexion of the neck, and severe muscle weakness can also be seen.[2] Ptyalism can be observed due to nausea or, less commonly, as a manifestation of hepatic encephalopathy due to hyperammonemia.[3]

Often, cats with HL present with some degree of hypoperfusion related to fluid losses, secondary to vomiting, anorexia, or adipsia. Hypoperfusion in cats can be evidenced by tachycardia (heart rate >220 bpm) or inappropriate bradycardia (heart rate <140 bpm), pale mucous membranes, prolonged capillary refill time, hypothermia, and/or (mild) hypotension.[2]

## Diagnosis

Common findings on a serum or plasma biochemical profile include an increased serum total bilirubin concentration and increased serum activities of alkaline phosphatase and alanine aminotransferase, while γ-glutamyltransferase activity is not usually increased to the same magnitude.[2,3,12] If icterus/hyperbilirubinemia is present, serum bile acid concentrations are expected to be increased, and measurement is not warranted.[3] Hyperglycemia is often present due to increased insulin resistance and increased concentrations of glucostatic counter-regulatory hormones.[2] Mild hypoalbuminemia is frequently found in cats with HL due to decreased hepatic function and secondary to decreased protein intake from anorexia.[2,5,12] Blood urea nitrogen has been reported to be decreased in 51% of cats and is most likely caused by a deranged urea cycle.[2,5,12] Hypercholesterolemia and hypertriglyceridemia can be present, although normal serum cholesterol and triglyceride concentrations have also been reported.[3]

For a summary of the biochemical and hematological abnormalities most frequently observed in cats with FHL, ▶box "Most common abnormalities."

**The most common abnormalities observed on biochemical and hematological tests in FHL**

- Increased liver enzyme activities (i.e., ALP, ALT)
- Hyperbilirubinemia
- Hyperglycemia
- Mild hypoalbuminemia
- Elevated BUN (51% of cases)
- Hypercholesterolemia
- Hypertriglyceridemia
- Hypokalemia (30% of cases)
- Hypomagnesemia (28% of cases)
- Hypophosphatemia (17% of cases)
- Mild non-regenerative anemia
- Mild leukocytosis (mature neutrophilia)
- Heinz bodies
- Increased clotting times: PT and APTT (45–73% of cases)

ALP = alkaline phosphatase; ALT = alanine transaminase; BUN = urea nitrogen; PT = prothrombin time; APTT = activated partial thromboplastin time

The most commonly reported electrolyte abnormalities are hypokalemia (30% of FHL cases), hypomagnesemia (28%), and hypophosphatemia (17%).[2,5] Hypokalemia is a potential precipitating factor for hepatic encephalopathy and can cause muscle weakness, paralytic ileus, anorexia, and cardiac arrhythmias.[2,5,12] Hypophosphatemia can cause hemolysis, sometimes requiring a blood transfusion.[2] The complete blood count (CBC) is usually normal in cats with HL, although mild non-regenerative anemia and mild leukocytosis (mature neutrophilia) can be seen.[3,5,12] Heinz bodies can be observed on a blood smear.[2,3,13] Coagulation abnormalities (e.g., prolonged prothrombin time and activated partial thromboplastin time) have been described in 45–73% of cats with HL as liver function is decreased, and consumption of coagulation factors is increased by activation of hemostasis.[2,12] Most cats with HL do not spontaneously

bleed, but excess hemorrhage can be observed after invasive (e.g., collection of a liver biopsy) or even minimally-invasive procedures (e.g., esophageal tube placement). Thus, it is recommended to administer vitamin $K_1$ before such a procedure is performed.

Ultrasonographic examination of the abdomen is highly recommended in any anorectic cat suspected to have HL to look for findings consistent with this process and to screen for any concurrent diseases (e.g., pancreatitis, gastrointestinal disease, cholangitis, or renal abnormalities).[3]

**NOTE**
Hepatomegaly and a diffusely hyperechoic liver, in comparison to the falciform fat, can be found on ultrasonographic examination in cats with HL, but these changes can also be observed in obese or diabetic cats.[2,3,14]

Documentation of increased fat in hepatocytes is required for diagnosis of FHL. Cytologic evaluation of an ultrasound-guided fine-needle aspirate is the authors' initial method of choice.[6] On cytology (macro- or microvesicular), steatosis of over 80% of hepatocytes is considered a hallmark feature of hepatic steatosis.[2,12] Hepatic cytology has diagnostic limitations, and underlying inflammatory or neoplastic disease could be missed. Liver biopsy for histological evaluation is not initially recommended because this procedure requires general anesthesia in a potentially cardiovascularly, metabolically, or hemostatically unstable patient. Automated Tru-Cut biopsy needles are not recommended for use in cats as these have been associated with the development of vagotonic shock (bradycardia and cardiovascular collapse for up to 30 minutes).[2] If a cat fails to respond to treatment, or underlying inflammatory disease or hepatic neoplasia is suspected, then a hepatic biopsy for histopathologic assessment (▶ Fig. 9-21) can be performed after initial stabilization and treatment.

### Treatment

Treatment of suspected FHL usually consists of two phases:

**The first phase** involves fluid resuscitation (e.g., 5–10 ml/kg IV of a balanced isotonic crystalloid solution, often administered over 30 minutes) of hypovolemic cats while slowly rewarming them and starting the correction of dehydration with an isotonic crystalloid solution (e.g., 0.9% sodium chloride, lactated Ringer's solution, or Ringer's acetate solution).[2] Fluids containing glucose should be avoided to prevent the worsening of the patient's glucose intolerance and potentially concurrent hyperglycemia.[2] Correction of electrolyte abnormalities should start during this phase. Serum potassium and phosphate concentrations can be challenging to manage when hypomagnesemia is present. Therefore, supplementation of magnesium may be necessary.[2,3,12] Frequent reassessment of electrolyte osmolalities is recommended.

**The second phase** of treatment consists of providing nutrition once the patient is cardiovascularly stable and major electrolyte abnormalities have been addressed. The preferred route of providing nutritional support is enteral over parenteral alimentation to help maintain intestinal architecture and function.[2,12] To decrease the risk of developing food aversion and aspiration pneumonia and to ensure daily energy requirements are met, forced syringe feeding should not be performed. A nasoesophageal feeding tube is often initially used in these patients because it does not require general anesthesia or heavy sedation, and it is the least invasive option.[2] Later on, during hospitalization and for home management, an esophagostomy tube is considered most effective. Due to the larger bore size of an esophagostomy feeding tube, a greater variety of diets that are nutritionally balanced can be fed, and these tubes are less likely to clog. Percutaneous endoscopically-placed gastrotomy (PEG) tubes (▶ Chap. 3.2.2) have also been described in the literature for the management of FHL. They require specialized equipment and training for placement.

On the first day of feeding, a commercially available high-protein recovery diet should be fed. The patient's resting energy requirement (RER) is calculated, and one-quarter of this amount is initially provided.[2,12] If feeding is well tolerated, this amount is slowly increased to full RER over the next 2–3 days.[2] This method of slowly increasing calories should decrease the risk of refeeding syndrome.[2] Refeeding syndrome can be observed when a sudden insulin release leads to severe hypophosphatemia, hypokalemia, and hyperglycemia.[2] Vomiting, diarrhea, and shock can also be observed with this syndrome. The RER can be estimated by using a formula[2] (e.g., RER = 70* body weight [kg]$^{0.75}$). Use of an illness factor is not recommended because this can lead to overfeeding. It is recommended to divide the total daily volume of food into 6–8 portions. Alternatively, feeding as a constant rate infusion may help reduce nausea, gastric discomfort, and vomiting due to gastric distention.[2]

To decrease nausea and vomiting, maropitant (0.5–1 mg/kg SC q24h) or ondansetron (0.1–0.5 mg/kg IV q8–12h) can be administered by themselves or as a combination.[2,15] Adding metoclopramide (0.2 mg/kg IV q6h or preferably 1 mg/kg/day IV as a CRI) should be considered a last resort due to its questionable efficacy.[2,15] If cats frequently vomit, using omeprazole (1 mg/kg PO q12h) to prevent reflux esophagitis may also be beneficial, but antacids should be used sparingly.[2,15] $H_2$ receptor antagonists, such as famotidine or ranitidine, might not be as effective in increasing gastric pH, and cats have been known to develop tolerance from daily use.[2] The efficacy of appetite stimulants in cats with FHL is questionable and successful management requires placement of a feeding tube.[2]

Additionally, vitamin $K_1$ (0.5–1.5 mg/kg SC q12h for 3 doses) should be administered when hemostasis is clinically affected or prior to invasive or even minimally-invasive procedures, such as hepatic fine needle aspiration or esophagostomy tube placement.[2,15] Supplementation of L-carnitine (250–500 mg/cat/day PO) has been shown to increase beta-oxidation of free fatty acids and decrease triglyceride (TG) accumulation in the liver, which may benefit cats with HL.[2,15,16] Additionally, recommended nutritional supplements for the treatment of cats with FHL can be found in ▶Tab. 9-7.

It is essential that if FHL is determined to be secondary to an underlying disease (e.g., pancreatitis or inflammatory bowel disease), this disease must be diagnosed and appropriately managed.

A recent study on novel treatments for FHL identified two potential drugs: a diacylglycerol O-acyltransferase 1 inhibitor (DGAT1 inhibitor, T863) and an adenosine monophosphate kinase activator (AMP kinase activator, 5-Aminoimidazole-4-carboxamide ribonucleotide) that both helped to decrease hepatocyte triacylglycerol accumulation in feline liver organoids.[17] Further studies are needed to assess the clinical utility of these drugs.

## Prognosis

Appropriately treated cats with FHL and in the absence of a serious underlying disease, recovery rates of 80–85% have been reported.[2] Reported risk factors associated with a significantly increased mortality are older age, dullness, weakness, ptyalism, hypoproteinemia, hypoalbuminemia, increased serum creatine kinase activity, hypocholesterolemia, and hepatic failure.[13] During hospitalization, a decrease of serum β-hydroxybutyrate has been significantly associated with survival, while worsening hypoalbuminemia, hyperam-

**Tab. 9-7** Nutritional supplements that can be considered for treating cats with feline hepatic lipidosis*

| Nutritional supplement | Dosage | Mechanism |
|---|---|---|
| Vitamin $B_{12}$ (cyanocobalamin) | 250 µg SC every 1–2 weeks or 250 µg PO q24h | Chronically malnourished cats with primary intestinal disease may have impaired availability of cobalamin, which plays a vital role in nucleic acid synthesis and the citric acid cycle. |
| N-acetylcysteine (NAC) | Initial dose 140 mg/kg IV over 20–30 minutes, subsequently 70 mg/kg IV q8–12h; must be diluted | NAC serves as a source of cysteine, which is needed for hepatic production of glutathione, which is involved in conjugation and detoxification in the liver; can be used instead of SAMe in cats that cannot tolerate oral medications |
| S-adenosyl-methionine (SAMe) | 20 mg/kg q24h PO 1 hour before food** | SAMe increases hepatic glutathione concentrations (involved in conjugation and detoxification), the central antioxidant apparatus in the liver; replaces NAC once the cat can tolerate oral medications |
| Vitamin $K_1$ | 0.5–1.5 mg/kg SC q12h for 3 doses | Vitamin K is a cofactor for the activation of certain proteins and factors essential in hemostasis |
| L-carnitine | 250–500 mg/cat/day PO | L-carnitine has been shown to increase beta-oxidation and decrease triglyceride accumulation in the liver |
| Taurine | 250 mg q12h PO for the first 7–10 days | Taurine is conjugated to bile acids; deficiency increases lipolysis in peripheral tissues and secondary accumulation of non-esterified fatty acids in the liver |

* The impact of many of the nutritional supplements listed on clinical outcome are unproven
** Recommended dosage; however, studies evaluating specific dosages are lacking
**PO** = per os; **SC** = subcutaneous; **IV** = intravenous

monemia, hyperbilirubinemia, hypophosphatemia, electrolyte disturbances (e.g., hypokalemia, hyponatremia, hypochloremia), and cavitary effusions or hypotension were significantly associated with mortality.[13]

#### 9.5.4.1.2 Feline lipoprotein lipase deficiency

A hereditary hyperlipoproteinemia, resembling lipoprotein lipase (LPL) deficiency in humans, has been described in a family of domestic cats originating from New Zealand.[18]

##### Pathophysiology

LPL deficiency in these cats is caused by a nucleotide change, resulting in a substitution of arginine with glycine in exon 8 at residue 412.[19] How this amino acid change specifically decreases LPL activity is unknown. Homozygous cats have been shown to have hardly any LPL activity.[18,19] Normally, LPL hydrolyzes triglycerides (TG), primarily in chylomicrons and very low-density lipoproteins (VLDLs), and is principally expressed in adipose tissue, muscle, liver, adrenal glands, and the ovaries.[20]

##### Clinical presentation

Cats with LPL deficiency show reduced growth rates and decreased body fat mass.[19,21] They develop xanthomas (lipid accumulations under the skin) in the kidneys, heart, spleen, mesentery of the small intestine, peripheral spinal nerves (often noted in the sciatic nerve), and liver, leading to dermatosis, lipemia retinalis, nerve paralysis (e.g., in the sciatic nerve, leading to bear footed stance), and organ dysfunctions.[18,19,22,23] A sex predilection has not been described.

Heterozygous carriers of LPL deficiency appear clinically normal unless they are challenged with a high oral fat load. In humans, recurrent pancreatitis is often mentioned, as a consequence of LPL deficiency, but this has not been described in cats.[18,21]

##### Diagnosis

Fasted serum samples from LPL-deficient cats show hypercholesterolemia and hypertriglyceridemia, with the majority of TG being present as chylomicrons and VLDLs.[23] These cats show a profound increase in serum TG concentrations when fasting (peaking around 7 hours postprandially).[19,21,22]

On histopathology, the accumulation of lipid deposits in many organs and cells can be seen, including tissue macrophages. Hepatocytes show cell swelling and hydropic degeneration from vacuolar changes in the cytoplasm.[22,24]

##### Treatment and prognosis

Usually, these cats can be managed successfully with a fat-restricted diet.[21,25–27] Not much is known about the life expectancy of cats with LPL deficiency. However, these cats have been described to survive to adulthood, and they are able to reproduce.[25] As LPL appears to be crucial for the mobilization and uptake of energy in the form of fatty acids, a higher frequency of stillbirths has been observed in homozygotes, independent of the genotype of their kittens.[19] Additional hand feeding of these kittens might be needed if the queen is LPL deficient.[21]

#### 9.5.4.1.3 Canine hereditary hyperlipidemia

Hyperlipidemia in dogs is often found secondary to other conditions, such as endocrine disorders (i.e., hypothyroidism, diabetes mellitus, and hyperadrenocorticism), pancreatitis, cholestasis, protein-losing nephropathy, obesity, and iatrogenic with certain drugs (e.g., glucocorticoids, estrogens, phenobarbital, and potassium bromide).[28,29] Primary (hereditary) hyperlipidemia is less common in the general dog population; however, it has been described more frequently in certain breeds, such as miniature schnauzers, Shetland sheepdogs, Briards, certain types of terriers, Doberman pinchers, Rottweilers, rough-coated collies, Pyrenees mountain dogs, and beagles.[29,30]

##### Pathophysiology

The exact cause of primary (hereditary) hyperlipidemia remains unknown. A genetic basis of this disease is suspected because 50–60% of the miniature schnauzers in the USA appear to be affected.[30] While no mutations could be identified in the *apolipoprotein C2* gene in affected miniature schnauzers, a genome-wide scan utilizing single nucleotide polymorphism (SNPs) is currently underway and may provide new insights into the potential genetic basis of this disease.[31] Miniature schnauzers have been shown to have different lipoprotein profiles than dogs of other breeds. Furthermore, the lipoprotein profiles of miniature schnauzers with hypertriglyceridemia (HTG) appear to differ from those of miniature schnauzers without HTG.[32] However, the observed changes do not appear uniform in all affected miniature schnauzers. The main difference between hyperlipidemic and normolipidemic miniature schnauzers appears to be a significant increase in the triglyceride-rich lipoprotein fraction in affected miniature schnauzers.[32] The significance of these findings and how this relates to the development of HTG requires further investigation.

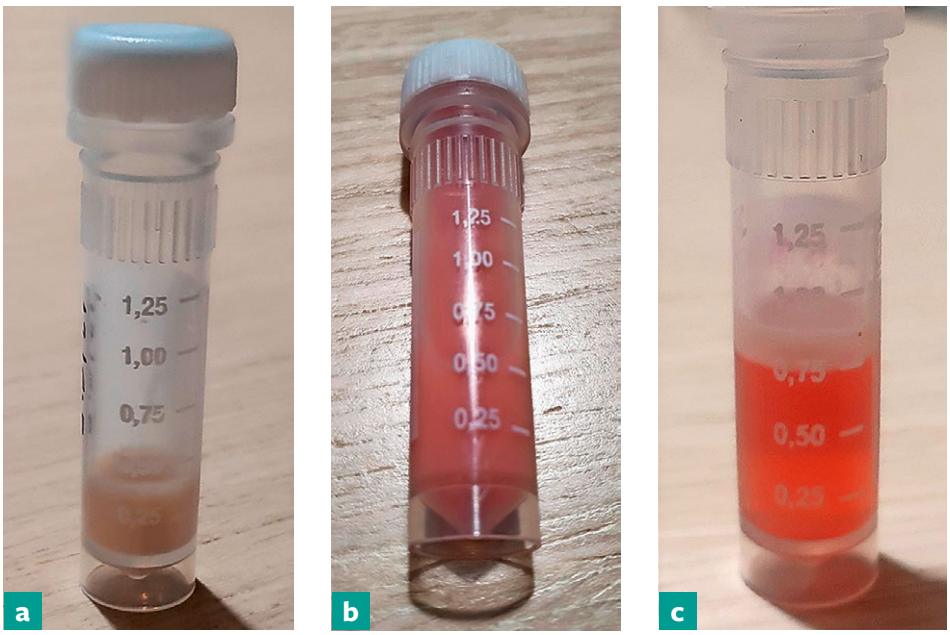



**Fig. 9-22** Lipemic canine serum

**a, b** Examples of lipemic canine serum samples associated with increased serum triglyceride concentrations.

**c** Example of a positive chylomicron test after resting of a lipemic serum for 12 hours at 4°C. Please note that samples in panels **b** and **c** are also moderately hemolyzed.

## Clinical presentation and diagnosis

Many dogs with primary HTG do not exhibit any abnormalities on physical examination and appear healthy.[29,33] Potential complications of HTG in dogs include pancreatitis, liver disease, such as vacuolar hepatopathy or gallbladder mucocele, insulin resistance, atherosclerosis, ocular disease (i.e., lipemia retinalis), cutaneous xanthomata, and seizures. These complications could lead to symptoms such as cranial abdominal pain, icterus, polyuria and polydipsia, decreased vision, seizures, or an abnormal neurological status.[28–30]

Postprandial hyperlipidemia is a normal finding and usually resolves within 7–12 hours after a meal. Therefore, to diagnose hyperlipidemia, a serum sample collected at least 12 hours after the last feeding is suggested.[29] Serum samples become visually abnormal (▶Fig. 9-22a and ▶Fig. 9-22b) at serum triglyceride concentrations of 200–300 mg/dL (2.3–3.4 mmol/L); however, measuring serum concentrations of triglycerides and cholesterol is recommended to get a baseline for monitoring the progress of management.

To exclude secondary causes and complications of hyperlipidemia, a CBC, biochemistry profile, and urinalysis should be performed. Additional tests to consider include serum total and free thyroxine concentrations, serum TSH concentration, serum pancreatic lipase immunoreactivity concentration (cPLI), serum bile acids concentrations, urine protein:creatinine (UPC) ratio, and if there are other signs of hyperadrenocorticism a low-dose dexamethasone suppression test.[29] Based on the secondary causes and potential complications of HTG, an abdominal ultrasound should also be considered. A UPC ratio is important as over 44% of miniature schnauzers and 60% of dogs of all breeds with (primary) HTG have been reported to be proteinuric (UPC ≥0.5) without azotemia or hypoalbuminemia, potentially indicating a protein-losing nephropathy due to the HTG.[34,35]

Recently, serum calprotectin was found to be increased in one-third of miniature schnauzers with HTG, which might suggest the presence of low-grade subclinical inflammation.[36] Malondialdehyde, a marker of oxidative stress, was also reported to be increased in affected dogs and could be considered an early marker for this condition in dogs.[33]

Further tests for canine HTG based on tests used in humans include the chylomicron test (▶Fig. 9-22c), lipoprotein electrophoresis, ultracentrifugation, measurement of specific apoproteins, and an indirect measurement of lipoprotein lipase activity (by heparin response test).[29] The chylomicron test is the easiest, most accessible test, where a serum sample is left at 4°C for 12 hours to assess if an additional layer of chylomicrons forms (positive test) on top of the serum or if the sample remains turbid (negative test).

### Treatment and prognosis

Treatment of primary hereditary HTG initially consists of dietary management with a lifelong low-fat diet containing <20–25 g of fat per 1,000 kcal of metabolizable energy.[29] After 4 weeks of initial treatment, a reassessment of serum triglyceride concentration is performed to determine if additional steps are required.[29] If serum triglycerides have normalized, periodic re-evaluation is strongly recommended for monitoring. If serum triglycerides have not decreased sufficiently, a stepwise additional treatment is suggested. Dietary fat can be further decreased with a homecooked diet. Alternatively, either bezafibrate, fenofibrate, or less preferably, gemfibrozil can be used (▶Tab. 9-8). Omega-3 fatty acids (200–300 mg/kg PO q24h with an upper limit of 4–5 g daily) can also be given. Statins (e.g., lovastatin) and vitamin $B_3$ (niacin; 50–200 mg/day PO) have been anecdotally used in dogs but are not recommended.[29]

If a gallbladder mucocele is present as a complication of HTG, a cholecystectomy is often indicated.[28,30] If additional complications of HTG are present, these need to be managed accordingly.

The prognosis is dependent on the complications that arise from persistent HTG, and whether or not the HTG can be successfully managed with diet and/or medication.

**Tab. 9-8** Drugs that have been described to lower serum triglyceride concentrations in dogs with hereditary hyperlipidemia.

| Medication | Dosage | Notes |
|---|---|---|
| Bezafibrate | 4–10 mg/kg PO q24h | Not available in the USA |
| Fenofibrate | 10 mg/kg PO q24h | Available in the USA as Tricor® (AbbVie Inc) and Triglid® (Skye Pharma Inc) |
| Gemfibrozil | 150–200 mg/kg PO q12h | Available in the USA as Lopid® (Pfizer) |

**PO** = per os

#### 9.5.4.1.4 Canine secondary hepatic lipidosis

Several causes for secondary hepatic lipidosis (HL) in dogs have been identified. These include diabetes mellitus, certain medications (e.g., excessive progestins, D-penicillamine), aflatoxin toxicosis, pancreatitis, idiopathic hyperlipidemia, and hypothyroidism.

### Pathophysiology

Secondary HL generally is a consequence of increased mobilization of fatty acids from fat stores, leading to increased presentation of triglycerides to the hepatocytes, overwhelming their processing capacity.

### Clinical presentation and diagnosis

In the history and upon physical examination of patients with secondary HL, signs of the underlying disease are most apparent. For example, polyuria and polydipsia in dogs with diabetes mellitus or abdominal pain, vomiting, and lethargy in dogs with pancreatitis. If HL is severe, hepatomegaly and increased abdominal size might be observed.

Serum hepatic enzyme activities (especially that of ALP) can be slightly or moderately increased. Despite increased hepatic enzyme activities in dogs with secondary HL, liver function is usually normal.

Abdominal ultrasonography might reveal an enlarged liver with generalized hyperechoic parenchyma and potential signs of the primary disorder (e.g., an adrenal nodule or bilateral adrenomegaly). Testing for underlying diseases in dogs with HL is highly recommended.

For a definitive diagnosis, cytology and/or histopathology showing fat accumulation in hepatocytes (either macro- or micro-vesicular) is required.

### Treatment and prognosis

Secondary HL usually resolves with the treatment of the primary disease process. However, it can take several weeks to months for hepatic tissue to normalize. Feeding a low-fat diet and administering the fibrate drugs described for primary hypertriglyceridemia can also be helpful.

In general, the prognosis for dogs with secondary HL is good if the primary disease is well-controlled.

#### 9.5.4.1.5 Glycogen storage diseases

Glycogen storage diseases are inborn errors of glycogen metabolism. In humans, eight different types of glycogen storage disease have been described in the literature. Five of these have also been described in dogs and Norwegian forest cats: type Ia (von Gierke disease), type II (Pompe disease), type IIIa (Cori disease), type IV (Andersen's disease), and type VII (Tarui disease).[37,38]

## Pathophysiology

All types of glycogen storage disease in dogs are a result of deficiencies of different enzymes related to gluconeogenesis or glycogenolysis and have been found to naturally occur in different dog breeds,[37,39–54] and Norwegian forest cats (▶Tab. 9-9).[38] Most of these defects are due to single recessive mutations.

In all types of glycogen storage disease, glucose production (either from glycogen, from amino acids, or from glycerol) is impaired. This leads to fasting hypoglycemia, as well as accumulation of glycogen and fat, particularly in the liver and kidneys, but sometimes also in muscles and other tissues.[45,55,56] Persistent fasting hypoglycemia is a hallmark of these diseases, and alterations in the glucoregulatory hormones occur (increased glucagon and decreased insulin). However, due to the defective enzyme, these regulatory actions are ineffective.[55]

In the long-term, glycogen storage diseases can lead to complications, such as metabolic acidosis (due to persistently elevated serum lactate concentrations), hepatic adenoma or hepatocellular carcinoma, chronic kidney disease, gout, osteoporosis, or pulmonary hypertension.[55]

## Clinical presentation

Glycogen storage diseases is a genetic disease. Therefore, puppies show severe lethargy and hypoglycemic seizures early after birth, and without intervention, often die within an hour of birth. If the puppies survive the initial hour and are nourished regularly, poor body condition, abdominal distension (caused by hepato- and/or nephromegaly), low activity levels, decreased mental alertness, delayed development of neurological reflexes, and failure to thrive can be observed.[55] Fetal mortality (e.g., stillbirths, fetal resorption, and mummification) and increased complications at birth and during early life are observed in up to 50% of the litters from heterozygote parents.[40,55]

Certain breeds are predisposed to glycogen storage diseases, and in the USA and Europe, there are specific research colonies of dogs and cats that are being used to study these diseases in humans. Heterozygote dogs usually have a decreased activity of the affected enzyme, and slightly elevated blood lactate levels compared with healthy dogs after a 12-hour fast, but without clinical signs or hypoglycemia.[55]

**Tab. 9-9** Description of the different types of glycogen storage diseases in dogs and cats

| Glycogen storage disease type | Enzyme defect | Breed |
|---|---|---|
| Ia | Glucose-6-phosphatase | Maltese terrier |
| II | Acid alpha-glucosidase | Lapland dog |
| IIIa | Amylo-1,6-glucosidase (glycogen debranching) | Curly-coated retriever |
| IV | 1,4-α-glucan 6-glucanotransferase (glycogen branching) | Norwegian forest cat |
| VII | Phosphofructokinase | English springer spaniel |

## Diagnosis

Biochemical analysis shows fasting hypoglycemia, persistently increased concentrations of lactate, uric acid, cholesterol, and triglycerides.[55]

Liver and kidney biopsies reveal increased storage of glycogen and triglycerides upon histopathology. Differential diagnoses of glycogen accumulation in hepatocytes are glycogen loading in neonatal animals, neonatal hyperadrenocorticism, and corticosteroid-induced hepatopathy. Decreased activity levels of the affected enzymes can be detected in liver, muscle, or kidney biopsies. However, these tests are not readily available and are often only used in a research setting.

Genetic tests have been described for some of the glycogen storage disease types, and these can be used to screen for carriers before breeding.

## Treatment

Traditionally, puppies with glycogen storage disease are managed with frequent feedings of puppy food with additional carbohydrates (e.g., glucose polymers, uncooked corn starch, or dextrose).[55] In adult dogs, frequent feedings (q2–4h) with additional uncooked corn starch can help manage hypoglycemia.[55]

Different studies have been performed using adeno-associated virus vectors for gene therapy early in life.[42,56,57] Depending on the time of first administration, these treatments appear to require re-administration of the viral vector.[57] These vectors have been reported to correct the glycogen storage disease phenotype and provide glycemic control to where dogs are able to maintain normoglycemia for up to 8 hours without additional feeding.[42,56]

Rapamycin has also been described as effectively reducing glycogen storage in muscle cells in glycogen storage disease IIIa.[53,54] Side effects of this treatment are hyperlipidemia and thrombocytopenia. Bezafibrate, a pan-peroxisomal proliferator-activated receptor agonist, has been shown to decrease liver triglyceride and glycogen concentrations and partially reverse autophagy in glycogen storage disease Ia.[58] More research is warranted for the clinical applicability of these drugs in dogs and cats with glycogen storage diseases.

### Prognosis

The initial prognosis for patients with glycogen storage disease is very poor: without intensive treatment and care early in life, puppies die soon after birth. Dogs with glycogen storage disease and good glycemic management have been known to reach adulthood, and even long-term survival has been described.[57]

## 9.5.4.1.6 Steroid hepatopathy

Steroid hepatopathy (aka. vacuolar hepatopathy or glycogen type vacuolar hepatopathy) in dogs has been described due to glucocorticoid excess that can be endogenous (i.e., hyperadrenocorticism of pituitary or adrenal origin) or exogenous (due to injectable or oral medications containing glucocorticoids, but also topical preparations).[59,60] Glycogen-type vacuolar changes can be appreciated upon cytology and/or histopathology. These changes are also found in dogs with hepatic nodular hyperplasia, hepatic adenomas, hepatic carcinomas, gallbladder mucoceles, and chronic hepatitis.

Cats are relatively resistant to the hepatic effects of glucocorticoid excess and less commonly develop steroid hepatopathy.

### Pathophysiology and clinical presentation

Glucocorticoids induce ALP and GGT synthesis from sinusoidal and canalicular membranes, which increases glycogen accumulation within hepatocytes, leading to vacuolar degeneration.[59,60] Sex steroid overproduction has also been described to cause steroid hepatopathy.[59]

On the history and physical examination of patients with steroid hepatopathy, signs of the underlying disease are usually apparent. For example, polyuria and polydipsia, abdominal distension, or bilateral symmetrical truncal alopecia in dogs with hyperadrenocorticism. If steroid hepatopathy is severe, hepatomegaly and increased abdominal size might be observed. Breed, sex, and age predilections are related to the primary disease.

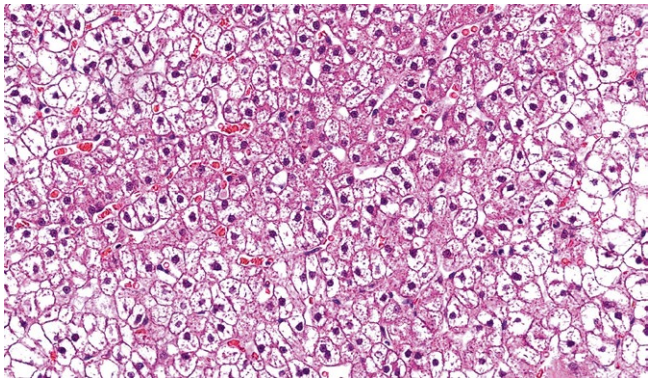


**Fig. 9-23** Steroid vacuolar hepatopathy

This histologic preparation shows severe glycogen storage in hepatocytes due to iatrogenic steroid excess. (HE staining, 40x)

(Courtesy of Dr. Randi Gold, Texas A&M University Veterinary Medical Diagnostic Laboratory, College Station, Texas, USA.)

### Diagnosis

A history of exogenous steroid administration or diagnosis of hyperadrenocorticism in a dog with glycogen accumulation in hepatocytes on cytology or histopathology is diagnostic (▶Fig. 9-23). However, a cytological diagnosis of hepatic glycogen accumulation does not rule out the presence of more serious underlying liver disease, such as chronic hepatitis. Serum hepatic enzyme activities (especially that of ALP, while ALT activity is often normal or only mildly increased) can be increased, but liver function is usually normal.[60]

Additional endocrine function tests may be advisable to exclude endogenous steroid excess. For example, a low-dose dexamethasone suppression test to screen for canine hyperadrenocorticism (sensitivity of 92–95%) or an ACTH stimulation test maybe be warranted.[61,62]

Abdominal ultrasonography might reveal a generalized hyperechoic hepatic parenchyma and potentially signs of the primary disorder (e.g., an adrenal nodule or bilaterally increased adrenal size).

### Treatment and prognosis

Glucocorticoid-induced changes in the liver generally resolve 1–3 months after glucocorticoid concentrations have normalized (either by discontinuation of exogenous glucocorticoids, by successful therapy of hyperadrenocorticism, or by treatment of a sex steroid hormone imbalance).[63] Dis-

continuation of long-term exogenous glucocorticoids should be performed gradually to prevent the development of an Addisonian crisis.[63]

In general, the prognosis for dogs with steroid hepatopathy is good if the primary disease can be well controlled.

### 9.5.4.2 Copper and iron hepatopathies

#### 9.5.4.2.1 Copper-associated hepatopathy in dogs

Copper is required for many vital functions in the body (e.g., energy production, iron metabolism, connective tissue synthesis, prevention of oxidative damage, and immune system function).[64] It is primarily absorbed in the small intestine and transported via the portal blood to the liver, where it is protein bound to copper scavengers (e.g., metallothionein and glutathione) to prevent oxidative damage before being transported throughout the body to exert its remaining functions.[64] However, when presented to the liver in excess or when it overwhelms the capacity of its transporters, it can accumulate to toxic amounts, causing oxidative injury, inflammation, and cell death, leading to copper-associated hepatopathy (CAH). Excessive hepatic copper accumulation has been reported to be the cause of primary hepatitis in one-third of dogs.[64,65]

##### Pathophysiology

The exact pathophysiology for CAH in dogs has yet to be fully elucidated. Suggested causes are impaired hepatic biliary copper excretion, excessive dietary copper uptake, or a combination of these. [64,66,67] Altered copper excretion can be due to primary disorders of copper metabolism or secondary to another hepatic disease. Cholestasis can also cause copper accumulation in some species but is not thought to be a common cause in dogs. [68,69]

Primary disorders of copper metabolism leading to CAH are often familial. In Bedlington terriers, an autosomal recessive genetic defect in exon 2 of the *COMMD1* gene and a defect in the *ABCA12* gene play a role.[64,70–73] These genes affect a group of intra-hepatocellular copper transporters (ATPases) facilitating biliary copper excretion. In humans, mutations in the *ATP7B* transporter cause hepatic copper accumulation (i.e., Wilson's disease).[64,73] In Labrador retrievers and Doberman pinschers, an autosomal semi-dominant mutation in the *ATP7B* transporter appears involved in excessive hepatic copper accumulation in affected or predisposed individuals, while in Labradors a (X-linked) mutation affecting the *ATP7A* transporter might be protective by decreasing hepatic copper accumulation.[73–75] The *COMMD1* gene, however, does not appear to play a major role in the etiology of CAH in these two breeds.[76]

Although these familial (genetic) factors have been described for CAH in dogs, and others are suspected, they do not fully explain the etiopathogenesis of this disease. For example, in Labrador retrievers, only 12.5% of the genetic variability in copper accumulation has been attributed to these known genotypes, and the prevalence of the *ATP7B* mutation is only 2–3% in the general Labrador population.[64,73,77] Therefore, it is likely that CAH is a multifactorial disease in most dogs.

Excessive dietary copper intake is another cause suspected to contribute to CAH. Since the late 1990s, there has been an increase in CAH observed in the US, as well as an increase in median hepatic copper concentrations in both healthy dogs and dogs with CAH.[78,79] These increases have been proposed to be related to a change in the type of copper used in commercial dog food premixes to more bioavailable forms (such as copper sulfate and copper chelate), as well as an excessively high minimum requirement and lack of an upper limit for copper in commercial dogs foods as mandated by the Association of American Food Control Officials (AAFCO).[78,79]

Different causes leading to CAH can coexist, and in some patients, a combination of these might contribute to the disease. Regardless of the exact cause, the consequences of increased hepatic copper concentrations are increased oxidative stress, which compromises glutathione availability, damaging nucleic acids, proteins, and lipids, and leading to hepatocyte necrosis, apoptosis, and inflammation.[64,66,79,80]

##### Clinical presentation

Dogs of any breed can develop CAH, although there are certain breeds that appear over-represented (i.e., Bedlington terriers, Labrador retrievers, Doberman pinschers, West Highland white terriers, Dalmatians, skye terriers, Anatolian shepherds, Pembroke Welsh corgis, Cardigan Welsh corgis, and Clumber spaniels).[64,66,69,79,81–97] However, dogs of other breeds and mixed breed dogs can also be affected.

The age at presentation varies among the different breeds. In Labrador retrievers, the age ranges from 2 to 12 years old, while in other dogs, a median age of six years is often reported.[64,66,87] In Labrador retrievers and Dobermans pinschers, females appear to be overrepresented, while in other dog breeds, both genders are equally represented. [64,66,87]

Before clinical signs become apparent, there is often a subclinical phase that varies in duration.[98] For example, in Bedlington terriers, copper accumulation starts as early as 6 months of age, while hepatocellular damage does not

become apparent until 12–16 months, and liver enzyme activities in serum do not increase until 18–24 months.[64,66,99]

Clinical signs often only become apparent when a large part of liver parenchyma has been affected. [100] Initial clinical signs are often nonspecific and include anorexia, lethargy, nausea, vomiting, and weight loss.[64,87,100] As the disease progresses, signs of hepatic failure (e.g., ascites, hepatic encephalopathy, polyuria/polydipsia, and icterus) may be observed.[64,66,87]

## Diagnosis

The best way currently to diagnose CAH in dogs is through a combination of histopathological examination of multiple liver biopsies from at least three different lobes and liver tissue copper quantification of a single liver biopsy.[64,66] As multiple studies have shown that copper distribution throughout the liver can be heterogeneous (▶Fig. 9-24), cytology of hepatocytes or other methods are not recommended to diagnose CAH and determine the amount of hepatic copper.[66,101]

When hepatic histopathology is performed, special stains for copper (i.e., rhodanine or rubeanic acid) should be routinely performed as part of a standard liver panel (▶Fig. 9-25). These special copper stains, together with a semiquantitative grading system, help subjectively quantify and localize copper in the liver.[111] In canine patients with primary CAH, copper usually starts to accumulate in the centrilobular region of the hepatic lobule (zone 3).[64,66,87,102] As copper accumulation becomes more severe, mid-zonal hepatocytes might also show increased copper staining, including copper-loaded hepatic macrophages (i.e., Kupffer cells).[64,66,87,102]

Besides the localization of hepatic copper accumulation, the type and extent of the inflammatory infiltrate also provide further insight. Hepatocytes that have accumulated copper often attract a mononuclear or mixed inflammatory infiltrate.[64,66,87,102] Lymphocytic infiltration in the liver with high levels of hepatic copper, on other hand, might indicate an underlying cause driving the copper accumulation.[66,102] Higher hepatic tissue copper concentrations have been shown to be associated with the severity of necrosis and inflammation.[69]

Hepatic tissue copper can be best quantified by true quantitative methods, such as flame atomic absorption spectroscopy (FAAS) or inductively coupled plasma mass spectrometry (ICP-MS). Qualitative methods based on scoring of special copper stains only appear to correlate to truly quantitative methods in one-third of dogs. To accurately quantify hepatic copper concentration, 20–40 mg (fresh, formalin-fixed, or dried) of liver tissue is needed.[66] If too little tissue is submitted, the amount of copper might be underestimated. Hepatic copper >400 µg/g dry weight is considered increased, and chelation therapy is recommended when concentrations are >1000 µg/g or when they are >600 µg/g with consistent copper staining.[64,66]

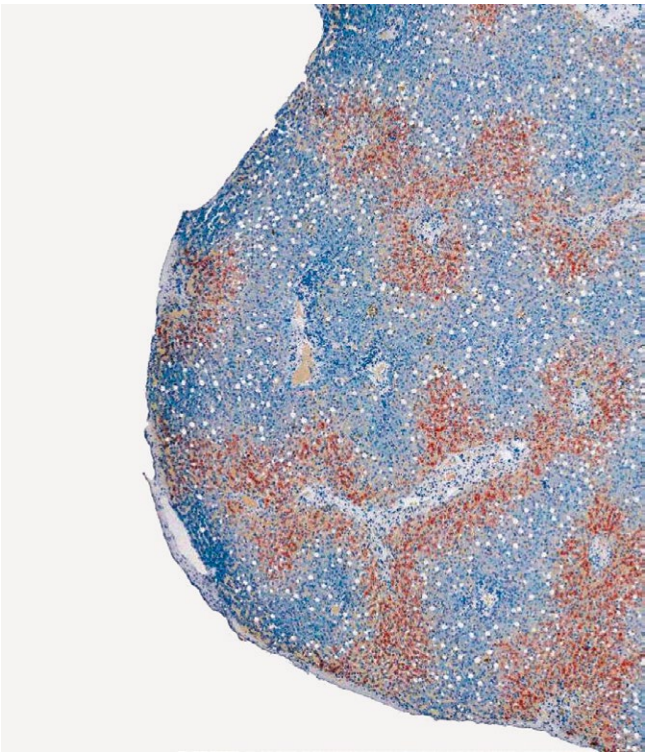


**Fig. 9-24** Copper-associated hepatopathy
This histological preparation shows the heterogeneity of hepatic copper distribution in a single liver biopsy of a dog with copper-associated hepatopathy (CAH). (Rhodanine staining, 5x; Courtesy of Prof. Dr. John Cullen, Texas A&M University, Gastrointestinal Laboratory, College Station, Texas, USA.)

A novel method of hepatic copper quantification is through digital image analysis of microscopic scanned rhodanine-stained liver sections.[103] This method allows more accurate quantification than qualitative histological copper assessment with less bias, while it allows simultaneous assessment of the zonal distribution of histological lesions and copper.[103] A major benefit of this technique is that it reduces the effect of variation in copper distribution (e.g., through parenchymal loss, extensive fibrosis, or regenerative nodules), which erroneously provides lower hepatic copper concentrations if quantified by other (quantitative) methods.[103]

Commonly used biochemical indicators for hepatocellular injury (e.g., increased serum ALT and ALP activities) might not be useful in diagnosing CAH, as they are nonspecific to CAH and take time for changes to be observed.[64,100] In the subclinical phase of hepatic copper accumulation, extensive hepatocellular injury is usually not present, and thus, serum ALT and ALP activities might be within normal limits.[64,87,100]

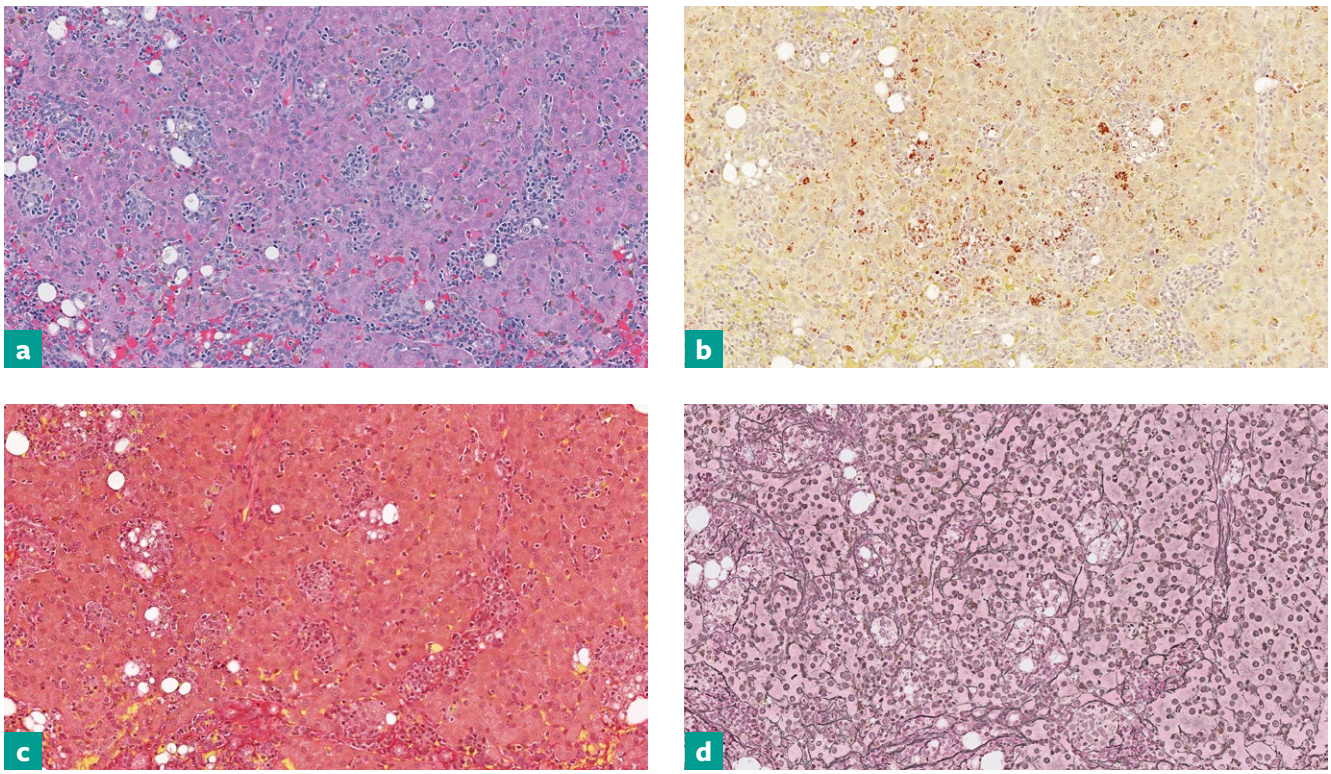



**Fig. 9-25** Histopathological liver staining panel of a dog with copper-associated hepatopathy (CAH)

**a** This histological preparation shows a mixed inflammatory infiltrate (i.e., moderate to large amounts of macrophages, neutrophils, and lymphocytes) in the portal region with areas of collapse. (HE staining, 40x).

**b** This histological preparation shows moderate to large amounts of intracytoplasmic copper granules. (Rhodanine staining, 40x).

**c** This histological preparation shows moderate portal-to-portal fibrosis. (Picrosirius red staining, 40x).

**d** This histological preparation shows areas of parenchymal collapse. (Reticulin staining, 40x).

(Courtesy of Dr. João Cavasin, Texas A&M University, Gastrointestinal Laboratory, College Station, Texas, USA.)

As the disease advances, increases in serum ALT and ALP activities can be observed, as well as decreases in serum albumin concentration, although it might still be within the reference interval.[100] Other altered laboratory measurements in advanced CAH can include increases in serum bile acids, ammonia, bilirubin, prothrombin time, and activated partial thromboplastin time, and decreases in fibrinogen and packed cell volume.[87] In dogs with CAH, transient acquired Fanconi syndrome has also been described.[41,42] However, none of these tests are specific for diagnosing CAH in dogs.

Non-invasive biomarkers for hepatic copper status in either blood or urine have been studied in dogs. For example, erythrocyte copper chaperone has been studied in a preliminary study on Labrador retrievers with CAH and appeared promising for future clinical use.[64,106] Serum hepatic microRNA-122 was shown to be significantly increased in Labrador retrievers with CAH, however, it is not specific for copper-associated disease.[107] Urinary copper/zinc ratios have been associated with hepatic copper concentrations in Labrador retrievers, but significant overlap between healthy dogs and dogs with CAH limits its diagnostic use.[108]

Genetic tests for the known mutations (i.e., of *COMMD1*, *ATP7B*, *ATP7A*, *ABCA12*) associated with increased incidence of CAH in dogs are widely available. These can help veterinarians identify dogs at risk early and might allow recommendations to owners on early dietary management to prevent excessive copper accumulation. However, the clinical utility of these tests has not been fully described.

### Treatment

Treatment of excessive hepatic copper consists of lifelong dietary restriction of copper, copper chelator treatment (e.g., with D-penicillamine), and supportive antioxidant treatment.[64,66,109–111] Treatment outcome is considered best early on in the disease when hepatocellular damage is still limited.[64,66,82] Dogs without clinical signs that have moderately elevated hepatic copper levels (i.e., 400–600 µg/g dry weight)

should be fed a low-copper diet and monitored as diet might be sufficient to restore normal copper levels.[111] Dogs with a markedly increased hepatic copper (>600 µg/g dry weight) should receive a copper-restricted diet (<0.12 mg/100 kcal) as well as chelation therapy.[64,66] The majority of copper-restricted diets available are also protein-restricted, which makes protein supplementation (0.5–1.5 g/kg body weight) recommended in these patients (e.g., dairy protein).[66] Other sources of copper intake should also be considered and controlled, including copper ingestion through water (e.g., by use of bottled water or running tap water when copper pipes are present).[66]

D-penicillamine (DPA) is the copper chelator best described for CAH treatment in dogs and the first choice (▶Tab. 9-10).[64,66,112] Copper binds to DPA and is excreted through the urine.[64,122] In addition, DPA also increases an intracellular copper detoxifier, metallothionein, in both hepatocytes and enterocytes and also has mild anti-inflammatory and anti-fibrotic properties.[64,66] Gastrointestinal signs are the most common adverse effects and can usually be mitigated by an initial dose reduction or co-administration of antiemetics (▶Tab. 9-10).[66,112,113] Co-administration of DPA with zinc is contraindicated as it decreases the effectiveness of the former.[66,112,113]

Current ACVIM consensus guidelines recommend chelation with DPA for 6 months if the initial hepatic copper level was ≤1,500 µg/g dry weight, for 9 months if hepatic copper was 2,000–3,000 µg/g dry weight, or even longer if hepatic copper was higher.[66,112] At this time, normalization of serum ALT activity is used as a surrogate marker to determine the effect of treatment. The sensitivity of serum ALT activity, however, is too low to correlate with residual copper accumulation and hepatic damage, and thus continuing treatment for 1 month after normalization of serum ALT activity is recommended.[66,100] As gold-standard, repeated liver biopsies are recommended to determine residual copper accumulation, amount of inflammation and tissue changes, and any other concurrent hepatopathies or causes that might become apparent throughout treatment. Life-long chelation treatment with DPA is not recommended for most dogs as this can lead to copper and zinc deficiency.[112] However, in some Bedlington terriers with CAH, normalization does not occur despite DPA treatment, and thus, life-long chelation treatment might be necessary.[114] In other dogs, repeated pulse therapy with DPA might be needed.

An alternative to chelation with DPA is oral zinc treatment. Zinc mostly reduces enteric copper uptake and therefore lowers hepatic copper concentrations slowly and thus is not recommended for acute treatment of CAH.[64,66] In the long-term management of CAH, however, zinc could be considered, although it is recommended to measure serum zinc concentrations regularly to prevent zinc toxicosis.[64,66] The most frequently observed adverse effects of zinc administration are gastrointestinal intolerance, which improves when the dose is reduced (▶Tab. 9-10).[64,66]

Other chelators, such as tetrathiomolybdate or trientine, have only been used to treat relatively small numbers of dogs with CAH.[115,116] Therefore, they cannot be recommended for the first-line treatment of CAH at this time.

Besides chelation and dietary copper intake management, antioxidant therapy with S-adenosylmethionine (20 mg/kg PO q24h on an empty stomach) and vitamin E (10 IU/kg PO q24h) are recommended to support the liver as the release of hepatic copper causes oxidative tissue injury.[66] Pyridoxine (vitamin $B_6$) deficiency has been reported as an adverse event of DPA treatment in humans, and therefore supplementation with vitamin $B_6$ (10–25 mg/day PO q24h) should be considered with prolonged DPA treatment of dogs with CAH.[66] Angiotensin receptor blockers (e.g., telmisartan) have been described to attenuate liver fibrosis in rodent models of chronic liver disease. However, recommending their usage in dogs with chronic liver disease (e.g., CAH) requires further study.

**Tab. 9-10** Therapy for copper associated hepatopathy (CAH) in dogs[64,66,112,113]

| Drug | Dosage | Adverse events |
|---|---|---|
| D-penicillamine | (initial dose) 10–15 mg/kg body weight PO q12h, ideally 30 min before or 2 hours after a meal<br><br>**Co-administration with zinc is contraindicated.** | • mostly gastrointestinal (vomiting, nausea, anorexia) signs, dermatological reactions, occasional glomerular nephropathy, increased serum ALP activity due to glycogen vacuolar hepatopathy<br>• rarely immune-mediated reactions, bone marrow dyscrasia, teratogenic reactions, copper or zinc deficiency, pyridoxine (vitamin $B_6$) deficiency |
| Zinc (gluconate/acetate) | Elemental zinc: 8–10 mg/kg/day PO | • gastrointestinal signs (vomiting, nausea, anorexia), slow chelation of hepatic copper, rarely hemolytic anemia<br>• should not be combined with D-penicillamine |

If, at initial or follow-up histological evaluation, lymphocytic inflammation becomes apparent, additional immunomodulation as recommended for the treatment of immune-mediated hepatitis in dogs (▶Tab. 9-12) should be considered.[66]

### Prognosis

Evidence about the long-term prognosis of CAH is limited. However, the prognosis appears best when the disease is diagnosed and treatment initiated early. Poor prognosis has been reported in patients that develop hyperbilirubinemia, coagulopathies, hypoalbuminemia, and/or hepatic synthetic failure.[117]

#### 9.5.4.2.2 Copper-associated hepatopathy in cats

There are few published studies on copper-associated hepatopathy (CAH) in cats. A few case reports describe primary CAH in different cat breeds; however, all cats were below 2 years of age at presentation.[118] Recently, some cats with primary CAH have been reported with a single-nucleotide variation of the *ATP7B* gene, the gene responsible for Wilson's disease in humans.[119] Cats also develop mild copper accumulation secondary to (experimentally induced) extrahepatic biliary obstruction (▶Chap. 9.6.1) and cholangitis (▶Chap. 9.6.3.2).[118–120]

Clinical signs in cats with CAH are nonspecific and include vomiting, anorexia, lethargy, and weight loss. On histopathology, cats do not appear to display sinusoidal copper accumulation but show a primarily centrilobular pattern.[118,120] In cats, the histological diagnosis and severity or localization of copper accumulation do not appear to be associated with evidence of histologic inflammation and copper-associated hepatocellular damage.[120] However, hepatic copper concentrations >700 µg/g of dry weight have been suggested to be consistent with primary CAH in cats.[120]

Treatment of feline CAH with D-penicillamine has been suggested and successfully attempted in a few cases, but adverse effects are common. Further studies are warranted to evaluate the efficacy and safety of D-penicillamine in this species.

#### 9.5.4.2.3 Hemochromatosis – Iron hepatopathy

Iron is an essential element used in every cell of the body as a component of hemoglobin and myoglobin and a cofactor for cytochrome enzymes. The amount of iron in the body is regulated by its absorption in the upper small intestines.[121] It is stored in the liver bound to hemosiderin and ferritin. When excessive amounts are stored in the liver, it leads to the accumulation of hemosiderin with or without signs of tissue damage (known as hemochromatosis or hemosiderosis, respectively). In humans, increased hepatic iron concentrations have been described to worsen liver damage caused by other insults. It has not been documented that a similar phenomenon occurs in dogs or cats.

### Pathophysiology

In dogs, primary hemochromatosis has not yet been described, but in humans primary hemochromatosis can occur due to a genetic defect. Secondary acquired hemochromatosis has been reported in a case of a dog with pure red cell aplasia that was treated with multiple blood transfusions over a 3-year-period, in a basenji dog with pyruvate kinase deficiency, in dogs with congenital portosystemic vascular anomalies, and also in dogs secondary to iron administration.[122–124] The liver has a large capacity for storing iron, but when this capacity is overwhelmed, tissue damage ensues, potentially resulting in fibrosis and cirrhosis as the disease progresses. The exact mechanism of tissue damage in hemochromatosis has not been identified in dogs; however, the generation of reactive oxygen species is likely.

### Clinical presentation and diagnosis

Clinical signs in dogs with hemochromatosis are usually nonspecific or related to the primary disease. Signs of advanced liver disease, such as anorexia, lethargy, nausea, vomiting, and weight loss, can be observed. Breed and sex predilections are related to the primary disease process.

Hemochromatosis can be diagnosed by a combination of histology and hepatic iron quantification. Histologically, iron is present in Kupffer cells and macrophages, but not in hepatocytes and can be visualized by Perl's Prussian Blue staining (▶Fig. 9-26).[123] Iron quantification can be performed on fresh or deparaffinized-archived tissue samples.[125] Elevated hepatic iron concentrations in dogs with necroinflammatory liver diseases have been described.[126] The clinical relevance of this finding requires further investigation.

Dual-energy CT has been described as a non-invasive modality to quantify hepatic iron in dogs.[127] This method requires local calibration as acquired Hounsfield units are not universally applicable. Less invasive methods of iron quantification, such as measurement of total iron binding capacity and percent saturation, might be useable for certain periods and cases of chronic hepatopathy.[128] Serum iron might be less useful as a marker, as it only represents <0.1% of the whole-body iron.[129]

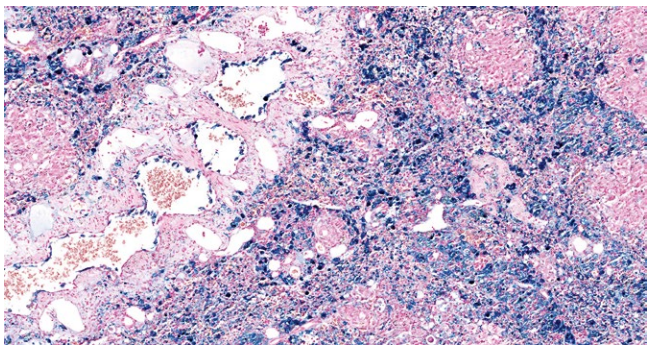


**Fig. 9-26** Iron accumulation in the liver of a dog

(Perl's Prussian Blue staining, 20x; Courtesy of Dr. Randi Gold, Texas A&M University Veterinary Medical Diagnostic Laboratory, College Station, Texas, USA.)

### Treatment and prognosis

Chelation should be considered for dogs with high (>1,200 ppm) iron concentrations and histologic evidence of hepatocellular injury. Deferoxamine is the treatment of choice and is recommended to be administered as a constant rate infusion at 15 mg/kg/h while monitoring the patient for arrhythmias.[15] If constant rate infusion is not possible or monitoring poses a challenge, the intramuscular administration at 40 mg/kg q4–8h has been recommended.[15,130]

Prognosis is dependent on the extent of the liver damage and the timeliness of treatment. If cases are treated early, partial recovery might be possible. If the disease has progressed with fibrosis or cirrhosis present long-term prognosis is guarded.

Hepatocellular iron accumulation is relatively common in cats (>80% of cats) with 50% of histological normal livers showing moderate to marked accumulation, suggesting that, in contrast to dogs, iron accumulation is normal in domestic cats.[131] In cats, there does not appear to be an association between histological diagnosis and the severity or localization of iron accumulation.[131]

## 9.5.4.3 Amyloidosis

Amyloidosis in dogs and cats is an uncommon condition observed secondary to persistent inflammatory responses, immune disorders (e.g., cats naturally infected with FIV[132]), or malignancy; or as primary disease process with a suspected familial disposition (e.g., in Chinese shar-peis). Genetic defects leading to familial amyloidosis have not been fully elucidated in dogs and cats.

### 9.5.4.3.1 Pathophysiology

Hepatic amyloidosis is due to the deposition of amyloid fibril sheets in the space of Disse, macrophages, and hepatic blood vessel walls. This leads to increasing hepatic dysfunction, and eventually hepatic failure. Often these amyloid sheets also form in other organs, such as the kidneys, heart, gastrointestinal tract, and skin.

The amyloid fibrils are derived from serum amyloid A, an acute-phase protein produced by the liver in response to proinflammatory cytokines (▶Fig. 9-27 for a schematic representation of the pathophysiology of amyloidosis).[133,134]

### 9.5.4.3.2 Clinical presentation

Clinical signs of hepatic amyloidosis are often vague, including lethargy, anorexia, weight loss, and recurrent fever.[135] Breed predispositions seem to exist in shar peis, Abyssinian cats, Oriental cats, and Siamese cats.[133,135–138] Hepatic amyloidosis has also been described in domestic short hair cats.[139] In Abyssinian cats and shar peis, the organ predilection for amyloidosis is for the kidneys, while in Siamese cats and Oriental cats it appears to be for the liver.[136,139,140] There does not seem to be an age or sex predilection for this disease, although animals of predisposed breeds usually present at a relatively young age.[134]

As hepatic amyloidosis advances, hemostatic abnormalities and decreases in other liver function tests can be observed.[141] Pale mucous membranes, hepatomegaly, and free abdominal fluid (hemoabdomen due to liver rupture) might be observed in patients with advanced disease.

### 9.5.4.3.3 Diagnosis

Serum biochemical analysis reveals increased liver enzyme activities and, if the disease is advanced, prolongation of coagulation times (aPTT and PT). Ultrasonographic examination shows an enlarged liver with diffuse heterogeneous echogenicity with highly echogenic areas and hypoechoic foci.[141] Determination of serum amyloid A or urine protein creatinine ratio does not seem to be helpful in the early identification of patients at risk.[142]

A definitive diagnosis of hepatic amyloidosis is made based on histopathological evaluation of a hepatic biopsy. Observation of a (green) birefringence under polarized light after staining of hepatic tissue with Congo Red is the gold standard

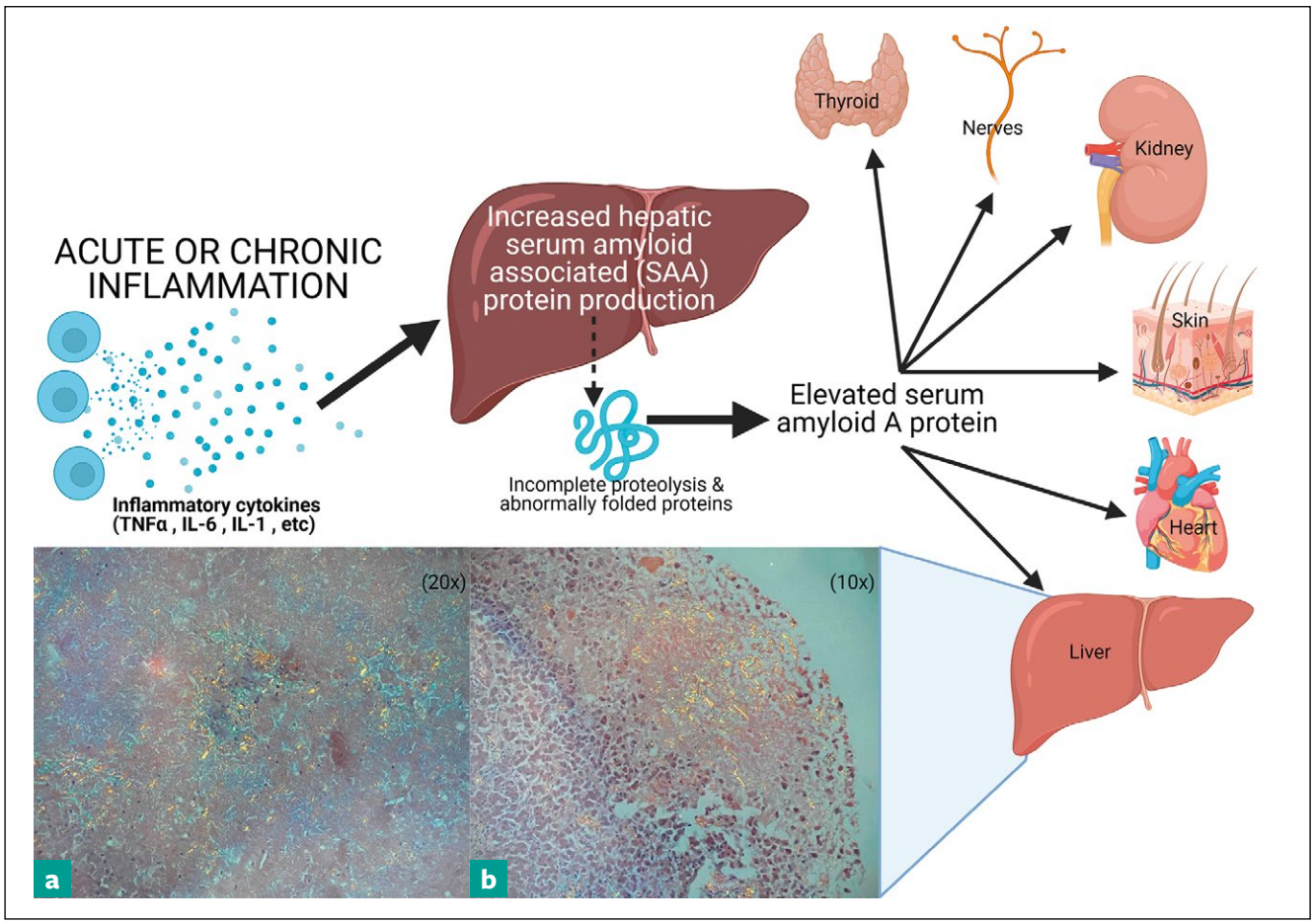



**Fig. 9-27** Amyloidosis

A schematic representation of the pathophysiology of amyloidosis, which can lead to hepatic amyloid deposition. The histopathologic images are feline hepatic tissue, showing (green) birefringence.

(Congo Red stain, **a** 20x, **b** 10x; Histological images courtesy of Dr. Randi Gold, Texas A&M Veterinary Medical Diagnostic Laboratory, College Station, Texas, USA; created with Biorender.com.)

for diagnosis ▶Fig. 9-27.[135] Cytologic evaluation of a fine needle aspirate may be used to help diagnose this disease, although, in the early stages, the disease may be patchy and therefore missed on hepatic cytology.[139] Immunohistochemistry with amyloid-specific antibodies has been described and can aid in the diagnosis if Congo Red staining is inconclusive.

#### 9.5.4.3.4 Treatment

To date, no treatment that can reverse the disease has been described for either dogs or cats. If amyloidosis is suspected to be secondary to an inflammatory response or immune disorder, dampening the immune response is recommended. Supportive treatments such as vitamin $K_1$ supplementation can be given. In shar peis, various treatments have been described anecdotally, such as colchicine (dogs only; 30 µg/kg PO q24h) or dimethyl sulfoxide (dogs only; 90 mg/kg PO three times a week or SC diluted 1:4 with saline) but their efficacy is uncertain, and side effects are common, especially with colchicine.[141]

In humans, in whom amyloidosis is diagnosed early, a combination of the chemotherapeutic agent melphalan plus immunosuppression with prednisolone or dexamethasone has shown some beneficial effects.[143] However, corticosteroid use in patients with amyloidosis is controversial, as this might also increase amyloid protein deposition. Autologous stem cell transplantation has been described for some human patients.[143] None of these treatments have been studied in dogs or cats and, therefore, cannot be recommended at this time.

#### 9.5.4.3.5 Prognosis

The prognosis for dogs and cats with amyloidosis in the long term is poor.[139] One of the complications seen in cats with hepatic amyloidosis is hepatic rupture and hemorrhage, which could be minor or fatal.[141] Since amyloidosis is often systemic, progressive renal failure also contributes to a decreased life expectancy.

### 9.5.4.4 Other hereditary metabolic liver diseases

#### 9.5.4.4.1 Alpha$_1$-antitrypsin/Alpha$_1$-PI deficiency

Alpha$_1$-protease inhibitor ($\alpha_1$-PI), formerly also known as alpha$_1$-antitrypsin, is one of the major serine protease inhibitors.[144,145] Inherited $\alpha_1$-PI deficiency is known to cause lung emphysema, chronic hepatitis, and cirrhosis in humans. Whether or not $\alpha_1$-PI deficiency plays a role in the pathogenesis of canine chronic hepatitis in certain breeds of dogs is controversial.[144]

##### Pathophysiology

$\alpha_1$-PI is produced by the liver, its major function being neutrophil elastase inhibition, thereby protecting tissues from enzymatic degradation.[144–146] In humans, $\alpha_1$-PI aggregates have been shown to initiate liver disease, but whether or not this occurs in dogs remains to be elucidated.[144] However, if $\alpha_1$-PI secretion is impaired, it could aggregate in the liver, forming globules of $\alpha_1$-PI and leading to apoptosis of hepatocytes. This could attract mononuclear cells that then produce cytokines, which would further induce $\alpha_1$-PI synthesis and accumulation.[91]

##### Clinical presentation

Possible signs of this disease in humans include pulmonary abnormalities, leading to a chronic non-productive cough and exercise intolerance, and signs of hepatitis (i.e., anorexia, lethargy, nausea, and vomiting) that might slowly become apparent.

Some American and English cocker spaniels were described to have an increased frequency of an intermediate type of $\alpha_1$-PI on immunohistochemistry, and these breeds are also over-represented among dogs with chronic hepatitis and cirrhosis.[144] However, these breeds are also believed to be susceptible to immune-mediated chronic hepatitis,[147] and accumulation of $\alpha_1$-PI may be a consequence rather than a cause of chronic hepatitis. Future studies are required to evaluate this possible relationship further.

##### Diagnosis

Concentrations of $\alpha_1$-PI can be measured in serum and do not appear to vary with age; however, they can be impacted by hospitalization.[145,146] Some studies describe increased serum $\alpha_1$-PI concentrations in female dogs.[146,148] In humans, a liver biopsy is not required to diagnose $\alpha_1$-PI deficiency; however, it is highly recommended to allow assessment of the extent of hepatic injury and for co-morbidities.

Serum $\alpha_1$-PI concentrations appear to be correlated to inflammatory activity in liver biopsies.[144] In dogs with chronic nonspecific hepatitis, serum $\alpha_1$-PI concentrations appear to be moderately increased, however, in canine acute hepatitis, serum $\alpha_1$-PI concentrations are elevated to twice that of healthy control dogs.[149] In dogs with late-stage cirrhosis, $\alpha_1$-PI is almost absent, probably due to impaired liver function.[149] In human patients, serum $\alpha_1$-PI is elevated in chronic active hepatitis and hepatic cirrhosis.[144] Genetic tests for $\alpha_1$-PI deficiency in dogs have not been described.

##### Treatment

In humans with multisytemic hereditary $\alpha_1$-PI deficiency, no cure has been described. $\alpha_1$-PI supplementation can potentially slow lung damage in humans. Administration of $\alpha_1$-PI through an aerosol has been described in dogs. However, further studies are needed before this can be recommended for clinical cases.[150] Also, this type of administration probably would not increase serum $\alpha_1$-PI levels sufficiently.

#### 9.5.4.4.2 Urea cycle enzyme deficiencies

Urea cycle enzyme deficiencies (UCEDs) in small animals are rare conditions in dogs and cats. Often these deficiencies go undiagnosed due to their vague clinical presentation. Most UCEDs are congenital, although deficiencies secondary to generalized liver dysfunction have been described in humans and cats with FHL, as well as those fed an arginine-deficient diet, and in two cats with underlying hypocobalaminemia.[151–153] In Irish wolfhounds, a hereditary transient juvenile hyperammonemia due to an UCED has been described, presenting most often between 7–13 weeks of age.[154,155] After this age, hyperammonemia resolves in affected dogs of this breed. In cats, one case report of a single cat with a congenital UCED has been described.[156]

### Pathophysiology

Any enzyme of the urea cycle or their related transporters can cause UCEDs, leading to increased blood ammonia concentrations (▶Fig. 9-28). Hyperammonemia leads to cerebral edema and symptoms similar to hepatic encephalopathy.

### Clinical presentation and diagnosis

Clinical signs can be diverse and include lethargy, loss of appetite, vomiting, abnormal behavior, altered mental status, seizures, hyper- or hypoventilation, coma, or death.[151,154] Often, clinical signs are related to the severity of hyperammonemia.

All UCEDs can cause hyperammonemia.[154] In dogs and cats with the clinical signs listed above and hyperammonemia, UCEDs should be considered as a possible cause. Typical cases have normal electrolytes and glucose, while if hyperammonemia is severe, respiratory alkalosis (due to initial hyperventilation from cerebral edema) can be present.[151] Definitive diagnosis is made based on measurement of urea cycle enzyme activities in liver biopsy specimens or by analysis of metabolites in urine (e.g., orotic acid).[154–156] Other markers for hepatic function are often normal.[154,155]

### Treatment and prognosis

Treatment of dogs and cats with UCEDs is supportive. Based on human treatment guidelines, patients showing neurological signs (e.g., seizures) or altered ventilation should receive treatment directed at reducing circulating ammonia concentrations (e.g., lactulose enemas at 1–3 mL/10 kg diluted 1:3 with warm water q6–8h, or some form of hemofiltration),

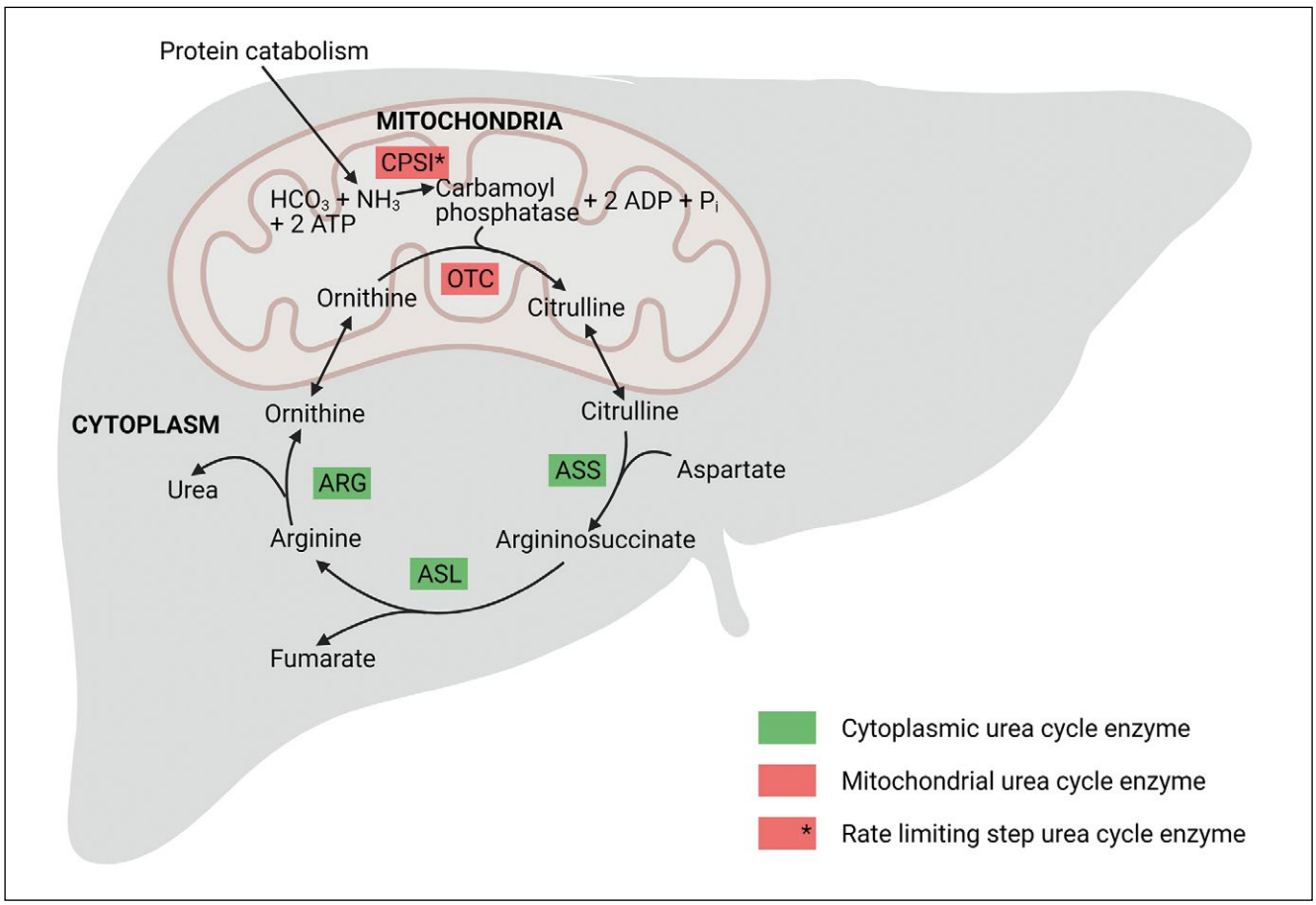



**Fig. 9-28** Urea cycle

Urea cycle enzyme deficiencies (UCEDs) can be the consequence of a defect in any of the urea cycle enzymes. UCEDs lead to multisytemic signs of disease, often in young animals.

**ASS** = arginosuccinate synthetase, **ASL** = arginosuccinase, **ARG** = arginase, **OTC** = ornithine transcarbamylase, **CPSI** = carbamoyl phosphatase synthetase I; created with Biorender.com

reversal of the catabolic state, scavenging of excess nitrogen, or arginine administration.[151] Also, the diet should be modified to prevent amino acid imbalances; finally, dehydration should be prevented.



If an Irish wolfhound is presented with signs of UCEDs and no other obvious cause for hyperammonemia can be found (e.g., a congenital portosystemic shunt), no specific treatment may be needed depending on the severity of the clinical signs. In Irish wolfhounds, the prognosis is excellent as this condition resolves with age.[155]



In cats with arginine deficiency, supplementation, and dietary change should resolve most signs.

However, in other cases, the prognosis is guarded.

#### 9.5.4.4.3 Lysosomal storage diseases

Lysosomal storage diseases are inborn errors of metabolism, leading to the accumulation of macromolecules in lysosomes. In humans, six different groups and 50 individual lysosomal storage diseases have been described, each leading to the accumulation of different macromolecules (e.g., lipids, glycolipids, glycosphingolipids, mucolipidoses, glycogen, or glycosaminoglycans/mucopolysaccharides). Lipid and mucopolysaccharide storage diseases have also been described in dogs and cats.

##### Pathophysiology

Lysosomal storage diseases are a consequence of a single enzyme deficiency, leading to a block of the catabolism of certain macromolecules. Subsequently, accumulation of these molecules leads to cellular dysfunction and a range of clinical signs.[157] Since lysosomes are not unique to the liver oftentimes lysosomal storage diseases present as multisystemic diseases.[158]

##### Clinical presentation and diagnosis

Lysosomal storage diseases are a heterogeneous group of diseases leading to a heterogeneity of clinical signs. Often, multiple organ systems are affected. Lysosomal storage diseases usually do not have a gender predilection and have a variable age of onset, probably reflecting the severity of disease.[158] Most lysosomal storage diseases that are recognized in dogs and cats have been described in young animals. Around 60% of lysosomal storage diseases have a central nervous system component to their phenotypic expression.[159]

In suspected cases, the diagnosis can be made based on either identification of the deficient enzyme by lysosomal enzyme activity assays or molecular genetic testing.[158] Genetic testing has not been described for all of the described defects in dogs or cats.

A high suspicion for lysosomal storage disease can be raised based on a comparison of clinical signs to the disease in humans, combined with histopathology of multiple organs showing lysosomal storage problems. In humans, screening for metabolites in urine and blood can be performed.[159] Screening of metabolites in urine has also been described for dogs and cats.[159,160] In the USA, the University of Pennsylvania School of Veterinary Medicine, PennGen laboratory offers testing for mucopolysaccharidosis in urine (http://www.vet.upenn.edu/penngen/).

##### Treatment and prognosis

In humans, treatment of lysosomal storage diseases is directed at enzyme replacement, bone marrow transplantation, and gene therapy.[157,158] Since there is a single enzyme deficiency, the possibility of gene replacement therapy has received much attention.[157,158] Genetic treatment of individual animals is costly and not routinely undertaken.

In clinical practice, treatment of these cases often remains supportive as a definitive diagnosis often cannot be made, and specific therapy has not been described.[158]

The prognosis for pets with LSD is poor. Lysosomal storage diseases progress, and if neurological features are apparent, most owners opt for euthanasia when signs progress rapidly.

### 9.5.4.5 Aminoaciduric canine hypoaminoacidemic hepatopathy syndrome

Aminoaciduric canine hypoaminoacidemic hepatopathy syndrome (ACHES; formerly hepatocutaneous-associated hepatopathy) is a rare condition in small animals that can be observed with or without characteristic skin lesions.[161,162] Historically, this syndrome has been described under several names, such as hepatocutaneous-associated hepatopathy, superficial necrolytic dermatitis, hepatocutaneous syndrome, necrolytic migratory erythema, glucagonoma syndrome, hepatodermal syndrome, and metabolic epidermal necrosis.

#### 9.5.4.5.1 Pathophysiology

The exact pathophysiology of ACHES remains unknown. Originally, the skin lesions observed (superficial necrolytic dermatitis) were suspected to be due to a glucagonoma, similar to humans with necrolytic migratory erythema.[162–166] However, case reports and studies have described dogs with normal serum glucagon concentrations.

ACHES is presumed to result from a profound hypoaminoacidemia, which is a hallmark feature in both dogs and humans.[162,163,165,167–172] Plasma amino acid concentrations are usually less than 60% of normal.[171] Hypoaminoacidemia is suspected to be caused by dysregulation of the proglucagon-derived hormones (i.e., glucagon and glucagon-like peptides, both are regulators of glucose and amino acid homeostasis) or by excessive hepatic amino acid catabolism.[162] In some cases, hypoaminoacidemia also leads to minor or more severe (characteristic) skin lesions.[162] The pathophysiology leading to these skin lesions is unknown.

Although most dogs with superficial necrolytic dermatitis have a primary or secondary hepatopathy, other cases have an endocrine disorder, such as diabetes mellitus, glucagonoma, or another neuroendocrine tumor (▶Chap. 11.4.4).[165,168,172,173] Some dogs develop signs of superficial necrolytic dermatitis secondary to phenobarbital-induced hepatopathy; however, skin lesions are not appreciated in all cases of phenobarbital toxicity.[165,174]

Further studies are warranted to elucidate the exact metabolic pathways leading to this disease and the skin lesions.

In shih tzu dogs, common ancestries might indicate a potential genetic component or predisposition for the pathogenesis of this syndrome.[169]

#### 9.5.4.5.2 Clinical presentation

At initial diagnosis, around half of dogs with ACHES have apparent skin lesions, including hyperkeratosis, erythema, crusting, exudation, ulceration, fissures, and alopecia involving footpads, mucocutaneous junctions (around the mouth, eyes, genitalia, and anal region), pressure points on the trunk and limbs (such as hocks, elbows, axillae, and groin), pinnae, and interdigital areas.[162,172] However, around 73% of ACHES-affected dogs develop skin lesions at some time after initial diagnosis.[162] Based on the skin lesions, differential diagnoses to consider in dogs include pemphigus, pellagra (niacin deficiency), and zinc-responsive dermatitis.

If footpads are affected by crusting, hyperkeratosis, and fissures, this can result in inactivity, lethargy, inappetence, weight loss, and reluctance to walk.[172,175] Other findings related to a concurrent disease (e.g., polyuria and polydipsia due to diabetes mellitus) might be seen. Concurrent diseases, such as diabetes mellitus, have been reported in 25–40% of the cases with ACHES.[162,172]

A predilection for male, medium- and small-sized, middle-aged to older dogs has been described for ACHES.[162,169,175] Mixed-breed dogs, Shetland sheepdogs, shih tzus, cocker spaniels, West Highland white terriers, and Scottish terriers appear to be overrepresented.[162,169,171,175]

Secondary infections of the skin by bacteria, fungi, and yeasts (such as *Malasezzia* spp.) are often present in dogs with ACHES and skin lesions.[171]

Although this disease is mainly described in dogs, there are a few reported cases of similar diseases in cats.[176]

#### 9.5.4.5.3 Diagnosis

Diagnosis is made based on a combination of characteristic findings on clinical examination: hypoaminoacidemia, aminoaciduria, clinicopathological abnormalities, and ultrasonographic findings.[162]

Common clinicopathological abnormalities include a distinct hypoaminoacidemia and aminoaciduria (in all cases), non-regenerative anemia, microcytosis, elevated serum hepatic enzyme activities, hypoalbuminemia, increased serum glucagon concentration (only in cases with glucagonoma), and in some cases characteristic histopathological skin lesions.[162,163,165,167–172,175]

Amino acids most consistently decreased include 1-methylhistidine, arginine, glutamine, glycine, cystine, cystathionine, proline, and hydroxyproline.[162] These amino acids are associated with the urea cycle, and synthesis of glutathione and collagen.[167,169,171,172] A diagnostic cut-off of <7 nmol 1-methylhistidine/mL plasma and <7.5 nmol cystathionine/mL plasma have shown sensitivities and specificities of 95% and 100%, and 85% and 100%, respectively.[162] In urine, increased concentrations of lysine, methionine, 1-methylhistidine, and proline have been described.[162,169] A diagnostic cut-off of >344 nmol lysine/mg creatinine and >68 nmol methionine/mg creatinine yielded sensitivities and specificities of 92% and 63%, and 92% and 74%, respectively.[109]

On abdominal ultrasonography, the liver has a distinctive honeycomb or Swiss cheese appearance where a hyperechoic reticular pattern of liver parenchyma is surrounded by hypoechoic areas.[162,166,175]

Histopathological evaluation of skin lesions in severely affected cases show a typical "red, white, blue" distribution caused by parakeratosis of the superficial epidermis, vacuolated pale keratinocytes in the middle layer, leading to striking intra- and intercellular edema, and a deeply basophilic hyperplastic basal cell layer (▶Fig. 9-29).[165,172,173]

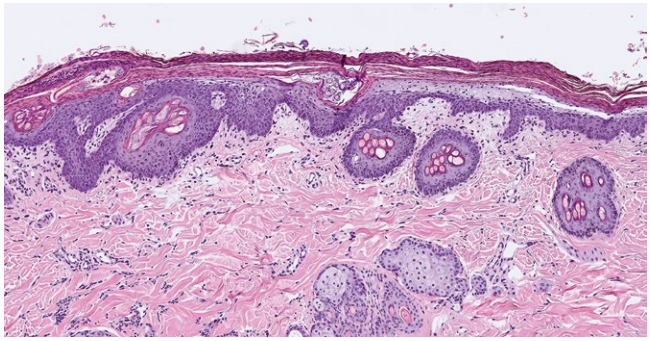


**Fig. 9-29** Superficial necrolytic dermatitis

This histological image of a skin biopsy from a dog with superficial necrolytic dermatitis shows the typical "red, white, and blue" image of parakeratosis of the superficial epidermis, vacuolated pale keratinocytes in the middle layer, and deeply basophilic hyperplastic basal cell layers. (HE staining, 5x)

(Courtesy of Dr. Josué Díaz-Delgado, Texas A&M Veterinary Medical Diagnostic Laboratory, College Station, Texas, USA.)

Liver histopathology usually shows a collapse of the affected parenchyma and multifocal nodular regeneration with swollen hepatocytes due to marked vacuolation, which resembles cirrhosis.[164,169] However, in contrast to cirrhosis, fibrosis is usually minimal or even absent.[169]

#### 9.5.4.5.4 Treatment

A recent study has shown that the optimal treatment of dogs with ACHES consists of a triple combination of two or more IV-amino acid infusions, three or more enteral supplements, and a balanced home-cooked diet (▶Tab. 9-11).[166]

Intravenous administration of amino acids and lipid emulsions through a central venous line has been described as the most effective way of treating ACHES with or without skin lesions.[165,166,169,170] However, peripheral administration of these infusions is also possible. Supporting the liver and the amino acid metabolism with S-adenosylmethionine (SAMe) and silybin, arginine with ornithine, glutathione, lysine, and proline (▶Tab. 9-11) is advised.[166] Additionally, oral supplementation of zinc and essential (omega-3) fatty acids (▶Tab. 9-11) has also been proposed.[163,166,170] A consultation with a board-certified veterinary nutritionist is advised for creating a well-balanced home-cooked diet with a high protein content (around 50% of the metabolizable energy).[166,170]

A glucagonoma can either be surgically excised or managed medically by giving a somatostatin analog.[165,176] If phenobarbital administration is suspected of contributing to a hepatic form of superficial necrolytic dermatitis, tapering and discontinuing this drug is advised. Secondary infections of the skin should be treated with appropriate antibiotics and antifungals.

One case report described the management of a dog with superficial necrolytic dermatitis for over 30 months with allogeneic adipose tissue-derived mesenchymal stem cells.[176] Further studies to evaluate these therapies are needed.

#### 9.5.4.5.5 Prognosis

Initially, the long-term prognosis for dogs with ACHES was considered poor, with an average survival time of around 6 months.[163,165,170,176] However, when the optimal triple treatment is provided, significantly longer median survival

**Tab. 9-11** Treatment pillars of aminoaciduric canine hypoaminoacidemic hepatopathy syndrome (ACHES). The treatment of ACHES consists of a triple combination of parenteral infusions, enteral supplements, and a home-cooked diet.[166]

| Parenteral infusions | Enteral supplements | Home-cooked diet |
|---|---|---|
| 25 mL/kg 8.5–10% amino acid solution | S-adenosylmethionine: 20 mg/kg q24h | Consult a board-certified veterinary nutritionist |
| 7 mL/kg 20% lipid solution | Proline: 500 mg/5–15 kg body weight PO q24h | Aim around 50% of metabolizable energy from protein |
| Initial two administrations 1 week apart | Lysine: 500–1,000 mg/5–15 kg body weight PO q24h | Supplementation with omega-3 fatty acids |
| Administration through a central line or peripheral catheter over 6–8 hours | Arginine/ornithine: 500–750 mg each/5–15 kg body weight PO q24h | Consider supplementing zinc: 11 mg elemental zinc/5 kg body weight. |
| Administer q7–10 days until skin lesions resolve, then reduce the frequency to q3–6 weeks | Glutathione: 500-1,000 mg/5–15 kg body weight PO q24h | Alternative for a home-cooked diet is a high-protein commercial diet. |

times (>4.5 years) are observed than when any combination of or partial implementation of the optimal treatment is provided.[166] Resolution of skin lesions and hepatic pathology have been described with adequate treatment.[166] Concurrent diabetes mellitus seems to decrease the risk of mortality.[166]

**KEY FACTS**

- Metabolic liver diseases in dogs and cats often lead to multisystemic clinical signs .
- Feline hepatic lipidosis is one of the most common liver diseases in cats, with treatment focusing on restoring hydration/euvolemia as well as reversing the negative energy balance.
- Hyperlipidemia in dogs occurs most often secondary to another disease, but primary hyperlipidemia has been described in certain breeds.
- Steroid-induced hepatopathy is common, especially in dogs, and either occurs due to exogenous or excess endogenous glucocorticoids; it typically resolves 1–3 months after glucocorticoid concentrations have normalized.
- Copper-associated hepatopathy is the cause of primary hepatitis in one-third of dogs, and despite multiple discovered genetic defects, is likely multifactorial in origin.
- Most canine cases of superficial necrolytic dermatitis are associated with a primary or secondary hepatopathy.

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
svg.to/9842-09-05-04

## 9.5.5 Inflammatory diseases of the liver

Emma O'Neill and Myles McKenna

### 9.5.5.1 Introduction

A variety of infectious, degenerative, or toxic insults can result in hepatic inflammation, which varies in location and characteristics dependent on both the nature and severity of the injury along with the stage of the response.[1,2] Cullen and Stalker (2016)[2] defined hepatitis as "focal or diffuse hepatic conditions that are either caused by infectious agents or characterized by a leukocytic infiltrative inflammatory response, irrespective of the cause." The more specific term, cholangitis, describes inflammation centered on the biliary tract, or cholangiohepatitis, when this biliary-centric inflammation extends to involve the hepatic parenchyma.[1]

In the dog, inflammatory hepatobiliary diseases most commonly affect the liver parenchyma, with acute and chronic hepatitis being the main subtypes recognized,[2] and the ones discussed further in this chapter. Less commonly recognized inflammatory parenchymal diseases include lobular dissecting hepatitis and eosinophilic hepatitis, along with abscesses and granulomas (▶ Chap. 9.5.2).[1]

The situation in cats is very different, with parenchymal liver inflammation, such as chronic hepatitis, occurring much less commonly in this species.[1] Cholangitis is the most frequent feline inflammatory hepatobiliary disease,[3,4] and is discussed in more detail in ▶ Chap. 9.6.3.2.

### 9.5.5.2 Pathophysiology

The liver performs a wide variety of core homeostatic functions, several of which expose it to a significant risk of injury, necessitating robust regenerative and protective responses.[2] Its key roles in detoxifying endogenously and/or exogenously derived toxins, and immune protection, place it at particular risk. Kupffer cells, or resident hepatic macrophages, are central to the orchestration of liver inflammation,[5] its responses to injury, and the reparative processes.[6] These cells phagocytose microorganisms and any associated molecules or toxins that gain entry to the portal circulation from the gastrointestinal tract. They also contribute to the regulation of the immune response by producing anti-inflammatory cytokines in response to bacterial molecules, aiding the maintenance of the default status of immune tolerance within the liver and avoiding inappropriate, potentially damaging responses to harmless pathogens or their associated molecules.[7] Any dysregulation of this delicate balance between immunotolerance and protective inflammatory responses has the potential to contribute to chronic inflammation within the liver.[8]

Overall, the liver responds to a wide variety of insults it is exposed to with a limited range of pathophysiological and histological responses,[2] outlined later in this section. These are important to appreciate when approaching animals with liver

disease, being of relevance diagnostically, therapeutically, and prognostically. Acute and chronic hepatitis are discussed in more detail below. Essentially, acute hepatitis (AH) occurs in response to a transient insult, such as a chemical, drug, or infection, and has the potential to completely resolve if this insult is self-limiting or successfully removed.[9] In a proportion of these cases, where the underlying insult becomes ongoing, or the resultant changes produced in the liver become self-perpetuating, chronic hepatitis (CH) results.[10] Many cases of CH are diagnosed at this later, chronic stage, with the original, underlying cause remaining elusive in the majority of cases.[10,11] Additionally, it is important to appreciate the potential impact of extrahepatic disease on hepatic inflammation. Nonspecific, reactive hepatitis, characterized by mild inflammatory infiltration in the portal regions of the liver and parenchyma without the hepatocellular necrosis/apoptosis typical of CH, is a histological response pattern observed in animals with inflammation or a disease process external to the liver.[1] This requires recognition and should prompt the initiation of a search for potential extrahepatic causes rather than managing the patient for hepatic disease.[12]

#### 9.5.5.2.1 Cell death

Hepatocyte injury results from various causes, with the potential to culminate in cell death mediated through a combination of apoptosis and/or necrosis. **Apoptosis**, or programmed cell death, is a caspase-dependent process resulting in controlled shrinkage and cell removal through phagocytosis, with minimal local tissue reaction. **Necrosis** involves swelling of the hepatocyte cytoplasm, loss of cell integrity, and the removal of cell contents with a local inflammatory cell response. There is an overlap between these processes, with the response observed reflecting both the nature and severity of the hepatic injury.[2] Apoptosis and/or necrosis is one of the key histological features recognized in the definition of chronic hepatitis in dogs.[12]

#### 9.5.5.2.2 Regeneration

The liver has a very high regenerative capacity, the overall mechanism of which is influenced by the degree of damage.[2,13] Mild to moderate loss of hepatic tissue is replaced by the proliferation of mature hepatocytes or cholangiocytes. With a more marked injury, or in situations where mature hepatocytes cannot proliferate, restitution occurs through the proliferation of bipotential progenitor cells in the periportal regions, a process termed ductular reaction. The extent of this regenerative capacity is demonstrated by the fact that a full recovery is possible even after massive hepatocellular necrosis;[14] if the reticulin framework is intact, sufficient hepatocytes remain, and they are afforded sufficient time and the appropriate supportive conditions.[2] A variety of factors are required to effectively support this process.[15] However, from a clinical perspective, it is important to appreciate the key role of adequate nutrition and appropriate dietary protein. Additionally, the maintenance of normal hepatic architecture is key to the preservation of hepatic function.[9]

#### 9.5.5.2.3 Ductular reaction

Ductular reaction or bile duct hyperplasia is an injury response pattern characterized by the proliferation of bile duct epithelium, bipotential progenitor cells, or potentially hepatocyte metaplasia, and the formation of irregular, tortuous ducts recognized histologically. This type of response pattern can occur with severe hepatic injury (▶Chap. 9.5.1), acute bile duct obstruction, in response to hypoxia, or following portal inflammation and fibrosis.[2] A chronic, persistent ductular reaction can, in turn, contribute to local fibrosis.

#### 9.5.5.2.4 Fibrosis

Fibrosis is the process whereby an abnormal quantity of scar tissue accumulates within the liver in response to attempts to regenerate and repair it; it is the hallmark of the development of chronic liver disease.[10,11] As already discussed, the extracellular matrix (ECM), containing collagen and a variety of other components, is produced by hepatic stellate cells as part of the normal regenerative response.[2] In health, this production is balanced by the degradation of excess ECM, maintaining normal quantities within the tissues, and allowing healing from injury without scarring. This typically occurs with AH; an insult results in hepatocyte injury, prompting a regenerative response, the production of ECM, and the repair of normal tissue with the re-establishment of the homeostatic balance upon completion of the process. However, with diseases such as CH, this normal balance becomes disrupted with ongoing injury, inflammation, and changes in the cytokine environment, resulting in the overproduction of ECM and the laydown of excessive collagen in the hepatic parenchyma.[10] The net result is fibrosis, and eventually the disruption of normal hepatic function by the resultant alterations in hepatic structure.[16]

Hepatic stellate cells are central to the development of fibrosis in humans, involved in ECM production along with regulation of the balance between fibrogenesis and recovery.[17] They transform from their typical quiescent, vitamin A-storing state to an activated, proliferative, contractile phenotype with enhanced capacity to secrete ECM and collagen. This

activation can occur as a direct response to some agents (e.g., alcohol) but is thought most commonly to result indirectly from cytokine release by inflammatory cells and activated Kupffer cells (e.g., transforming growth factor-beta; TGF-β), with inflammatory mediators released from necrotic hepatocytes also likely to contribute to the process.[10] Oxidant stress and lipid peroxidation products are thought to play a crucial role in the overall progression of chronic liver disease by stimulating cytokine release from hepatocytes and inflammatory cells, and contributing to fibrogenesis,[18] a situation that is further exacerbated by bile acids whenever cholestasis occurs.[19] The extent to which all of these processes occur in dogs needs to be confirmed, but there are many similarities in the overall pathogenesis of chronic liver disease between dogs and humans.[10,11,17]

#### 9.5.5.2.5 Cirrhosis

The importance of extensive fibrosis is the impact it has on hepatic function. With increasing fibrosis, the liver becomes less able to regenerate, forming disorganized hyperplastic nodules.[2] Disruption of the portal blood flow also contributes to this process and the morbidity associated with chronic liver disease.[17] The net result is a gradual reduction in functional hepatic mass, and progressively worsening clinical signs once the hepatic functional reserve is exceeded. Cirrhosis is the term used to refer to late-stage CH, where there is extensive fibrosis within the tissue, resulting in architectural distortion.[16]

#### 9.5.5.2.6 Portal hypertension and ascites

Portal hypertension refers to abnormally high pressure within the portal circulation and is important clinically in patients with chronic liver disease, given its association with significant morbidity and mortality.[20] Portal pressure in health is typically low and relatively constant, reflecting the net combination of portal blood flow and portal resistance. With disease, portal resistance increases resulting from a combination of fixed structural changes that occur with fibrosis and inflammation, and dynamic changes from hepatic stellate cell activation, inflammatory mediator release, and changes in the balance between vasoconstriction and vasodilation. Vasodilation of the splanchnic vasculature further aggravates this situation by increasing portal blood flow. The result of this increased portal pressure is the development of multiple acquired portosystemic shunts (▶Chap. 9.5.6.2.1) and ascites, with or without hepatic encephalopathy (▶Chap. 9.4.4).[21]

#### 9.5.5.2.7 Cholestasis

Cholestasis refers to impaired bile flow and can result from various intra- and extrahepatic causes.[21] Intrahepatic cholestasis can result from situations that mechanically disrupt the normal flow of bile (e.g., swollen hepatocytes, fibrosis, or inflammatory cells), disrupt the tight junctions between bile canaliculi and sinusoids, or interfere with the function of sinusoidal and canalicular membrane transporters.[22] This type of cholestasis occurs commonly with chronic liver disease,[21] although it is often not appreciated clinically due to the large hepatic reserve capacity and ability for overall compensation if focal cholestatic lesions occur. Clinically, recognition that cholestasis occurs is important from several perspectives. Mild cholestasis may be recognized on the clinical biochemistry panel (e.g., increased serum ALP activity). More severe ALP increases, hyperbilirubinemia, and clinical jaundice occur if there is a marked, more generalized loss of liver function, as occurs with end-stage liver disease and cirrhosis.[21] It is also important clinically to appreciate the toxic effects of accumulated bile acids in disease pathogenesis,[19] and the changes in the composition of the bile acid pool known to occur with chronic liver diseases.[23]

### 9.5.5.3 Acute hepatitis

AH is characterized histologically by inflammation, often predominantly periportally and within the perisinusoidal space, combined with foci of hepatocellular apoptosis and necrosis and, in some cases, signs of a regenerative response.[2] The extent, pattern, and exact characteristics vary, reflecting the etiological agent, level of exposure, and the timeframe involved.[1] However, while a variety of potential causes of AH have been defined,[1,24] for example, drugs or toxins (▶Chap. 9.5.1) or infectious agents, such as infectious canine hepatitis (▶Chap. 9.5.2), the underlying cause remains undetermined in a significant number of cases.[25,26] Approximately 75% of cases were reported to be idiopathic in a retrospective review of referral cases in the Netherlands.[27] However, it is important to acknowledge the selection bias in this population; cases with known causes, such as drug exposure that can easily be removed, are probably more likely to be managed symptomatically and not referred.

#### 9.5.5.3.1 Clinical presentation and diagnosis

The clinical spectrum of AH presentation varies widely, depending on the nature and extent of the injury, the scale of the hepatocellular necrosis, and resultant inflammatory response.[9] Clinical signs are often vague, and include general

malaise, loss of appetite, vomiting, and dehydration, unless there is a significant loss of liver function when more specific signs occur, such as icterus or hepatic encephalopathy.[26] Pyrexia can result from exposure to endogenous or exogenous pyrogens, due to tissue necrosis and reduced removal of bacterial endotoxins from the portal circulation.[9] Liver enzyme activities, particularly ALT and AST, are typically increased, reflecting hepatocyte injury, but not necessarily correlating with its severity.[24] If there is extensive hepatocyte necrosis or fulminant hepatitis, significant impairment of hepatic function can ensue, with the potential to develop hypoglycemia, hepatic encephalopathy, icterus, and disseminated intravascular coagulopathy (DIC), all triggering a rapid progression to coma and death.[26]

Confirmation of a diagnosis of AH requires a liver biopsy. However, care must be taken if there is any concern of coagulopathy, which occurs commonly,[25] and coagulation profiles should be evaluated in all cases prior to invasive procedures. A presumptive diagnosis with symptomatic management is reasonable when there is known toxin exposure with compatible clinical signs and clinical pathology changes, or concern for the patient's clinical stability.

#### 9.5.5.3.2 Treatment and prognosis

Management of AH is largely symptomatic with removal of the inciting cause, if identified (also see a recent review of acute liver injury/acute hepatic failure for more details[26]). Intravenous fluid therapy is important to manage fluid deficits, hypoglycemia, acid-base abnormalities, or electrolyte disturbances. The specific management of toxic liver disease is covered in ▶Chap. 9.5.1. Corticosteroids are contraindicated due to their potential for adverse effects in acute infections. Broad-spectrum antimicrobial therapy is prudent when there is significantly impaired liver function, given the potential for bacteremia with reduced hepatic clearance of the portal blood.[24] The overall prognosis varies, depending on the severity of the original hepatic insult. The majority of cases recover well with appropriate supportive care, but some cases develop CH with additional clinical signs developing several months later.[9,27] Because of this, it is important to monitor hepatic enzyme activities after the acute injury, following up with a liver biopsy should these fail to continue reducing over the next 4–6 weeks.[9] The prognosis for cases with acute hepatic failure is far poorer, with only 14% surviving to discharge in one large retrospective study.[28]

### 9.5.5.4 Chronic hepatitis

Canine CH is a histological diagnosis defined by the World Small Animal Veterinary Association (WSAVA) to include the following key features: hepatocellular apoptosis or necrosis, a variable mononuclear or mixed inflammatory cell infiltrate, regeneration, and varying amounts of fibrosis.[1] A variety of agents have been implicated in the pathogenesis of CH, including excess copper accumulation,[29] hepatotoxic drugs,[30] toxins,[1] and infectious diseases.[1,27,31] The condition may be immune-mediated in some dogs.[12,32–34] However, the majority of cases remain idiopathic,[10,11] likely to reflect both the fact that it is a histological diagnosis made relatively late in the course of disease progression, and the limited range of response patterns the liver shows with injury.[2] CH is a progressive disease, and ultimately can lead to hepatic cirrhosis, characterized histologically by severely distorted hepatic architecture, fibrosis, and sinusoidal portal hypertension.[12] As a variant of CH, lobular dissecting hepatitis (LDH) is characterized by lobular inflammation with disruption of hepatic cords by fine fibrous septa, hepatocyte necrosis, and a marked ductular reaction.[35]

#### 9.5.5.4.1 Copper-associated chronic hepatitis

Excess hepatic copper accumulation is the most commonly identified cause of toxic injury resulting in canine CH.[2,27] This accumulation may result from excessive copper intake, altered biliary excretion, or a combination of these mechanisms.[12] Free copper is toxic by virtue of its ability to create reactive oxygen species, resulting in oxidative damage to hepatocytes and contributing to the progression of hepatic inflammation.[12] In the Bedlington terrier, an autosomal recessive defect affecting exon 2 of the *COMMD-1* gene appears to be responsible for the copper-accumulating phenotype.[36] A genetic predisposition to copper storage hepatopathy is also suspected, but remains unproven, in the Labrador retriever, skye terrier, Dalmatian, West Highland white terrier, and Doberman pinscher.[37–41] Chronic cholestasis can also result in copper accumulation and may cause toxic levels if combined with increased dietary intake (see two recent articles that review this condition and its management in more detail[12,29]). There is still much more to be elucidated about the role of copper in canine CH, but the frequency of hepatic copper accumulation in these cases,[27] and its potential to contribute to disease progression, necessitate the measurement of copper in all cases and the management of increased levels.[12]

#### 9.5.5.4.2 Drugs and toxins

AH, triggered by drugs or toxins, can progress to CH, as discussed above. Additionally, chronic administration of some drugs not commonly associated with AH can lead to CH (e.g., phenobarbital).[42]

#### 9.5.5.4.3 Infectious diseases

Infectious diseases of the liver and biliary tract are discussed in ▶ Chap. 9.5.2. Despite the huge role played by infectious agents, particularly viruses, in human liver diseases, this has not been demonstrated in dogs.[10,11] AH caused by any infectious agent can progress to CH. The potential mechanisms for this include the persistence of the organism within the liver, persistence of the inflammatory response initiated by the organisms, an immune-mediated reaction triggered by the infection, or immune dysregulation resulting from loss of the normal immune homeostasis and failure to clear "danger signals" or appropriately regulate activated immune responses.[8] Documentation of bactibilia in some dogs with CH may implicate a role for bacterial cholangitis in the development of some cases of CH.[43] Additional infectious agents documented to be associated with CH include *Leptospira* spp., *Ehrlichia canis*, and *Leishmania* spp.[44–46] However, at present, there is little evidence to confirm or refute the role of infectious agents in canine CH. As work in humans explores the impact of the gut and biliary microbiome on hepatic immune responses,[47,48] and the interplay between these organisms, bile acid homeostasis,[49] and the resultant alterations in bile acid signaling,[23] it is clear that far more work is required in this area to gain a better understanding.

#### 9.5.5.4.4 Immune-mediated disease

There is significant evidence to suggest an immune-mediated basis for the disease in some dogs with idiopathic CH. Interested readers are referred to the ACVIM consensus statement for a summary of this information.[12] The positive response to immunosuppressive therapy in many dogs with CH,[50–53] female predisposition in many reports, and association with particular MHC class II haplotypes in some breeds,[54–56] all provide evidence for at least an immune-mediated component to the disease pathogenesis. However, this theory remains unproven due to the difficulty in demonstrating immune-mediated damage to hepatocytes.

#### 9.5.5.4.5 Clinical presentation

The mean age of dogs presenting with clinical signs of CH is 7.2 years,[12] but the age at which subclinical disease begins is unknown. LDH typically affects dogs at a younger age, with an average age of 2 years at the time of presentation.[12] Increased prevalence of CH has been recorded in several breeds across multiple countries, including the Doberman pinscher, Labrador retriever, Dalmatian, American and English cocker spaniel, Bedlington terrier, West Highland white terrier, and English springer spaniel. Additional breed predispositions are reported in specific geographical regions along with sex predispositions in certain breeds.[12]

CH is believed to have a long subclinical phase. This is supported by the fact that up to 20% of cases are diagnosed in clinically healthy dogs with increased serum liver enzyme activities,[12] which likely reflects the large functional reserve capacity of the liver and its regenerative capacity.[11] This also impacts the typical presenting clinical signs that tend to initially be gradual in onset and nonspecific, with animals only showing signs more specific to the liver later in the disease course, as at least 70–80% of the functional capacity are lost.[11] The most commonly reported clinical signs, collated from a number of studies, are inappetence (61%) and lethargy (56%), with gastrointestinal signs such as diarrhea and vomiting occurring in 20 and 25% of cases, respectively.[12] Other clinical signs that are more specific for liver disease occur less commonly, requiring the loss of a greater proportion of the functional hepatic mass. These include icterus (34%), ascites (32%), polyuria/polydipsia (30%), and melena (6.1%). Ascites is also a particular feature of CH in certain breeds, especially the English springer spaniel, American cocker spaniel, and in cases with LDH.[27,57,58]

#### 9.5.5.4.6 Diagnosis

##### Clinical pathology

Documentation of a persistent (>2-month duration) increase in serum ALT activity is currently the most sensitive screening test for CH.[12] However, histopathological evidence of CH has been documented in dogs with a normal serum ALT activity.[59,60] Increases in ALP, AST, and GGT activities usually occur later in the disease process than increases in ALT activity.[12] A decrease in transaminase activities may be noted in end-stage CH due to the loss of functional hepatocytes.[61] Hyperbilirubinemia, a negative prognostic indicator,[62] is present in approximately 50% of dogs with CH.[12] Decreased concentrations of cholesterol, urea, albumin, and (less commonly) glucose may be noted in dogs with late-stage CH or

cirrhosis due to decreased hepatic function.[12] Approximately 30% of dogs with CH present with mild anemia,[12] which may reflect anemia of inflammatory disease, or chronic blood loss from gastrointestinal ulceration or hepatic coagulopathy. Mild thrombocytopenia is also described in almost 25% of cases,[61] possibly reflecting decreased production secondary to decreased hepatic thrombopoietin production, or increased consumption. Hepatic function tests, such as the bile acids stimulation test or blood ammonia concentration are insensitive for diagnosing early-stage CH,[12,63] with abnormalities usually occurring in the later stages of the disease when cirrhosis or acquired portosystemic shunts have developed.[12]

### Diagnostic imaging

The preferred imaging modality for dogs with suspected CH is ultrasonography, allowing assessment of the hepatic parenchyma in addition to identifying potential disease complications, such as portal vein thrombosis and portal hypertension.[64] Ultrasonographic changes in the liver of dogs with CH are usually diffuse. Common findings include a generalized increase in parenchymal echogenicity, heterogenous echotexture, and decreased liver size. However, ultrasonographic findings with CH are variable and can be impacted by patient size and conformation, along with operator skill and the equipment used.[12,64] With early or mild CH, ultrasonographic changes may be minimal; hence, CH cannot be excluded based on a normal hepatic ultrasound examination.[65] Conversely, in end-stage CH, ultrasonographic lesions may be dramatic, and the presence of ascites, gallbladder wall edema, and changes in portal blood flow (decreased blood flow velocity and/or hepatofugal flow) are all consistent with portal hypertension.[66–68] Acquired portosystemic shunts are another indicator of portal hypertension.[69] These shunts can be technically challenging to locate but are usually identified as plexuses of tortuous vessels located caudal to the kidneys. Radiography may identify microhepatica in advanced CH cases but has minimal value diagnostically in dogs with CH.[64] Data are currently lacking on the clinical utility of advanced imaging modalities (i.e., computed tomography and magnetic resonance imaging) in dogs with CH.

### Sampling of the liver

Histopathology is required for the definitive diagnosis of CH (▶ Fig. 9-30). Cytology of fine-needle aspirates of the liver is not sufficient to diagnose this condition or determine its etiology.[70,71] Biopsy specimens obtained laparoscopically or via laparotomy are preferred, as these allow the collection of larger samples than those collected via percutaneous ultrasound-guided methods.[72,73] The recommendations in the ACVIM consensus statement on the diagnosis and treatment of CH in dogs are that at least five biopsies are obtained from at least two liver lobes, at least three to be submitted for histopathology, one for copper quantification, and one for aerobic and anaerobic bacterial culture.[12] At least 12–15 portal triads should be present in a biopsy to allow accurate histopathological assessment. Approximately 20–40 mg (wet weight) of liver tissue is required to quantify copper using the gold standard technique of atomic absorption spectrometry.[12] Bacterial culture of a bile sample should also be considered, as there is evidence to suggest that this is more sensitive for the detection of bacterial infection than the culture of hepatic tissue.[43]

The information gained from histopathology in dogs with CH is currently the most valuable way of tailoring treatment strategies in individual cases and offers important prognostic information.[10] Thus, it is imperative to gain as much information as possible from a histopathologist who has experience working with canine liver disease. The key histopathological features that must be assessed include the type and degree of inflammation present, along with the extent of hepatocellular apoptosis and/or necrosis (disease activity), the presence of fibrosis (disease stage), ductular reaction, and any pigment deposition.[1,10] In addition to a standard hematoxylin and eosin (H&E) stain, special stains must be applied to allow full assessment: Masson's trichrome or Sirius red (for evaluation of fibrosis) and rubeanic acid or rhodamine (for evaluation of copper).[12] Characterizing the type of hepatic inflammation can provide clues to the underlying pathogenesis. For example, suppurative inflammation may suggest bacterial involvement,[74] whereas a primarily lymphocytic infiltrate would be more aligned with immune-mediated disease. Documenting granulomatous or pyogranulomatous inflammation could suggest an unusual infectious etiology (e.g., leptospirosis or mycobacteriosis) and should prompt consideration of additional testing of biopsy samples such as fluorescent in-situ hybridization (FISH), acid-fast staining, and/or PCR analysis. However, there is currently only limited information about the potential diagnostic yield from these methods.[74–76] Copper-associated hepatopathy is characterized by copper accumulation detected primarily in centrilobular areas, whereas periportal copper accumulation is usually regarded as a nonspecific finding.[12] Normal canine liver typically has copper levels ≤600 µg/g dry weight, whereas in copper storage hepatopathies, these concentrations usually exceed 1,000 µg/g dry weight liver, although substantial individual variability exists.[77,78]

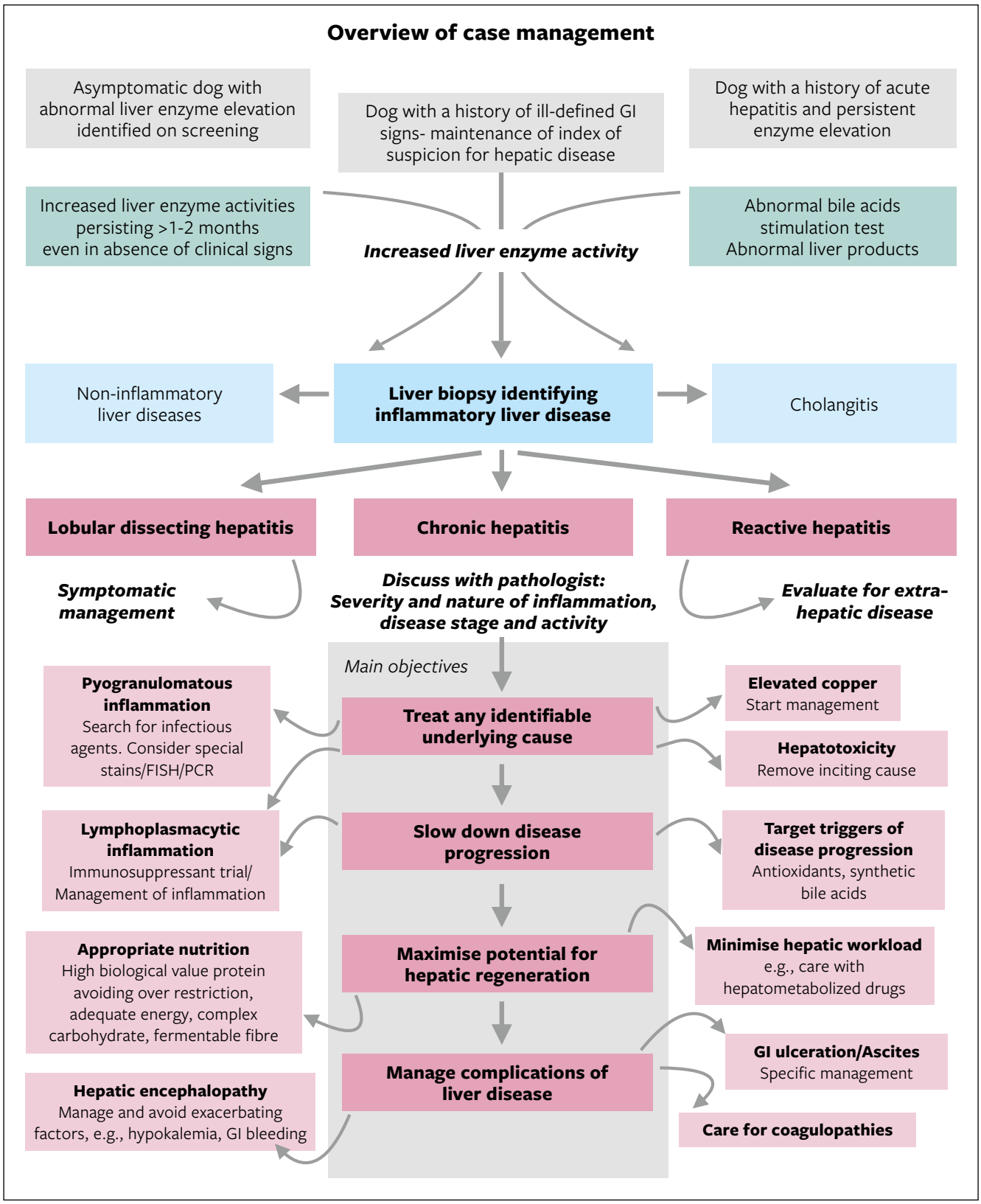



**Fig. 9-30** Overview of case management of dogs presenting with possible liver disease, from the typical presentation of these cases through to the histopathological categories of disease, and then finally the approach to the management of cases with chronic hepatitis based on the main treatment objectives

#### 9.5.5.4.7 Treatment and prognosis

The management of canine CH should focus on treating the underlying cause (if known) in addition to the provision of nonspecific hepatic support, such as appropriate dietary support, management of specific clinical signs, and the symptomatic treatment of complications of the disease (e.g., ascites or hepatic encephalopathy). If a specific cause of CH cannot be identified, then a trial of immunosuppressive therapy is indicated, assuming that liver histopathology supports an immune-mediated disease process. The provision of agents that target known triggers of disease progression (e.g., antioxidants or synthetic bile acids) can also be tailored to biopsy results. An overview of the medications commonly used to manage CH is provided (▶Tab. 9-12). The authors recommend reviewing the ACVIM 2019 consensus statement on the diagnosis and treatment of CH in dogs for detailed information on the management options.[12]

Chronic hepatitis is a progressive disease, and many affected dogs will ultimately die from causes linked to the disease. The median survival time after diagnosis has been reported as 561 days; however, this varies significantly between individual dogs.[12] Reported survival times of dogs with lobular dissecting hepatitis and hepatic cirrhosis are typically much shorter, with most dogs only surviving 1–2 months after diagnosis.[12]

**Tab. 9-12** Overview of broad aims for the management of canine chronic hepatitis (CH)[12,39] along with a summary of commonly used medications

| | Medication/ management | Rationale | Suggested dosage | Main adverse effect(s) |
|---|---|---|---|---|
| **Aim 1:** | **Treat any identifiable underlying cause** | | | |
| **Copper storage hepatopathy** | Restricted copper diet | Decreases dietary copper intake | <0.12 mg copper/100 kcal | Usually well tolerated |
| | D-penicillamine* | Copper chelator | 10–15 mg/kg PO q12h | Vomiting, inappetence |
| | Trientine* | Copper chelator | 5–15 mg/kg PO q12h | Renal toxicity |
| | Zinc (acetate/gluconate) | Decreases copper absorption from the gastrointestinal tract | 8–10 mg/kg elemental zinc PO q24h | Vomiting, hemolytic anemia |
| **Infectious hepatitis** | Antimicrobial therapy; choice is usually guided by bacterial culture and sensitivity of biliary cultures or hepatic biopsies<br>Specific antimicrobial treatment is indicated for leptospirosis, leishmaniosis, mycobacteriosis, etc. | If infection is an inciting cause of CH, treating the infection may delay progression but is unlikely to result in a cure. | Varies depending on the antibiotic used. A total of 4–6 weeks of antibiotic therapy is usually recommended. | Varies depending on the antimicrobial agent used |
| **Immune-mediated hepatitis** | Predniso(lo)ne | Immunosuppressive | 2 mg/kg q24h or 1 mg/kg q12h PO (taper to 0.5 mg/kg PO q48h) | Polyuria/polydipsia, ALP induction |
| | Cyclosporine | Immunosuppressive | 5 mg/kg PO q12h (taper to q24h) | Vomiting, nausea |
| | Mycophenolate** | Immunosuppressive | 10 mg/kg PO q12h | Diarrhea |
| | Azathioprine** | Immunosuppressive | 2 mg/kg PO q24 for 2 weeks, then maintain on 2 mg/kg PO q48h | Bone marrow suppression, hepatotoxicity |

**Tab. 9-12** Overview of broad aims for the management of canine chronic hepatitis (CH)[12,39] along with a summary of commonly used medications (Continuation)

| | Medication/ management | Rationale | Suggested dosage | Main adverse effect(s) |
|---|---|---|---|---|
| **Aim 2:** | **Slow down disease progression** | | | |
| **Management of inflammation** | Prednis(ol)one | Anti-inflammatory | 1 mg/kg q24h or 0.5 mg/kg q12h PO (taper to 0.5 mg/kg PO q48h) | Polyuria/polydipsia, ALP induction |
| | Drugs as above for immunosuppression | Anti-inflammatory | Doses as above | As above |
| **Hepato-protectants, targeting triggers of disease progression** | S-adenosylmethionine | Increases hepatic glutathione synthesis | 20 mg/kg PO q24h | Nausea (rare) |
| | Ursodeoxycholic acid | Synthetic bile acid with choleretic, antioxidant, and anti-inflammatory properties | 15 mg/kg PO q24h*** | Nausea, diarrhea (rare) |
| | Silymarin | Antioxidant, choleretic, anti-inflammatory, anti-fibrotic | 4–8 mg/kg PO q8–12h | Usually well tolerated |
| | Vitamin E (α-tocopherol) | Antioxidant, anti-inflammatory, anti-fibrotic | 10 IU/kg (do not exceed 400 IU per dog) | Usually well tolerated at standard dose |
| **Aim 3:** | **Maximize potential for hepatic regeneration** | | | |
| **Appropriate nutrition** | Adequate plane of nutrition | Required to maximize hepatic regeneration | N/A | N/A |
| | Moderate/normal amount of high biological value protein | Poor biological value protein requires additional hepatic metabolism and impairs hepatic regenerative capacity | Restriction only indicated if necessary to control hepatic encephalopathy | Over-restriction of protein results in catabolism and enhances hepatic workload + potential for ammonia genesis |
| | Normal fat levels | Valuable source of energy and enhances palatability | Avoid high-fat diets in cases with cholestasis or portal hypertension, which may exacerbate gastrointestinal signs | Maldigestion and steatorrhea due to cholestasis (rare) |
| | Complex carbohydrates | Primary calorie source; reduces the need for hepatic gluconeogenesis | Must be easily digestible; complex carbohydrates in combination with fats are better utilized than simple sugars | Avoid simple sugars as carbohydrate metabolism is likely to be disrupted |
| | Fermentable fiber | Broken down by colonic bacteria to generate short-chain fatty acids with the net effect of increasing nitrogen trapping by incorporation into gut bacteria and decreasing intestinal transit time, overall reducing ammonia production | Some non-fermentable fiber may aid in the avoidance of constipation. | Too much non-fermentable fiber is to be avoided as it impacts the digestibility of the diet and nutrient absorption. |

▶▶

**Tab. 9-12** Overview of broad aims for the management of canine chronic hepatitis (CH)[12,39] along with a summary of commonly used medications (Continuation)

| | Medication/ management | Rationale | Suggested dosage | Main adverse effect(s) |
|---|---|---|---|---|
| | • Fat-soluble vitamins<br>– Vitamin $K_1$<br>– *See comments on vitamin E above.* | • Reduced vitamin K absorption with cholestasis | • Vitamin K supplementation if abnormalities are identified on the clotting profile | • Vitamins D and A should not be supplemented, as both can cause toxicity |
| | • Water soluble vitamins | • Increased loss of B vitamins in any patient with polyuria/polydipsia | • B vitamins should be supplemented | • Vitamin C supplementation should be avoided as it can exacerbate tissue damage associated with copper or iron in liver disease |
| **Minimize hepatic workload** | Care with hepatometabolized drugs | Avoid increasing hepatic demands through requirements for drug metabolism | N/A | N/A |
| **Aim 4:** | **Manage the complications of liver disease** | | | |
| **Hepatic encephalopathy** | Lactulose | Decreases colonic ammonia absorption | Starting dose: 1–10 mL/dog PO q8h. Adjust the dose to achieve 3–4 soft stools per day.**** | Diarrhea |
| | Amoxicillin | Decreases colonic ammonia absorption | 20 mg/kg PO q12h | Hypersensitivity, gastrointestinal upset |
| **Ascites** | Spironolactone | Aldosterone antagonist | 1–2 mg/kg PO q24h | Hyperkalemia |
| **Gastrointestinal ulceration** | Omeprazole | Proton pump inhibitor | 1 mg/kg PO q12h | Usually well tolerated |
| **Hemostasis** | Coagulation profile evaluated prior to any invasive procedure | Abnormalities of hemostasis are well recognized in dogs with impaired hepatic function | N/A | N/A |

* Consider vitamin $B_6$ supplementation in dogs receiving long-term copper chelation therapy
** Azathioprine and mycophenylate should not be used together due to risk of increased severity of adverse effects.
*** Consider 7.5 mg/kg PO q12h in dogs that experience gastrointestinal upset on q24h dosing
**** Consider lactulose retention enema in acute encephalopathic crisis (10–15 mL/kg of a solution made up of three parts lactulose to seven parts warm water as a retention enema for 4–8 hours)
**CH** = chronic hepatitis; **PO** = per os; **ALP** = alkaline phosphatase

**KEY FACTS**

- Inflammatory liver disease in the dog is most commonly parenchymal; common causes include acute and chronic hepatitis.
- The most common inflammatory liver disease in the cat is cholangitis, with chronic hepatitis much less commonly observed in this species.
- Documenting persistently increased ALT activity is currently the most sensitive screening test for canine chronic hepatitis.
- Histopathology of liver biopsies is required for diagnosis of chronic hepatitis; cytology of fine-needle aspirates is not sufficient.
- With a clinical suspicion of chronic hepatitis, liver biopsies should be submitted for histopathology, bacterial culture (aerobic and anaerobic), and copper quantification.

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
svg.to/9842-09-05-05

## 9.5.6 Developmental disorders of the liver

Penny Watson

### 9.5.6.1 Introduction

Congenital and developmental disorders are relatively common in dogs but are less common in cats. They can be divided into vascular disorders, abnormalities of the portal triads/ductal plates, parenchymal disorders, and gross anatomical disorders, although there is some overlap among these disorders (▶Tab. 9-13). The causes of developmental disorders are poorly understood. In humans and experimental animal models, hypoxia and nutritional deficiencies *in utero* result in vascular changes and hepatic asymmetry with vascular abnormalities being more likely in multiple births. In dogs and cats, similar interactions between genetic susceptibility and the uterine environment are also likely to be involved.

### 9.5.6.2 Vascular disorders

#### 9.5.6.2.1 Congenital portosystemic shunts

The most common congenital vascular disorders recognized in dogs and cats are congenital portosystemic shunts (CPSS), which are discussed in detail in ▶Chap. 9.5.3.2. CPSS are much more common in small animals than in humans and can occur concurrently with microscopic vascular disorders (i.e., portal vein hypoplasia and microvascular dysplasia; discussed below), which are also common in small animals but rare in humans. Limited studies suggest that there may be common genetic and environmental causes for both.

#### 9.5.6.2.2 Portal vein hypoplasia

**Microvascular dysplasia (MVD)**, **portal vein hypoplasia (PVH)**, and **non-cirrhotic portal hypertension** are all congenital abnormalities of the intrahepatic portal veins characterized by a reduction in portal vein branches in portal triads in the absence of a larger shunting vessel. The WSAVA Standards for Canine and Feline liver diseases place all these microscopic portal vein abnormalities under the single term "portal vein hypoplasia."[1] It is not possible to differentiate between these conditions and congenital PSS by histopathol-

**Tab. 9-13** Developmental abnormalities of the liver in dogs and cats

| Vascular disorders | Ductal plate abnormalities | Parenchymal disorders | Gross anatomical disorders (rare; often occur together with other disorders) |
|---|---|---|---|
| Congenital portosystemic shunt | Congenital hepatic fibrosis | Copper storage disease | Hepatic liver lobe agenesis |
| Portal vein hypoplasia<br>Microvascular dysplasia | Caroli's disease | Lysosomal storage diseases | Duplex gallbladder (relatively common; incidental finding)<br>Gallbladder agenesis (rare) |
| Hepatic arterio-venous fistula/malformation | Choledochal cysts (segmental dilations of the common bile ducts of controversial etiology – may be congenital or acquired) | – | Midline defects secondary to toxicity *in utero* |

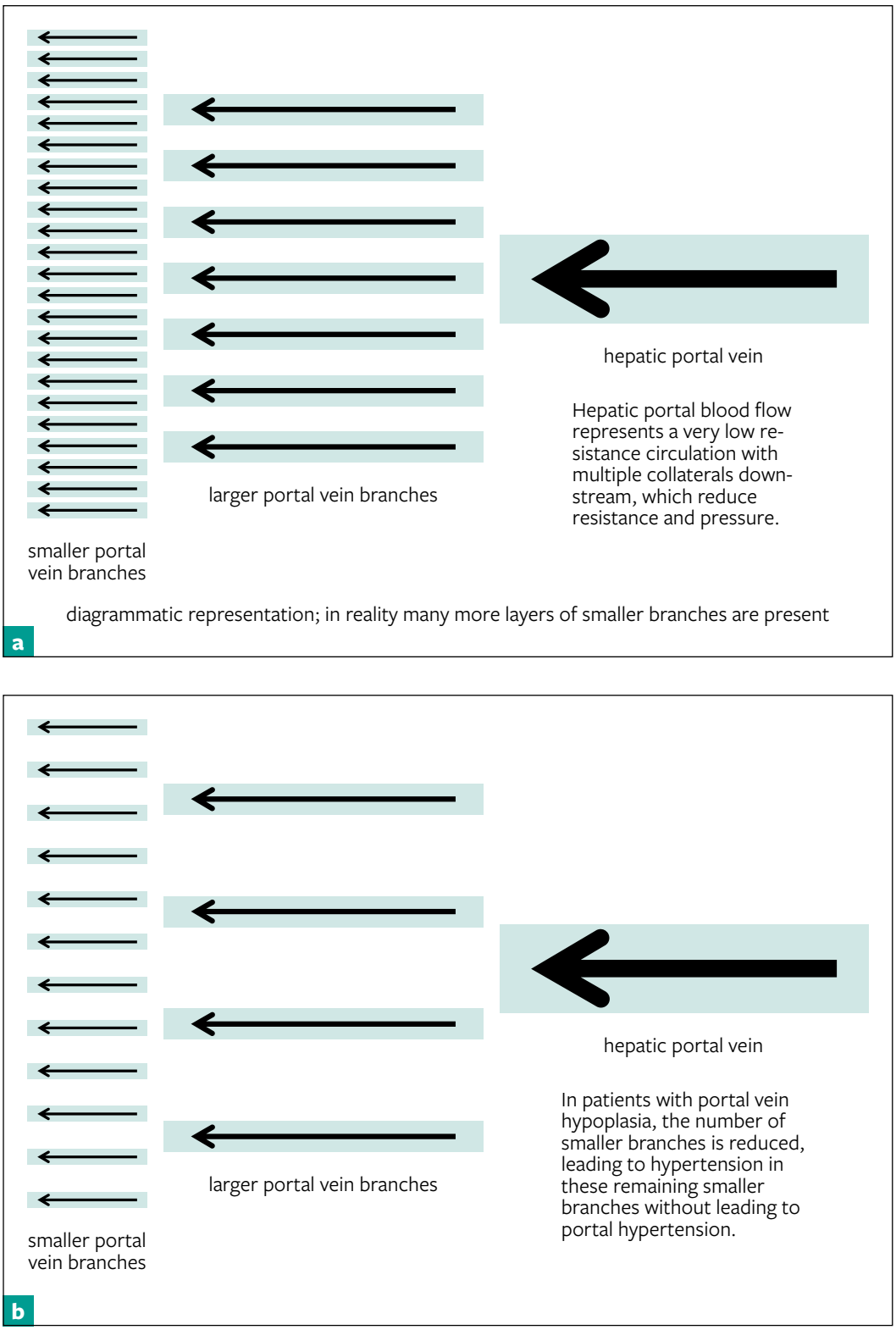
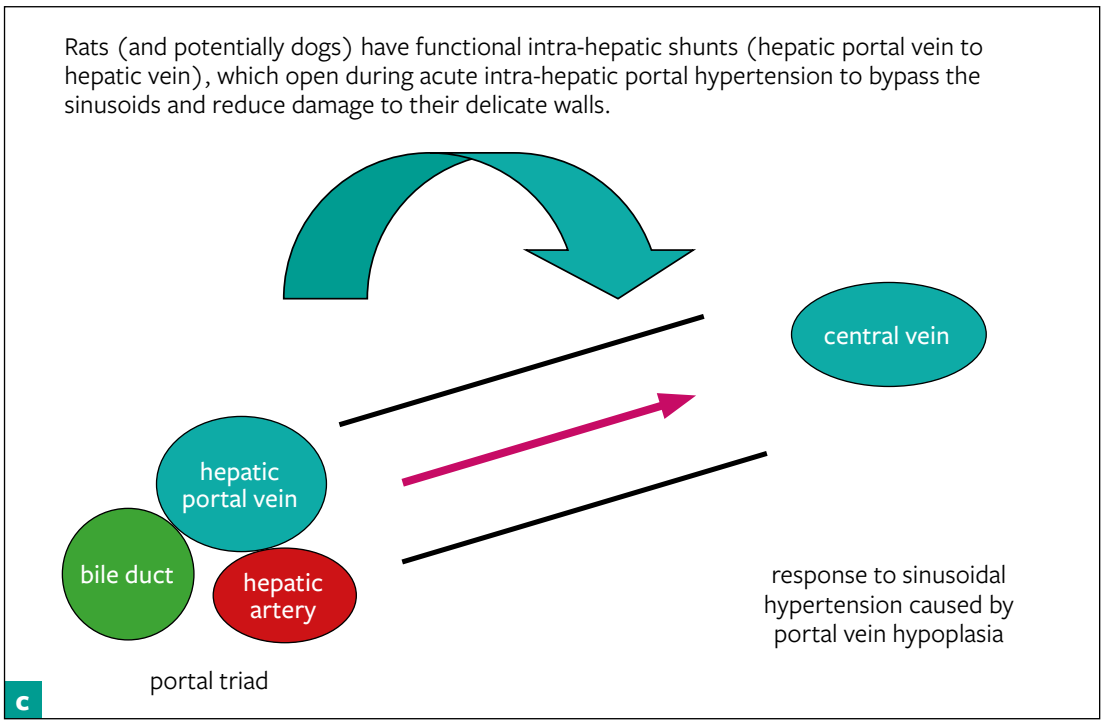



**Fig. 9-31** Diagrammatic representation of portal duct blood flow

**a** Portal blood flow. This figure shows a diagrammatic representation of normal hepatic portal blood flow.

**b** Portal vein hypoplasia. This figure shows a diagrammatic representation of a reduction of smaller portal vein branches.




**c** Portal vein hypoplasia. This figure shows a diagrammatic representation of the hypothetical shunting at the lobular level, which would reduce portal hypertension in dogs with portal vein hypoplasia and may explain why dogs with microvascular dysplasia do not show portal hypertension. Failure of this shunting would result in portal hypertension, as seen in dogs with non-cirrhotic portal hypertension.

ogy alone as the findings are very similar.[2] There are some clinical differences between these conditions, suggesting they may encompass a number of genetically or developmentally different conditions. It should be stressed that "portal vein hypoplasia" in this context refers to hypoplasia (i.e., lack of development) of the smaller branches of the portal veins within the liver rather than a lack of development of the extrahepatic portal vein.

### Portal vein hypoplasia in dogs

MVD is reported mostly in smaller breed dogs and is usually not associated with portal hypertension. Both American and Japanese studies report MVD more commonly in toy poodles, Yorkshire terriers, and papillons,[3,4] and one study in Japan found that MVD was the most common liver disease, accounting for 29% of all cases of liver disease at one institution.[5] An early study of a kindred of cairn terriers with MVD included dogs with CPSS, and test matings of affected dogs suggested an autosomal inheritance and a genetic and familial relationship between CPSS and MVD.[6] CPSS has also been reported to be inherited in cairn terriers.[7] In contrast to MVD, non-cirrhotic portal hypertension and portal vein hypoplasia (PVH) associated with portal hypertension are more often reported in large-breed dogs.[8,9]

**NOTE**

The histological appearances of MVD, PVH, and non-cirrhotic portal hypertension are very similar, with a lack of portal vein branches in smaller portal triads being the hallmark, hence the unifying term suggested by the WSAVA of "portal vein hypoplasia."

It has been proposed that the development of the portal venous system is interrupted, such that, instead of dividing into multiple parallel branches within the hepatic parenchyma similar to the branches of a tree, the division stops at the larger branches, resulting in a stunted pollard-tree like pattern (▶Fig. 9-31). The difference between the conditions summarized under the term "portal vein hypoplasia," if there is one, is largely related to the response of the liver and the presence or absence of portal hypertension. The portal vasculature is a large, parallel, low-resistance vascular system (like a tree with multiple branches), so portal pressure is usually low. A

reduction in portal vein branches, such as occurs with MVD, should result in portal hypertension due to a reduction in the number of parallel vessels and, thus, an increase in resistance in the portal vein (▶Fig. 9-31). It will also increase flow, and thus pressure, in the remaining portal vein branches, increasing pressure in the delicate sinusoids and risking damage to their walls with subsequent fibrosis. The fact that this does not happen in some dogs with PVH/MVD argues strongly for a form of intrahepatic shunting via vascular shunts from the portal vein to the hepatic vein, bypassing the sinusoids. This has been demonstrated to occur in other species as a protective mechanism against sudden increases in sinusoidal pressure. In contrast, in non-cirrhotic portal hypertension, it is assumed that these shunts are not functioning and hence lead to the development of portal hypertension.

The median age at diagnosis of PVH/MVD is approximately 3 years in most studies, ranging from 0.3–13 years. This is older than is typically seen with congenital PSS and probably reflects mild clinical signs and the fact that many cases are picked up incidentally during routine blood work.

**Clinical signs** vary depending on the presence or absence of portal hypertension and the degree of shunting. In one older study of cairn terriers with MVD, none of the affected dogs showed clinical signs,[6] and in another, more recent study of 28 dogs with PVH, 16/28 showed no clinical signs.[3] Cases are usually identified on routine blood work because of increases in serum/plasma liver enzyme activities and/or serum bile acids concentrations, which trigger further clinical investigation. In dogs that show clinical signs, neurological and gastrointestinal signs are most commonly reported, reflecting shunting of blood and portal hypertension.[3,4] Ascites is occasionally reported and more common in large-breed dogs.[8]

**Clinicopathological findings** are nonspecific. Dogs often have mild to moderately increased liver enzyme activities, although in some cases, the only abnormalities are increases in pre- and post-prandial serum bile acids concentrations. Affected dogs tend to have less marked increases in bile acids than dogs with CPSS, although there is some overlap.[6] Increases in serum/plasma bilirubin concentrations are not seen with PVH. Diagnostic imaging is often unremarkable: in cairn terriers with MVD, liver size was normal, whereas microhepatia has been seen in cairn terriers with CPSS.[6] In cases with portal hypertension, ascites, and multiple extrahepatic acquired portosystemic shunts can often be demonstrated on ultrasound.

Definitive diagnosis is made by a liver biopsy, combined with ruling out a single CPSS. Portal veins are often small or absent, with increased arterioles and abnormal lobular architecture. There is hepatic fibrosis in some animals.

**NOTE**

It is important to note that the histologic appearance of a liver biopsy taken from a dog with a CPSS cannot be differentiated from that of a dog with portal vein hypoplasia/microvascular dysplasia, and diagnosis of a CPSS requires visualization of a shunting vessel by imaging studies (▶Chap. 9.5.3.2).

In dogs with PVH/MVD, the changes can be patchy, with some liver lobes appearing more normal than others, whereas with CPSS, histological changes are uniform in all liver lobes. Inflammation is absent unless there is a concurrent disease process.

**Treatment** of PVH is symptomatic. It should be stressed that if a dog presents with no clinical signs and simply mild to moderately elevated serum bile acids concentrations, the disease should be considered an incidental finding, and changes in diet and other management are not necessary. PVH can be picked up incidentally when serum bile acids are measured on routine blood work. Importantly, invasive investigations, such as a liver biopsy, are difficult to justify in these dogs if there is a strong suspicion of PVH. If the animal has portal hypertension, symptomatic treatment could include spironolactone to reduce ascites and frequent feeding of small amounts of a highly digestible, high-quality protein diet, preferably soy- or dairy-based, such as a diet designed for dogs with GI disease. Overt protein reduction is not indicated in most dogs with hepatic encephalopathy because the main source of ammonia is glutamine metabolism by small intestinal enterocytes. Glutamine serves as the major energy source of small intestinal enterocytes. The observation of clinical signs of HE usually 1–2 hours after feeding coincides with small intestinal digestion and a burst of ammonia into the portal vein. When the patient is fed a diet with normal digestibility, no undigested protein will reach the colon for bacterial fermentation, and there is ample evidence in humans and dogs with experimental shunts that patients with PSS not only tolerate normal levels of dietary protein but may actually benefit from such diets by avoiding a negative nitrogen balance and protein malnutrition, which both themselves lead to release of ammonia from muscle and reduce the muscle mass,

thus reducing local ammonia detoxification by muscle.[10,11] In contrast to protein restriction, attention should be given to feeding small amounts frequently and addressing any known triggers of encephalopathy, such as inflammatory disease or hypokalemia.[12] Lactulose and antibiotics are rarely necessary in dogs with portal vein hypoplasia because the clinical signs are often less pronounced than in patients with CPSS. The long-term prognosis is good in these dogs, with most studies reporting dogs living 5 years or longer after the time of diagnosis.[3,4,6]

### Portal vein hypoplasia in cats

Portal vein hypoplasia is very rare in cats and has only been reported in three cases: a Birman, a Scottish fold, and a domestic short-haired cat. Clinical signs consistent with hepatic encephalopathy, including increased salivation, were described, and imaging showed multiple acquired shunts in the absence of ascites in one cat, which responded well to long-term management with a commercial "liver" diet, lactulose, and metronidazole.[13]

#### 9.5.6.2.3 Intrahepatic arteriovenous fistula/malformation

Intrahepatic arteriovenous fistula, or malformation, describes a direct communication between a branch of the hepatic artery and the hepatic portal vein. In most cases in dogs, this condition is congenital, although it can be acquired secondary to trauma or neoplasia. As would be expected, the fistula results in a marked increase in portal pressure with portal hypertension, which in turn is responsible for the clinical signs of the disease. In the largest published case series of 20 dogs, a variety of breeds were affected, and the mean age at diagnosis was 9.7 months with a range of 1–37 months.[14]

Clinical signs reported included ascites, diarrhea, vomiting, lethargy, polydipsia/polyuria, reduced size compared with litter mates, and hepatic encephalopathy. Pre- and post-prandial serum bile acids concentrations were usually markedly increased, consistent with acquired portosystemic shunting. Also, mild to moderate increases in serum/plasma liver enzyme activities were reported. Changes in portal vein blood flow were evident on ultrasonography with pulsatile flow, increased size of the portal vein, and reversal of flow. However, in less than half of the dogs, an aneurysm could be identified. CT angiography is necessary for diagnosis in some cases. Reported treatments include surgical liver lobectomy or closure of the fistula with glue and coils by interventional radiology.[14,15]

#### 9.5.6.3 Ductal plate abnormalities

The ductal plate is the embryonic precursor of the interlobular and intralobular bile ducts. It is made up of a double layer of embryonic epithelium surrounding the portal veins. Bile duct development involves many signaling molecules, and abnormalities result in a wide variety of presentations in both human and veterinary patients, with persistence of embryonic bile ducts and varying amounts of periportal fibrosis. The drivers of fibrosis in this context remain incompletely understood, but it appears that immature bile ducts persisting into adulthood produce pro-fibrotic substances. There are a variety of genetic mutations involved in humans, many of them being reported to be autosomal dominant, and affected individuals may have concurrent renal cysts or skeletal abnormalities.[16,17] The disease phenotype in the liver depends on which bile ducts are affected. A maturation arrest of small interlobular bile ducts results in **congenital hepatic fibrosis,** whereas a maturation arrest of medium-sized intrahepatic bile ducts results in **Caroli's disease**. The genetics of ductal plate anomalies are currently unknown in dogs.

#### 9.5.6.3.1 Congenital hepatic fibrosis

Congenital hepatic fibrosis (CHF) is a form of ductal plate disease associated with multiple tiny immature bile ducts and fibrosis that, at least in the past, has been more commonly diagnosed in cats than in dogs, although it remains uncommon in both species. In the first trimester of gestation, the developing portal area contains multiple small bile ducts that are replaced by one or two mature bile ducts later during gestation. In patients with CHF, multiple immature bile ducts persist.[17] In some cases, this is combined with portal vein hypoplasia. Congenital hepatic fibrosis should be considered in any cat with marked hepatic fibrosis in the absence of a fluke infection. In some cats, there is an association with polycystic kidney disease.[18] The first report of CHF in a dog was published in 2010.[19] Additional reports have been sparse since this time, but it is likely that the disease is under-recognized as a number of affected dogs may be miss-diagnosed on histology as having portal fibrosis, cirrhosis, chronic hepatitis, or cholangitis.[20] Such misdiagnosis may, unfortunately, lead to euthanasia because of a perceived poor prognosis, whereas, in fact, many dogs with ductal plate abnormalities can live long and happy lives if appropriately managed, probably because the disease is patchy and non-progressive. Increased reporting of the disease should help improve recognition. A recent report of CHF in 30 boxer dogs from the histology archive at Cornell University suggests an increased prevalence in

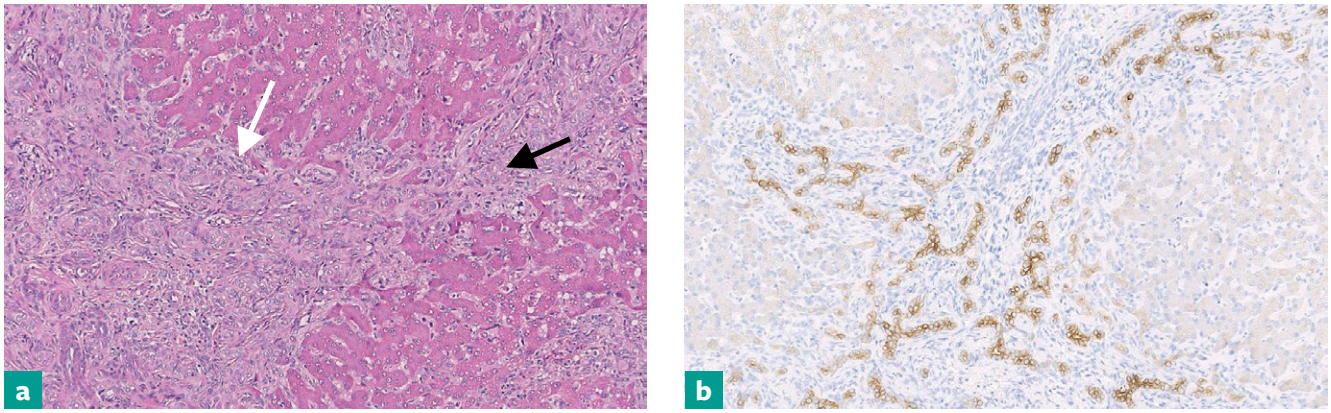



**Fig. 9-32** Portal vein hypoplasia and congenital hepatic fibrosis

**a** Histological section of liver from a 6-month-old Staffordshire bull terrier with congenital hepatic fibrosis and portal vein hypoplasia. The dog presented with a 2-week history of lethargy and inappetence. Note a marked increase in collagen in the portal areas and bridging between them (**white arrow**) and multiple small bile ducts (**black arrow**). There are no obvious portal vein profiles and very few inflammatory cells. (Hematoxylin and eosin stain; courtesy of the Pathology Department, Department of Veterinary Medicine, University of Cambridge.)

**b** Histological section from the same liver as ▶Fig. 9-32a. Immunohistochemistry for cytokeratin makes the numerous bile ducts clearly visible (light brown stain). (Dako monoclonal mouse anti-human cytokeratin clone MNF116. Courtesy of the Pathology Department, Department of Veterinary Medicine, University of Cambridge.)

this breed.[20] Interestingly, there was a high prevalence of concurrent congenital hepatic abnormalities: three dogs also had gallbladder atresia, one had an intrahepatic CPSS, and one had a complex intrahepatic arterio-venous malformation. Two dogs also had Caroli's disease, but no dog had evidence of cysts in the liver, pancreas, or kidney. A third of the dogs in this study also had a significant accumulation of copper in the liver, although the reason for this finding is unclear, and hepatic copper accumulation was potentially due to increased dietary copper.

### Clinical presentation

The two case series of canine CHF in the literature describe dogs presenting with a median age of 1.5 years with a range from 3 months to 10 years old.[19,20] Affected dogs are not always diagnosed when young, which again stresses the importance of differentiating this relatively benign disease from end-stage chronic hepatitis and cirrhosis. Clinical signs usually reflect portal hypertension, with gastrointestinal signs predominating and ascites and acquired portosystemic shunts identified in one-third to half of the cases. Routine blood work shows increased liver enzyme activities and increased serum concentrations of pre- and post-prandial bile acids, but jaundice and elevation in bilirubin are rare. Diagnostic imaging usually shows a small liver, although hepatic size can also be normal. Portal hypertension and multiple acquired portosystemic shunts may also be found on ultrasound.

### Diagnosis

Diagnosis is made based on a liver biopsy (▶Fig. 9-32), which shows a non-inflammatory marked porto-portal fibrosis containing multiple immature bile ducts with cuboidal epithelium. Portal triads are abnormal in shape with multiple abnormal bile ducts and often concurrent portal vein hypoplasia. The marked fibrosis can be misdiagnosed as cirrhosis by an inexperienced pathologist. Cytokeratin staining to highlight the biliary hyperplasia can help confirm the diagnosis, together with a lack of inflammation (unless there is a secondary biliary tract infection) and usually normal hepatic lobular structure without hepatocyte necrosis or apoptosis.

### Treatment and prognosis

Treatment is symptomatic for portal hypertension, ascites, and encephalopathy as necessary and as described for portal vein hypoplasia. Prognosis is reported to be good, much better than with end-stage chronic hepatitis with cirrhosis, with affected boxers showing median survival times of 7.5 years with acquired portosystemic shunts and 8.8 years without them.

#### 9.5.6.3.2 Caroli's disease

Caroli's disease is a congenital marked dilation of intra- and extrahepatic bile ducts, often associated with renal cysts and reported most often in dogs.[21–25] Histologically, large, dilated

bile ducts and marked periportal, and often, bridging fibrosis can be seen, which explains why affected animals can present with portal hypertension. Unlike CHF, where the biliary hyperplasia is microscopic, in Caroli's disease, the intrahepatic biliary cysts are visible on ultrasound and CT and are often calcified. Extrahepatic biliary obstruction should be ruled out as a cause of biliary dilation. The gallbladder appears normal in most cases. A variety of dog breeds can be affected. A report in two affected golden retriever littermates suggested an inherited cause, but this condition has otherwise not been frequently reported in this breed.[23]

Clinical signs reported include vomiting, polyuria/polydipsia, and anorexia. Ascites is also common, which is consistent with portal hypertension. Serum activity of alkaline phosphatase has been reported to be increased in all cases but that of alanine aminotransferase only in about 50% of the cases. The prognosis is unclear since most of the published cases were euthanized upon first presentation.

Caroli's disease has only been reported in one cat, a 4-month-old Russian blue, with a concurrent congenital portosystemic shunt.[24] Cholodochal cysts (cystic dilations of the common bile duct) are more commonly seen in cats. They are usually diagnosed in adult cats, but it is unclear if they are congenital or acquired.[25]

#### 9.5.6.4 Gross anatomical disorders

Gross anatomical disorders, such as liver lobe agenesis, gallbladder agenesis, duplex gallbladder, or midline defects, have been described in both dogs and cats, but these conditions are rather rare in either species. They are usually reported concurrently with more common congenital disorders such as ductal plate abnormalities.[20]

**KEY FACTS**

- The most common congenital vascular disorder recognized in dogs and cats is a congenital portosystemic shunt.
- Portal venous hypoperfusion can be caused by portosystemic shunts, portal vein hypoplasia/microvascular dysplasia, or non-cirrhotic portal hypertension.
- Ductal plate malformations are under-recognized developmental conditions with variable phenotypes (including congenital hepatic fibrosis and Caroli's disease).
- Ductal plate abnormalities are diagnosed by histological assessment of liver tissue. They may be misdiagnosed as other conditions, such as cirrhosis.

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
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## 9.5.7 Neoplasms of the liver

Brandan Wustefeld-Janssens, Emma Warry

### 9.5.7.1 Introduction

The prevalence of primary hepatic neoplasia in dogs and cats is low. In early reports, the prevalence of neoplasia of the liver and biliary system in dogs was quoted as 0.6–1.3%[1] and 1.5–2.3% in cats.[2] Recent large epidemiological studies based in Europe and Japan confirmed these numbers.[3–7] It is very common for older dogs to develop non-neoplastic nodules in the liver, representing nodular hyperplasia or regenerative nodules. The former has no sex or breed predilection, but a major factor in development is age. These nodules first appear by 6–8 years of age, and it is estimated that by 14 years, between 70–100% of dogs will have these.[8,9] The pathogenesis is unknown, and there is no link between liver injury and regeneration or future progression of hyperplastic nodules to a neoplastic tumor. In contrast, regenerative nodules occur in response to significant liver parenchymal injury and represent a compensatory proliferation of viable hepatocytes. The lesion pattern is distinct and is an important differential diagnosis for hepatic adenoma, especially in small sample-size biopsies.[10] The liver is a predilection organ for metastatic disease, most commonly from other areas of the gastrointestinal tract, spleen, and pancreas.

In dogs, metastatic lesions within the liver are diagnosed 2.5 times more often than primary tumors. When a primary liver tumor is diagnosed, it is more likely to be malignant in dogs.

In cats, primary liver tumors are more common than metastatic lesions, and primary tumors are most likely benign.[10–12]

Liver tumors are subtyped according to the tissue of origin. These are hepatocellular, bile duct, mesenchymal, or neuroendocrine tumors (NET). Within these groups, tumors are

further classified into three forms according to their morphology: massive, nodular, and diffuse. The massive morphology is defined as a single relatively large tumor affecting a single liver lobe. Nodular morphology tumors are multifocal, affecting two or more lobes, while diffuse tumors have a multifocal pattern but affect all liver lobes, and the lesions may coalesce or diffusely efface normal liver parenchyma.[12] Outcomes are generally better for massive morphology tumors because the biology tends to be more favorable, and the tumors are amenable to surgical resection.

#### 9.5.7.2 Clinical presentation

Generally, there are no definitive breed or sex predispositions to hepatic neoplasia. Dogs presenting with a malignant hepatocellular tumor tend to be older (>10 years), and there is considerable overlap with the increasing incidence of nodular hyperplasia. Dogs with NETs generally are younger than 10 years of age.[1]

Presenting complaints may be vague and nonspecific, including lethargy, anorexia, vomiting, diarrhea, weight loss, polyuria, polydipsia, and ascites.[1,2,11,13–16] Weakness and collapse may be the predominant clinical signs secondary to tumor rupture and hemoperitoneum.[17,18] Symptomatic animals have a higher risk of malignant disease, but this is not specific to tumor type. More specific clinical signs related to hepatic disease (e.g., hepatomegaly, icterus) are also seen. Icterus is common with extrahepatic biliary tumors or diffuse NETs. A palpable mass in the cranial abdomen is reportedly being found in up to 75% of dogs and cats with liver tumors, but given the anatomic position of the liver, the absence of a palpable mass should not be used to exclude the presence of one, and the morphology may be nodular or diffuse.[1,2,11,13,15,16,19–22] Cats with hepatocellular carcinoma (HCC) or biliary carcinoma can have alopecia.[23]

#### 9.5.7.3 Diagnosis

Abnormal blood test findings are common in dogs and cats with liver tumors but also are not specific. The majority of cases will present with anemia (57%), which tends to be mild and nonregenerative. Leukocytosis with neutrophilia is very common in dogs (90%) but less so in cats. The theory behind the increase in white cell counts is secondary inflammation and necrosis in large tumors.[1,16] Many theories have been postulated to explain the anemia, including chronic disease, sequestration, iron deficiency, and/or microangiopathic destruction. Changes to platelet counts are variable and, depending on the biology of the tumor and clinical course, can be increased or decreased. In a study of dogs with massive morphology HCC, 46% of cases had thrombocytosis.[16] Serum liver enzyme activities are frequently increased in dogs and cats with hepatic tumors. These changes are nonspecific, nor have ratios or combinations of serum liver enzyme abnormalities been shown to reliably predict malignancy or outcome. In early reports, up to 20% of dogs with a hepatic neoplasia had hyperbilirubinemia.[1]

Diagnostic imaging of hepatic tumors is an area of interest in human and veterinary medicine. It is well accepted that tomographic imaging is required to determine the extent of disease, liver lobes or divisions involved (tumor morphology), patency of the biliary system, abnormalities in regional lymph nodes, and other changes indicating extrahepatic metastatic disease. The gold standard in veterinary medicine is dynamic computed tomography (CT), where aberrant tumor vascularization in relation to normal liver parenchyma can be leveraged to delineate the lesion. B-mode and contrast-enhanced ultrasound are highly specific for identifying single massive-morphology tumors and correctly assigning them to a division.[24,25] However, this is not a reliable method on its own to predict histologic subtypes.[26] When combining clinical data such as the presence of thrombocytosis and maximal lesion diameter >4 cm with the finding of heterogenous echogenicity of the tumor, the sensitivity, specificity, and diagnostic accuracy in identifying malignant hepatic lesions were 89%, 78%, and 85%, respectively.[27]

Correctly predicting the lobe or division single massive-morphology tumors are arising from is important in clinical decision-making. The division affected is directly related to the complexity of surgical excision and the risk of intra-operative complications. Two studies using pre- and post-contrast CT images found the accuracy of correctly predicting the division from which the tumor arises was 84% and 93%, respectively.[25,28] The latter study found the use of the hepatic lobar vein or portal vein branch adjacent to the tumor to correlate highly with the lobe the tumor arose from.[28] Several studies focused on the usefulness of dynamic CT in predicting benign vs. malignant disease. Heterogenous attenuation in the delayed venous phase was an independent predictor of malignant disease (OR 14.7), and when combined with a lesion size >4.5 cm, the accuracy was 87%.[29] Similarly, using the lowest absolute delayed contrast enhancement of the tumor was 91% accurate for malignant disease if the Hounsfield units (HU) were <37.[30]

The clinical utility of liver cytology or biopsy in massive-morphology primary liver tumors is, in the authors' opinion, uncertain. In certain clinical scenarios, having a cytologic or histologic diagnosis is an important step in decision-making. Guidelines have been published describing the indications and contraindications for liver biopsy, and care-

ful patient selection should be made by the clinician.[31] The agreement of cytology collected by fine-needle aspiration and the final histopathologic diagnosis is low. In one study, the agreement between cytology and histopathology samples for the same general disease process (e.g., inflammation or neoplasia) was 30% in dogs and 51% in cats.[32] However, cytology remains a very useful diagnostic tool for diagnosis of infiltrative disease (e.g., lymphoma, mast cell tumor) or diffuse-morphology primary liver tumors (e.g., NETs). Generally, the risk appears low even in liver cancer patients, with an overall risk of short-term technique-related complications between 0–6%.[33,34] Dogs that have prolonged prothrombin times, cats that have activated thromboplastin times >1.5 times the baseline, and any patients with hypofibrinogenemia (50% of baseline), platelet dysfunction, or platelet counts <80,000 cells/µL are at an increased risk for biopsy-related complications.[34–36]

#### 9.5.7.4 Staging

Staging tests are recommended in all cases with hepatic neoplasia and consist of a complete blood cell count (CBC), serum biochemistry profile, urinalysis, and thoracic and abdominal diagnostic imaging. Keeping in mind that it is common for hepatic neoplasia to represent metastatic disease from another organ system, this systematic approach is warranted. Predilection sites for metastasis are commonly regional lymph nodes, lungs, and peritoneum, and less commonly, the kidneys, adrenal glands, and intestine.[1] Extrahepatic metastatic disease for the most common primary liver tumor, massive-morphology HCC, at presentation is rare. In two case series of massive-morphology HCC totaling 85 dogs, no dogs were found to have metastatic disease at presentation.[16,37] In a study of central-division liver lobectomy surgical outcomes, two of 35 dogs (5.7%) with massive-morphology HCC had metastatic disease at presentation.[38] In another study of canine liver tumors, of the 57 HCCs, 30 (57%) were massive, 14 (25%) nodular, and five (9%) diffuse in morphology. The metastatic rate was 61% overall for HCC, with no further breakdown by morphology subtype. The same study included 15 primary liver NETs and 14 sarcomas. The majority of NETs were diffuse in morphology (five nodular and ten diffuse), and most sarcomas were nodular (nine nodular and five massive). The metastatic rate was 93% for NETs and 86% for sarcomas.[1] Therefore, clinical staging of massive-morphology hepatic tumors tends to be a low-yield test, but finding metastatic disease at presentation for nodular and diffuse tumors is common.

#### 9.5.7.5 Treatment and prognosis

Surgical resection is the preferred treatment in massive-morphology primary liver tumors. The overall survival rate for 118 dogs that underwent liver lobectomy, independent of tumor type, was 77%, with 75% of the dogs surviving to 1,336 days.[39] The tumors in this study were mostly epithelial in origin (HCC: 61%, hepatocellular adenoma: 22%), followed by mesenchymal tumors (hemangiosarcoma: 5%, fibrosarcoma: 2%, leiomyosarcoma: 1%). Most tumors were massive in morphology (81%), with the remainder having two tumors of the same histotype in two different lobes. The majority of literature on surgical treatment of hepatic tumors in dogs report outcomes for massive-morphology HCC. In a study of 48 dogs, 42 had surgical resection of their tumor compared with six that had a diagnostic biopsy only.[16] The median survival time (MST) was not met in the surgery group, with more than half of the dogs alive at 1,460 days. In comparison, the MST for the dogs not undergoing resection was 270 days. Additionally, no statistical difference in MST between dogs with a complete histologic resection versus those with incomplete histologic resection was found. However, with only four dogs in the incomplete resection group, this may be more indicative of the indolent nature of the tumor type than the effectiveness of histologic margins. In another study, the impact of histologic margins on overall survival (OS) and progression-free survival (PFS) was evaluated in 37 dogs with surgical resection of massive-morphology HCC.[37] Completeness of excision was determined from histology reports and defined as incomplete with neoplastic cells present at the surgeon-cut margin and complete with no such cells regardless of distance. Again, case numbers were small, with twelve dogs in the incomplete margin and 25 dogs in the complete margin group. Nevertheless, the results contrast those by Liptak et al. (2004), where PFS (1,000 vs. 521 days) and OS (>1,836 vs. 765 days) were significantly improved if a complete resection was achieved. This warrants further study, but a consistent finding is that most dogs with massive-morphology HCC will have a relatively indolent disease course, and outcomes can be very good regardless of histologic margin if surgical resection is undertaken. Progression rates (local recurrence and/or metastatic disease) range between 12–58%[37] with low rates of surgical complications.[16,38]

There is very limited outcome information on primary liver sarcomas and NETs.[1,20] In a study of 15 dogs with primary liver NETs, all liver lobes were involved in all cases, and in 14 dogs, the disease extended to include the mesentery, peritoneum, and lymph nodes. No survival data was available from this study.

#### 9.5.7.5.1 Surgical considerations

Assessment of patients for surgery involves assessment of resectability and prediction of surgical risk. As part of this assessment, general considerations include:

1. Evaluation of tumor extent
2. Surgical planning based on anatomy
3. Evaluation of functional reserve of the future liver remnant
4. Pre-operative management strategies to reduce risk and increase the probability of complete resection

Determining the tumor extent is achieved through staging and abdominal exploration during the surgical procedure. In veterinary medicine, the gold standard imaging modality is multiphasic CT scanning that includes pre-contrast, arterial, portal, and delayed venous phases. This takes advantage of tumor perfusion being arterial dominant compared with normal liver, which is portal vein dominant. Surgical planning is done on an anatomic basis and, in the most basic form, is achieved by assigning the tumor to a division of the liver based on major blood vessel anatomy and lobulation.[25,28] This informs the surgeon of what approach to take, the extent of dissection, and potential risk of resection. Generally, right-division tumors have a higher risk of intra-operative complications due to the proximity to the caudal *vena cava*.[12] In small animals, functional liver remnant (FLR) and regenerative capacity evaluation are not as critical as in people but are important factors in postoperative morbidity and outcome. In people, some aspects of the disease and overall therapeutic plan are incorporated to calculate the FLR required post-resection. For example, 20% is the accepted minimum FLR required, but if a person is to undergo postoperative chemotherapy, a minimum of 30% is required, or if cirrhosis is present, 40% is required.[40] Similar to people, dogs have a remarkable capacity for liver regeneration. Healthy dogs can lose up to 65–70% of their functional liver volume acutely with no ill effect,[41] but most dogs will not tolerate an 80% loss. The survival rate at 7 days was 28% in dogs with 80% of their livers removed in a study, and post-hepatectomy portal pressures >16 mmHg were predictive of poor outcomes.[42] Liver regeneration begins within hours of resection and peaks at 3 days. Remarkably near-complete liver hypertrophy and hyperplasia are seen on average 6 days after a 70% hepatectomy.[43] Factors known to reduce the regenerative capacity of the liver are biliary obstruction, diabetes mellitus, malnutrition, male gender, and advanced age.[44,45]

#### 9.5.7.5.2 Alternative therapies

Alternative therapies explored in veterinary medicine include transarterial chemoembolization (TACE, ▶Fig. 9-33), stereotactic body radiation therapy (SBRT), percutaneous tumor ablation (e.g., microwave ablation), and chemotherapy.

**Transarterial chemoembolization (TACE)** offers a minimally invasive approach that selectively delivers chemotherapy to the tumor at concentrations of 10–50 times that of chemotherapy delivered systemically.[46] Chemotherapy combined with particle embolization induces tumor cell necrosis and cessation of chemotherapy excretion by the tumor cells, reducing the systemic concentrations and associated risk for toxicity.[47] The expectation with this therapy is palliation and in some cases cytoreduction. Another interesting application with this technique, albeit without chemotherapy, is to selectively embolize the portal flow to the division of the liver to be resected, with subsequent hyperplasia and hypertrophy of the proposed liver remnant. This is likely driven by the process known as hepatic arte-

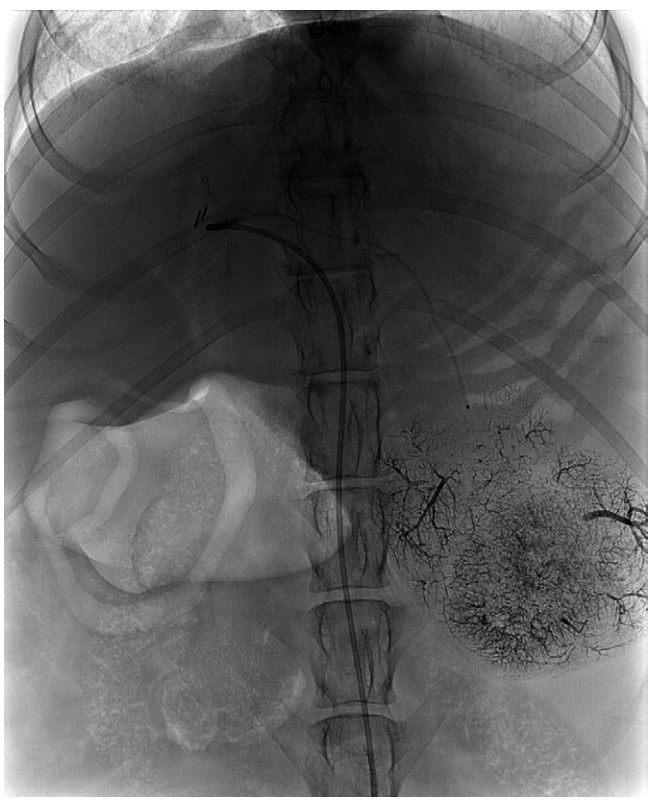


**Fig. 9-33** A ventrodorsal fluoroscopy image following the transarterial chemoembolization (TACE) procedure of a left lateral massive morphology hepatocellular carcinoma

The embolic agents used were mitoxantrone, ethiodized oil, and Embospheres®.

rial buffer response, whereby disrupting the portal flow to a segment of the liver, the arterial flow is dramatically increased and induces compensatory regeneration. The process is thought to be mediated by reduced clearance of adenosine and allows surgeons to remove more liver volume than would otherwise be considered risky.[44,48,49] This concept was demonstrated in a dog, where repeated hepatectomy allowed 95% resection of the original liver volume and only the native papillary process remaining without complications related to an inadequate FLR.[50]

**Radiation therapy** is rarely reported in dogs in a clinical setting. However, with the increasing use of SBRT in veterinary medicine, renewed interest in treating liver tumors has ensued. The advantage of SBRT is a relatively sharp dose drop-off between tumor and normal tissue, sparing the volume of normal tissue included in the radiation field while allowing larger doses per fraction.[51] This allows higher doses to be delivered in a short period of time with theoretically less acute toxicity. An important complication of using radiation to treat liver lesions is radiation-induced liver disease (RILD), and, in theory, highly conformal treatment strategies will mitigate this risk.[52] In a case series of 6 dogs treated with 3D-conformal radiation therapy (3D-CRT), only one dog experienced non-classic RILD, defined as an increase in serum alanine aminotransferase (ALT) activity 5 times above the reference interval or pre-treatment level.[53] This dog, however, did not exhibit any clinical signs, had a tumor volume reduction of 40%, and was alive at 1,057 days. Using RECIST (response evaluation criteria in solid tumors version 1.1.) criteria,[58] five of the six dogs had a partial response, and the remaining dog had stable disease.[54] Median survival time was 567 days (range 281–1,057 days) overall, which is slightly improved from symptomatic treatment alone (MST 270 days).[16,52] This treatment option needs further investigation and clinical trials before a definitive conclusion on efficacy can be made.

**Chemotherapy** for liver cancer in dogs has largely been unsuccessful. Few studies have reported the efficacy of cytotoxic chemotherapy agents specifically in HCC, and dogs with HCC have been included in phase 1 studies.[55,56] With single-agent gemcitabine, MST for dogs treated in a gross disease setting was 197 days, whereas dogs with incomplete resection or with massive or nodular tumor morphology had an MST of 1,339 days.[56] In an open-label study evaluating the efficacy of mitoxantrone, one of four dogs (25%) that were treated had a partial response with more than 50% reduction in size.[55] In another study, seven dogs were treated with the multi-kinase inhibitor sorafenib.[57] Sorafenib targets and inhibits Raf kinase, VEGF receptors 1, 2, and 3, and $PDGF_{\beta}$ and is the only FDA-approved first-line treatment option for people with advanced HCC.[58] Using RECIST criteria,[59] three dogs had a partial response consisting of a reduction in liver lesion size (n = 3), resolution of malignant effusion (n = 2), and reduction of lung nodules (n = 1). The response rate was 57%, and the rate of disease control was 100%.[58] This agent shows promise and requires larger studies before being recommended as a frontline drug in dogs. No chemotherapy studies in cats for malignant primary liver tumors have been published.

### References

The complete list of references for this chapter can be downloaded from vetline.de:
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## 9.6 Diseases of the biliary tract

### 9.6.1 Extrahepatic biliary obstruction

Vanna Dickerson, Kelley Thieman Mankin

#### 9.6.1.1 Introduction

Extrahepatic bile duct obstruction (EHBO) refers to an obstruction of the biliary system outside of the hepatic biliary tree and can be further classified into intraluminal and extraluminal causes. Extraluminal causes include pancreatitis (▶Chap. 10.3.1), pancreatic abscessation, biliary neoplasia (▶Chap. 9.6.6), or neoplasia of any surrounding organ, which applies pressure to the biliary tree, congenital malformations, or herniation.[1] Intraluminal causes include mucocele formation (▶Chap. 9.6.2), cholelithiasis (▶Chap. 9.6.4), inspissated bile, or neoplasia.[1]

The most common cause of extraluminal EHBO in veterinary patients is pancreatitis, either due to secondary scar tissue formation surrounding the common bile duct or compression from actively inflamed pancreatic tissue.[1] Extraluminal EHBO of any etiology typically should not be treated with cholecystectomy. Removing the gallbladder will not relieve the extraluminal obstruction and may be detrimental to the patient as the biliary system will remain obstructed. Surgical management is typically aimed at either removing the source of extraluminal obstruction or, more commonly, at providing a bypass to the common bile duct (either temporarily or permanently).

#### 9.6.1.2 Non-surgical management

In animals in which EHBO is suspected to be secondary to a reversible etiology, such as acute pancreatitis, intervention to resolve the obstruction may not be necessary. When needed, ultrasound-guided cholecystocentesis (PUC) can be attempted before committing to surgical intervention. Selecting the case for which PUC is appropriate is challenging and not well-defined in the current literature. In a study evaluating 201 dogs and 51 cats who underwent PUC to treat various causes of EHBO, major complications occurred following 3% of the procedures. These included two cases of bile peritonitis and three cases of cardiac arrest under anesthesia.[2] Though bile is typically sterile, 21% of 294 animals with bile cultures performed in this study were culture positive. This highlights that, while bile peritonitis seems to be an uncommon complication related to PUC, it must be considered a risk, given the implications to the patient.

#### 9.6.1.3 Surgical management

##### 9.6.1.3.1 Cholecystostomy tube

Relief of EHBO can be achieved with the use of a cholecystostomy tube. These tubes can be placed using an open ventral midline approach, a right lateral paracostal incision, or laparoscopic guidance. Ultrasound-guided placement has been described, but difficulty advancing the catheter over the trocar once the gallbladder has been punctured makes its use less reliable than surgical placement.[3]

The theoretical benefit of a cholecystostomy tube is the ability to efficiently and continuously relieve EHBO. The tube can be left in place for several weeks, if necessary, to allow recovery of the pancreas in cases of acute pancreatitis or in cases where definitive surgery will be indicated to allow recovery of liver function, improved nutritional status, and reduction in anesthetic risk.[3] Successful completion of a cholecystoenterostomy procedure after a cholecystostomy tube has been in place has been reported.[3] However, there is no literature supporting any survival benefits gained by using of a cholecystostomy tube to delay definitive surgery.

###### Techniques

In an open procedure, a **standard midline abdominal approach** is made, and the abdomen is explored. The gallbladder should be carefully inspected, as the wall of the gallbladder must be healthy enough to hold the catheter. After abdominal exploration, a small stab incision is made ventral to the last rib on the right lateral body wall. The stab incision should be just large enough to accept the catheter being used. Locking pigtail catheters with an internal trocar are often used, given the ease of placement.[3] However, the use of a Foley catheter is also described.[4] Typically, an 8–10-French catheter is used. If a pigtail catheter is used, the catheter with a trocar is inserted from the cutaneous stab incision into the peritoneal cavity. The tube can be introduced through a single layer of omentum before inserting it into the gallbladder to assist with the formation of a seal and prevention of bile leakage,[4] although omental adhesions will occur regardless of whether this step is taken or not. The catheter can also be placed through hepatic parenchyma before entering the gallbladder. However, this can make positioning more difficult and may prevent placing a purse string suture in the gallbladder when needed.[1] With non-locking loop catheter types, a purse string suture is placed in the gallbladder with 3–0 monofilament absorbable suture where the catheter will enter. The catheter is then inserted through the center of the purse string. This step is performed to help prevent bile leakage. If a Foley catheter is used, the balloon is then instilled with saline. If a pigtail catheter is used, the straight trocar is removed, and the string is pulled to engage the loop. The string and loop are then locked in place with the cap. The catheter is secured to the skin with a finger trap suture using a non-absorbable suture.

Alternatively, the procedure can be performed in an **open approach through a smaller paracostal incision**.[4] The surgical approach is similar to that used for a grid gastropexy.[5] Briefly, a 4–5 cm vertical skin incision is made caudal and ventral to the last rib on the right side. For a grid approach, blunt dissection in the direction of the fibers of the external abdominal oblique, internal abdominal oblique, and transversus abdominus muscles is performed, and the peritoneum is punctured and opened. Alternatively, the muscles can be sharply incised in the direction of the original incision. A Gelpi retractor can be used in the incision to improve visualization. The gallbladder is carefully grasped with Babcock forceps, and the catheter of choice is placed as described above. The catheter should exit the body wall through a separate stab incision rather than the primary paracostal incision and be secured with a finger trap suture. The paracostal incision is closed routinely, ensuring each muscle layer is re-apposed before closing the subcutis and skin. This technique may be a useful option in animals in which full abdominal exploration is not necessary, but laparoscopic equipment is not available. Because of the smaller incision size, it may be possible to perform the procedure with less morbidity than through a typical ventral midline incision.

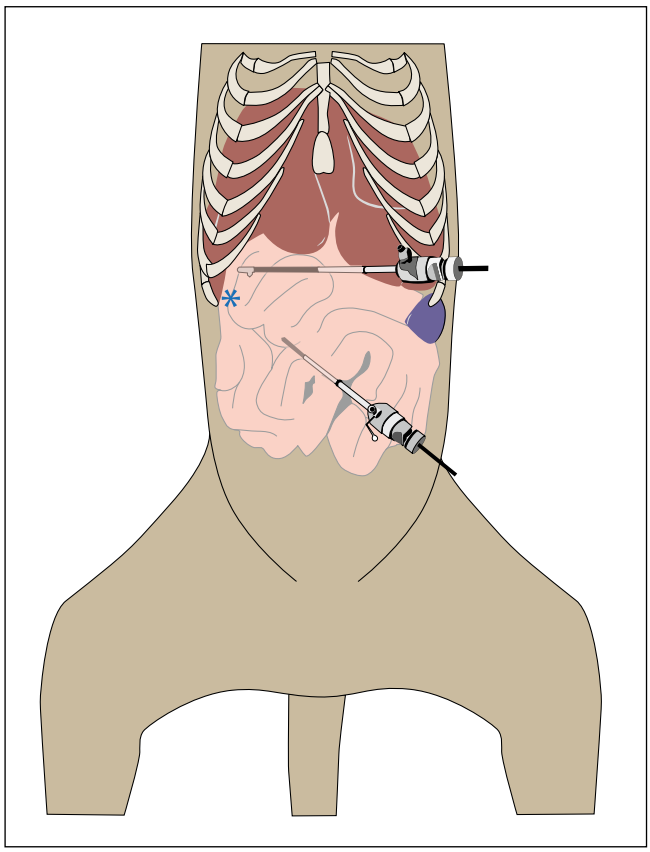


**Fig. 9-34** Laparoscopic cholecystostomy tube placement

The patient is placed in dorsal recumbency. A standard sub-umbilical camera port is established. An instrument port is established approximately 4 cm caudal to the xiphoid process, slightly lateral to the midline. The **asterisk** depicts the approximate location for entry of the cholecystostomy catheter.

(Image produced by VeLisa Bayer, Texas A&M University.)

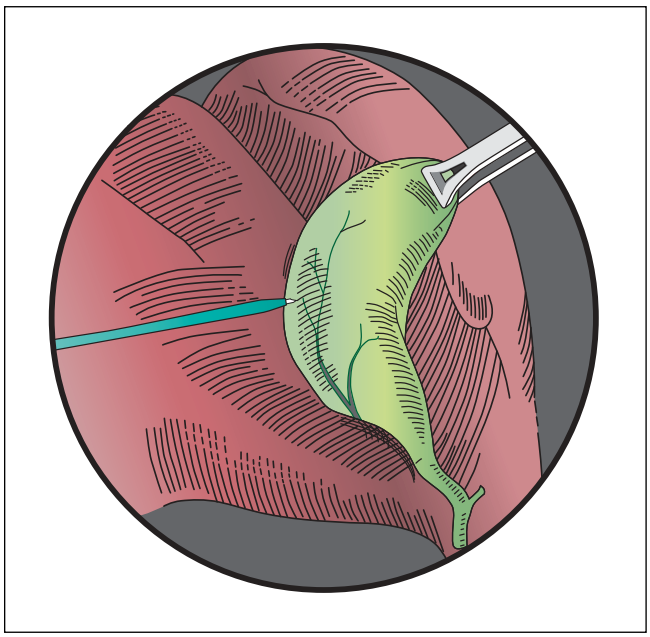


**Fig. 9-35** Once the gallbladder has been grasped with laparoscopic Babcock forceps, the cholecystostomy catheter with trocar is inserted through the body wall and into the gallbladder, 1–2 cm craniodorsal to the Babcock forceps.

(Image produced by VeLisa Bayer, Texas A&M University.)

Finally, the procedure can be performed with **laparoscopic guidance**. Similar to the paracostal approach, this procedure is desirable in patients where a full abdominal exploration is not deemed necessary, and biliary drainage needs to be established as quickly as possible. Given the unstable nature of most patients undergoing this procedure, it is preferred to set up the surgical table, including all laparoscopic equipment, and ensure it is functioning properly before the patient arrives in the operating room. The patient is placed in dorsal recumbency. A camera port is established routinely in a sub-umbilical position, and the abdomen is insufflated with $CO_2$ (▶Fig. 9-34). The abdomen can be explored as needed, with particular attention given to the appearance of the gallbladder. A second instrument port is then established, approximately 4 cm caudal to the xiphoid proces, and slightly lateral to midline to avoid the falciform fat.[3] A 5 mm laparoscopic Babcock forceps is inserted through the instrument portal and used to grasp and stabilize the caudal aspect of the fundus of the gallbladder. The camera is used to visualize the right side of the body wall to identify the site of entry of the catheter, which should be just caudal to the insertion of the diaphragm. A small (2–3 mm) stab incision is made if needed, and a locking loop pigtail catheter with a straight trocar is introduced into the peritoneal cavity under direct visualization with the laparoscope. The sharp trocar is inserted into the gallbladder, 1–2 cm craniodorsal to the Babcock forceps stabilizing it (▶Fig. 9-35).[3] The trocar is then backed out, and the locking loop mechanism is engaged as described above. The catheter is secured to the skin with a cutaneous finger trap suture, and the port incisions are closed routinely.

### Complications

Complications reported with cholecystostomy tubes include tube obstruction and premature dislodgement with subsequent bile peritonitis.[3] Positive contrast cholangiography can be utilized to determine cholecystostomy tube patency and help determine when common bile duct patency is re-established.[1] Guidelines for the minimum recommended time to leave the cholecystostomy tube in place are lacking. In two clinical cases reported by Murphy et al. (2007),[3] fistulograms of the catheter tract following removal at 9 and 25 days showed a lack of maturation of the tract with leakage of bile into the abdominal cavity, necessitating additional surgery. This involved debridement and closure of the stoma in one dog and cholecystojejunostomy in the other due to concurrent continued EHBO. This information, combined with human medicine recommendations, suggests that leaving the tube in place for 3–4 weeks, regardless of common bile duct patency, may be ideal, though some reports suggest 5–10 days is sufficient.[3,6] If the bile is very viscous, some authors recommend careful aseptic flushing of the tube daily to prevent premature occlusion, though ascending infection is a concern.[6] If a feeding tube is in place concurrently with a cholecystostomy tube, a portion of the aspirated bile can be fed back to the patient via the tube to facilitate normal fat digestion and restore intestinal barrier function.[7] Guidelines on the frequency and quantity of bile to refeed are lacking.

#### 9.6.1.3.2 Choledochal stenting

Choledochal stenting is another option that can be considered when temporary or long-term relief of EHBO is needed, but other, more permanent solutions are not possible or desired. The most common indications are pancreatitis, or nonresectable neoplasia, which is causing EHBO. Though this procedure can be performed endoscopically in human beings, open placement is the only option currently available for veterinary patients.

### Technique

Following complete exploratory laparotomy and acquisition of any necessary biopsies, a **duodenotomy** is performed 2–4 cm distal to the pylorus on the antimesenteric surface of the duodenum, over the expected location of the major duodenal papilla. Placement of stay sutures on either side parallel to the duodenotomy may facilitate atraumatic manipulation of the bowel during stent placement. The major duodenal papilla is identified, and the common bile duct is catheterized

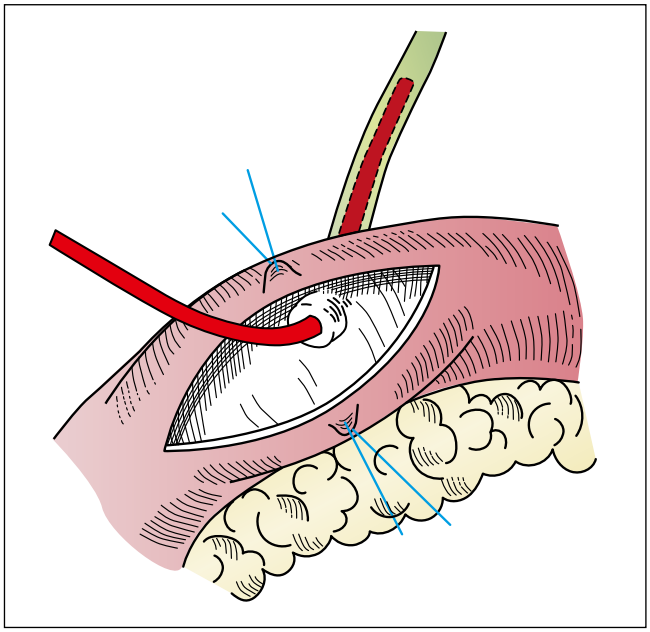


**Fig. 9-36** Following an antimesenteric incision in the duodenum, 2–4 cm distal to the pylorus, the major duodenal papilla is catheterized in a retrograde fashion to place a choledochal stent. (Image produced by VeLisa Bayer, Texas A&M University.)

(▶Fig. 9-36). A red rubber catheter or silicone feeding tube is typically used. Given concerns for stent occlusion, some authors recommend cutting off the rounded end of the catheter with preservation of the fenestrations.[4] Generally, bile is expected to flow primarily around rather than through the stent, so this may not be necessary. In cats and small dogs, 3.5–5-French size is usually appropriate. Stents up to 8–12-French may be usable in larger dogs. Alternatively, a dedicated biliary stent can be used; these stents are available in various sizes, are placed with the assistance of a guidewire, and have pre-cut flaps in place to help prevent proximal or distal migration.[8] Regardless of the type of stent used, the portion of the stent within the common bile duct should expand at least 2 cm proximal to the obstructive lesion when possible, and 2–5 cm of the stent should extend into the duodenal lumen. Unless a dedicated biliary stent is used, the portion of the wall of the stent within the duodenal lumen is secured to the duodenal submucosa with one or two simple interrupted monofilament absorbable or non-absorbable sutures (▶Fig. 9-37). The choice of suture material should take into consideration the reason for placement and desired duration of stenting. Absorbable suture should be sufficient for pancreatitis induced EHBO, whereas a non-absorbable suture may be preferred when the stent is placed for more permanent palliation of neoplasia. The duodenotomy is closed routinely.

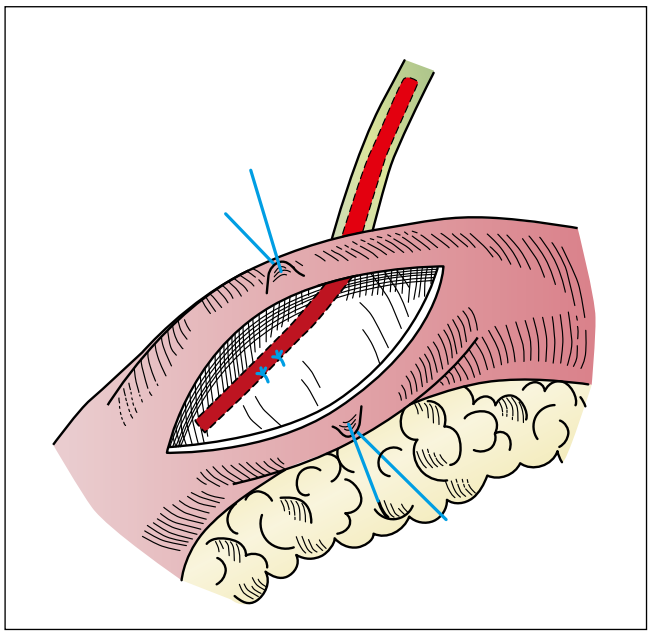


**Fig. 9-37** After catheterization of the major duodenal papilla, the choledochal stent is sutured in place with one or two simple interrupted monofilament absorbable or non-absorbable sutures. (Image produced by VeLisa Bayer, Texas A&M University.)

#### 9.6.1.3.3 Cholecystotomy and choledochotomy

There are few indications for cholecystotomy or choledochotomy in veterinary patients. Cholecystotomy is most commonly performed before committing to cholecystectomy to obtain access to the gallbladder lumen to attempt normograde flushing of the common bile duct (▶Chap. 9.6.2) or in preparation for a cholecystoenterostomy procedure. Cholecystotomy has been reported in the treatment of cholelithiasis in dogs. However, cholecystectomy is preferred to prevent recurrence. Recent literature on the topic is lacking. However, one study found the survival rate in dogs undergoing cholecystectomy for the treatment of cholelithiasis to be much higher (86%) than those undergoing cholecystotomy (50%).[11] In this study, recurrence of clinical signs was the most common reason for euthanasia or death, though dehiscence of the surgical site is also of concern, particularly if the wall of the gallbladder or common bile duct is compromised. A recent study found that while incidental choleliths did not resolve with medical treatment, only one of 33 dogs with long-term follow-up went on to develop clinical signs related to cholelithiasis.[12] As such, surgical treatment in asymptomatic patients with cholelithiasis is likely not warranted.

To perform a cholecystotomy, the gallbladder is packed off with laparotomy sponges. A stay suture is placed in the gallbladder near the site of the proposed incision. If gallbladder necrosis is present, a cholecystotomy should not be performed. The incision is made to the desired length, starting at the apex of the gallbladder. Following removal of all material and flushing of the common bile duct, if the cholecystotomy incision is to be closed, this is achieved with 2–0 to 4–0 monofilament absorbable suture in a simple continuous inverting pattern.[8] A double-layer closure is not recommended.[4]

In some cases of obstructive cholelithiasis, it may not be possible to dislodge the stone(s) from the common bile duct with retrograde or normograde flushing alone. Gentle external manipulation of the obstructive material can be attempted; however, caution must be exercised not to tear the common bile duct. In such cases, choledochotomy has been described as a viable solution with the successful recovery of both dogs and cats included in one study.[13] A longitudinal choledochotomy incision is made directly over the obstruction to remove the material. After patency of the duct is established, the incision is closed with 4–0 to 6–0 monofilament absorbable suture in a simple continuous pattern, taking care not to occlude the lumen during closure. Some authors prefer to place a choledochal stent before closure to support the repair, though the benefits of this step have not been proven.[8]

#### 9.6.1.3.4 Cholecystoenterostomy

When more permanent rerouting of the biliary tract is required, a cholecystoduodenostomy or cholecystojejunostomy is considered. This procedure is most frequently indicated in malignant EHBO, fibrosing pancreatitis, conditions necessitating excision of the proximal duodenum containing the major duodenal papilla, or irreparable trauma to the common bile duct. It is generally not necessary in acute pancreatitis cases (▶Chap. 10.3.1), for which more temporary solutions should be sufficient. However, in a 2008 study,[14] pancreatitis remained the most common reason for the procedure. Biliary flow diversion is typically not considered a first-line treatment option, given the long-term consequences in some patients.[15] When it is possible to appose the gallbladder to the duodenum without causing excessive tension or torsion of the cystic duct, most authors recommend a cholecystoduodenostomy be chosen.[8] If bile cannot be deposited into the duodenum (as in cholecystojejunostomy), the risk of gastric acid over-secretion is higher, which may lead to duodenal ulceration.[8] However, a survival benefit for pets undergoing cholecystoduodenostomy versus cholecystojejunostomy has not been elucidated in the available literature.[15,16]

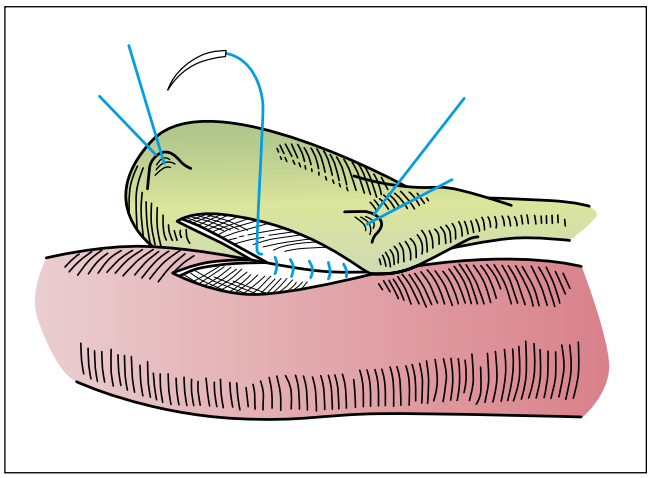


**Fig. 9-38** For single-layer closure of a cholecystoenterostomy, stoma incisions in the gallbladder and small intestine are closed with full-thickness simple continuous lines on each side. Two separate simple continuous lines are used to prevent a purse-string effect. (Image produced by VeLisa Bayer, Texas A&M University.)

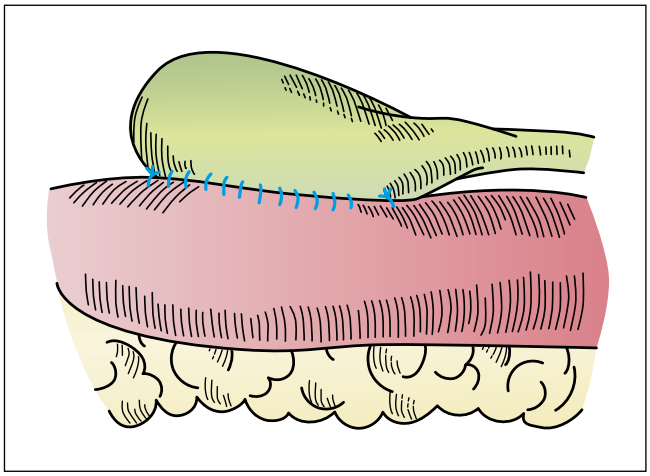


**Fig. 9-39** After both sides of the cholecystoenterostomy stoma are closed in a single-layer fashion, one or two simple interrupted sutures are placed at the proximal and distal aspects to pexy the gallbladder to the duodenum.
(Image produced by VeLisa Bayer, Texas A&M University.)

## Technique

A standard ventral midline incision is made, and the abdomen is explored routinely. Before beginning the procedure, the abdomen is packed with laparotomy sponges to prevent spillage of bile or intestinal contents into the peritoneal cavity. The gallbladder is mobilized from the hepatic fossa as described for cholecystectomy (▶Chap. 9.6.2.4). Some surgeons prefer to leave the gallbladder within the fossa or only partially remove it to help prevent damage to or torsion of the cystic artery or cystic duct, especially when performing a cholecystojejunostomy.[17] The duodenocolic ligament can be transected to improve the mobility of the duodenum. The gallbladder is then mobilized towards the anti-mesenteric surface of the descending duodenum. If this can be achieved without excessive tension, the procedure is continued. If it cannot, then a section of the proximal jejunum should be utilized. The proximal jejunum is preferred over the mid- to distal jejunum to minimize the risk of abnormal fat digestion.[1] The stoma is created in the same manner regardless of the section of the intestine used.

For a **double-layer closure**, the serosa of the gallbladder should be sutured to the serosa of the intestine near the mesentery on the side nearest to the liver.[1] A 3–4 cm continuous line with a 3–0 or 4–0 absorbable monofilament suture should be used. The tags can be left long to facilitate manipulation of the surgical site for the remainder of the procedure. A cholecystostomy incision is then created next to this suture line, parallel to and overlying the anti-mesenteric surface of the intestine it will be sutured to. Initially, a stab incision should be created, and the gallbladder drained of bile with suction. The cholecystotomy incision should then be extended 2.5–4 cm in length.[15] The stoma is expected to stricture by approximately 50%; thus, a large initial stoma size is essential. A matching enterotomy incision is created on the antimesenteric surface, with either atraumatic Doyen forceps or an assistant's fingers occluding the bowel to prevent leakage. The mucosa of the gallbladder is sutured to the submucosa/mucosa of the intestine on both the far and near sides with 3-0 or 4-0 simple continuous monofilament absorbable suture. After completing this portion of the closure, the serosa on the opposite side is closed in the same manner as the first serosal line.

Some surgeons prefer a **single-layer closure** to decrease the chances of narrowed intestinal luminal diameter and stomal stricture.[8] After the gallbladder is freed from the hepatic fossa, the cholecystotomy and enterotomy incisions are created as described above. The incisions are apposed by suturing the far and near walls with separate simple continuous suture lines, taking care to achieve mucosal apposition (▶Fig. 9-38). Rather than placing the two serosal suture lines as described in the double layer closure, one or two simple interrupted sutures are placed at the proximal and distal-most aspects of the anastomosis to pexy the gallbladder to the duodenum, removing as much tension as possible from the anastomosis (▶Fig. 9-39). Regardless of the closure technique, some degree of stomal stricture should be expected, and thus it is still imperative to ensure the length

of the stoma is >2.5 cm. There is currently inadequate literature in veterinary medicine to conclude whether single- or double-layer closure is superior.

Use of a **surgical stapling device** to complete cholecystoduodenostomy has been described.[14] Small duodenotomy and cholecystotomy incisions are created, with the placement of stay sutures aborad to each incision to facilitate manipulation. A 30 mm Endo-GIA® stapler is inserted with one arm in each of the incisions. Within the gallbladder, the stapler arm should span the distance from the apex to the neck. Traction is applied on the stay sutures to help maintain the proper positioning of the stapler arms. The stapler is fired, creating the cholecystoduodenostomy. The remaining openings within the gallbladder and duodenum are closed with 3–0 or 4–0 monofilament absorbable suture in a simple continuous pattern. An additional simple interrupted suture is placed orad to the suture line between the gallbladder and the duodenum to help alleviate tension on the staple line. One study reported a 64% 2-week survival rate in 24 dogs and four cats in which this procedure had been performed. Dehiscence of the cholecystoduodenostomy site was not reported, though the cause of death was not known in all cases.[14] Long-term follow-up was not reported in this study.

### Complications

Very little recent literature exists assessing the outcomes of dogs and cats following cholecystoenterostomy.[15,16] After cholecystoenterostomy, complications include dehiscence, stomal stricture, ascending cholangitis, and gastric or duodenal ulceration.[8] Formation of a hepatic abscess, acquired portosystemic shunts, pancreatitis, and vomiting have all been reported as long-term complications in dogs following cholecystoenterostomy.[15] Eight of 15 dogs included in this study ultimately died of complications related to the surgery or hepatobiliary disease. Chronic ascending cholangiohepatitis may have contributed to some of these complications, which may be mitigated by creating a large enough stoma to prevent inadequate drainage of refluxed intestinal contents.[17] In one study evaluating 22 cats having undergone cholecystoenterostomy procedures, the median survival time when the underlying cause was neoplasia was only 14 days, but was 255 days in cats where a chronic inflammatory condition was the cause of EHBO.[18] However, the proportion of cats surviving discharge in these two groups did not differ. Anemia was a common complication in these cats, with a transfusion being administered to approximately 70%.

### 9.6.1.4 Postoperative management

Regardless of the procedure performed, patients undergoing biliary surgery must be closely monitored postoperatively, ideally in an intensive care unit setting. In a study evaluating variables associated with outcomes following extrahepatic biliary surgery, an overall mortality rate of 28% was identified.[16] In this study, septic bile peritonitis, pre-operative azotemia (specifically increased creatinine), and immediate postoperative hypotension were associated with poor outcomes. Careful (at least daily) monitoring of renal values, total bilirubin, and electrolyte status is recommended after surgery to ensure hydration status is maintained and to diagnose potential renal injury or lack of resolution of EHBO quickly. Refractory hypotension has been described both during and following biliary surgery. It is theorized to be related to a vagal response when manipulating the gallbladder, endotoxin release leading to endotoxemia, prolonged anesthesia time, systemic inflammatory response (SIRS), and/or inadequate hydration.[19,20] Thus, close blood pressure monitoring and management are recommended. In patients where postoperative bile leakage is of particular concern, placement of an abdominal Jackson-Pratt drain can be considered to facilitate monitoring. Cytology and fluid analysis of abdominal fluid are of utmost importance, as the survival rate with septic bile peritonitis may be as low as 50% compared with near 100% survival with sterile bile peritonitis.[16] Given the potential for coagulopathies associated with EHBO or primary liver disease, careful monitoring of the red blood cell count (RBC) is recommended to treat anemia as needed. Coagulation panel testing should be considered prior to surgery.

**KEY FACTS**

- Extraluminal extrahepatic biliary obstruction generally should not be treated with cholecystectomy.
- Temporary biliary diversion techniques should be considered prior to permanent techniques when appropriate.
- Patients undergoing biliary surgery should be closely monitored during and after surgery.

### References

The complete list of references for this chapter can be downloaded from vetline.de:
svg.to/9842-09-06-01

## 9.6.2 Gallbladder mucocele

Kelley M. Thieman Mankin,
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### 9.6.2.1 Introduction

Diagnosis of a gallbladder mucocele has become increasingly common over the last several years. In part, the increase in gallbladder mucocele diagnosis is likely due to the increasing use of abdominal ultrasound.[1–3] Regardless of the reason for diagnosis, the occurrence of gallbladder mucocele requires the attention of veterinarians. Biliary mucocele is uncommon in cats but has been reported.

Gallbladder mucoceles are an abnormal accumulation of thick bile and mucous within the gallbladder lumen. Dogs with a gallbladder mucocele are reported to have histologic findings of mucosal hypertrophy, termed cystic mucinous hyperplasia.[4] The thick, inspissated bile can extend into the biliary tree, resulting in varying degrees of biliary obstruction.[1,5] Progressive distension of the gallbladder secondary to biliary obstruction can lead to increased pressure within the gallbladder, ischemic necrosis of the gallbladder wall, and gallbladder rupture and bile peritonitis. The treatment of choice for gallbladder mucocele is cholecystectomy, although medical management has been attempted and is successful in some cases.[6,7]

### 9.6.2.2 Etiology

Of small animal species, dogs are the most commonly diagnosed with a gallbladder mucocele.[5,8] Gallbladder mucocele is uncommonly reported in cats.[9,10] The Shetland sheepdog, border terrier, Chihuahua, Pomeranian, American cocker spaniel, miniature schnauzer, bichon frise, beagle, shih tzu, and mixed breed dogs all are predisposed to gallbladder mucocele formation.[1,3,8,11,12.] Affected dogs are often middle-aged with a median age of 10 years,[1,8] but have been reported to be as young as 2 years.[8]

Dogs with gallbladder mucoceles often suffer from comorbidities such as hyperadrenocorticism, hypothyroidism, pancreatitis, hyperlipidemia, diabetes mellitus, protein-losing nephropathy, cholestasis and gallbladder hypomotility, hypercholesteremia, and hypertriglyceridemia.[1,5,8,11,13–15]

Dogs with hyperadrenocorticism are 29 times more likely to develop a gallbladder mucocele than dogs without hyperadrenocorticism.[13] Rapid gallbladder mucocele development has been reported following the initiation of glucocorticoid therapy.[2] However, no direct correlation has been drawn between hyperadrenocorticism and the development of gallbladder mucocele.[13] The fact that excessive steroid results in immunosuppression may play a role as bacterial infection within the biliary tree may result in cholecystitis (▶Chap. 9.6.3.1) and subsequent increase in mucous formation.[13] Excessive steroids may also result in abnormal gallbladder emptying and/or abnormal bile composition, potentially resulting in gallbladder mucocele formation.[13] Dogs with hypothyroidism are almost 3 times more likely to develop gallbladder mucocele than dogs without hypothyroidism.[13] Again, a direct relationship has not been determined but may be related to gallbladder emptying or bile composition.[6,13]

In Shetland sheepdogs, a genetic mutation in the *ABCB4* gene has been associated with gallbladder mucocele formation.[16] The gene product (ABCB4 protein) is a phospholipid translocator.[16] Phospholipids and phosphatidylcholine protect the epithelial cell membranes in the biliary tree from the cytotoxic actions of bile salts.[16] Decreased amounts of phosphatidylcholine can injure epithelial cells of the biliary tree.[16] Therefore, a defect in the ABCB4 protein could decrease phosphatidylcholine with resultant injury to the biliary epithelium. Injury to the biliary epithelium causes increased mucin secretion, mucinous hyperplasia, and possibly mucocele formation.[16] A different study found a lack of association between the *ABCB4* gene defect and gallbladder mucocele formation.[17] That study evaluated the mutation in the *ABCB4* gene in dogs with and without gallbladder mucocele and in comparison with age- and breed-matched controls.[17] They found no association between the *ABCB4* mutation and gallbladder mucocele in Shetland sheepdogs or other dog breeds.[17] It serves to reason that because damage to the biliary epithelium results in increased mucin production, any cause of damage to the epithelium may play a role in gallbladder mucocele formation.

Drug administration may be associated with gallbladder mucocele formation. Shetland sheepdogs with gallbladder mucocele were 9.3 times more likely to have a history of imidacloprid administration than control dogs.[14] The authors of that report suspected that imidacloprid was not a cause of gallbladder mucocele but instead that it may be a contributing factor to gallbladder mucocele formation, although a mechanism was not identified.[14]



Biliary sludge is a common finding in dogs.[18,19]

Biliary sludge may correlate with gallbladder dysmotility,[19] which may predispose to gallbladder mucocele formation, although this association has not been proven.[1,2,6] One study assessing the progression of biliary sludge over a one year

duration in 45 healthy dogs showed that biliary sludge did not develop into clinically apparent gallbladder disease.[18] Therefore, at this time, cholecystectomy should not be recommended for dogs with only biliary sludge and no signs of biliary disease.

#### 9.6.2.3 Clinical presentation and diagnosis

In the largest study of dogs with gallbladder mucocele to date,[8] the most common clinical signs were: vomiting 80%, lethargy 47%, anorexia 46%, diarrhea 18%, painful abdomen 17%, hyporexia 11%, and jaundice 10%. Presumably, clinical signs in dogs are secondary to gallbladder pain, biliary obstruction, and/or gallbladder rupture. In the same study, 17% of dogs with gallbladder mucocele were asymptomatic.[8] The median duration of clinical signs was 4 days.[8]

Diagnostic evaluation prior to surgery for gallbladder mucocele is similar to any other work-up for hepatopathy. Bloodwork should include a CBC, serum biochemistry profile, and coagulation profile. A serum biochemistry profile is often helpful in identifying hepatobiliary disease but not in identifying the specific disease. Typical findings on routine bloodwork are leukocytosis and increases in serum ALT (alanine transaminase), ALP (alkaline phosphatase), GGT (gamma-glutamyl transferase), and AST (serum aspartate transaminase) activities, and total bilirubin concentrations.[2,20] As discussed above, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, and other bloodwork abnormalities consistent with endocrine abnormalities may increase the suspicion of gallbladder mucocele in sick animals.[8,11,13] A coagulation profile should be performed, particularly in patients suspected to have extrahepatic biliary obstruction.

Measurement of microRNAs (miR) may be a useful blood test to aid in diagnosing gallbladder mucocele.[21] MicroRNAs are small non-coding RNAs that regulate gene expression[21,22] and are used as biomarkers for hepatobiliary diseases in humans.[22] MicroRNA testing is a blood serum test that is currently not widely available in dogs but may become so in the future.[21] In one study, a microRNA panel was run on the blood of dogs with a variety of hepatobiliary diseases.[21] The group showed that the measurement of concentrations of five different microRNAs aided in the differentiation between biliary, parenchymal, and neoplastic hepatobiliary diseases.[21] Specifically, miR-122 was shown to have the highest concentration in dogs with gallbladder mucocele, with a 267-fold increase.[21] Measurement of microRNA concentrations is a promising blood test that may aid in the diagnosis of gallbladder mucocele in dogs.[21]

Abdominal imaging should be performed, with abdominal ultrasound being the most commonly utilized modality. Ultrasound images can be used to diagnose and classify the gallbladder mucocele[7,23,24]:

- Type 1 = immobile echogenic bile
- Type 2 = incomplete stellate pattern
- Type 3 = typical stellate pattern
- Type 4 = kiwi-like pattern and stellate combination
- Type 5 = kiwi-like pattern with residual central echogenic bile
- Type 6 = kiwi-like pattern

In one study, classification into the type of gallbladder mucocele was helpful with prognosis.[7] However, a different study did not relate ultrasound-based gallbladder mucocele type and prognosis.[24] The sensitivity of abdominal ultrasound in detecting gallbladder rupture in patients with gallbladder mucocele is only 56%, whereas the specificity is 92%.[25]

#### 9.6.2.4 Treatment

##### 9.6.2.4.1 Medical management

Dogs in which gallbladder mucocele was an incidental finding, in which no clinical signs are present or biliary tree obstruction is not detected based on clinicopathologic and imaging findings, may be managed medically if elected by the owner. In these dogs, ursodeoxycholic acid (UDCA) and S-adenosylmethionine (SAMe) should be administered.[2,15] UDCA is administered as a choleretic agent. It protects hepatocytes and biliary epithelium against the effects of cholestasis and may improve gallbladder motility.[2] SAMe is administered to provide antioxidant and metabolic benefits, although a choleretic influence has been detected in cats.[2,26] Underlying metabolic disorders should also be addressed.[6,15] Medically managed patients should be monitored for clinical improvement, clinicopathologic improvement, and ultrasound features (static or improved).[2] These parameters should be checked every 2–4 weeks,[5] and if progression is detected in the above parameters, surgical intervention is warranted.[2]

##### 9.6.2.4.2 Surgical technique

Surgical removal of the gallbladder is the treatment of choice for gallbladder mucocele. Different surgical techniques have been described. Most commonly, an exploratory celiotomy is performed. The gallbladder is often distended and firm. Before gallbladder excision, the common bile duct (CBD) is identified and inspected for pathology. If the CBD is ruptured or obstructed by a neoplasm, a biliary diversion technique is selected rather than cholecystectomy (▶Chap. 9.6.1).

The gallbladder is freed from the fossa using blunt dissection. Dissection begins by disrupting the visceral peritoneum between the gallbladder and the liver. The visceral peritoneum is incised using sharp or blunt dissection or judicious use of electrosurgery. Once a plane is visible between the gallbladder and the liver, the gallbladder is freed by blunt dissection (▶Fig. 9-40). The authors frequently use the inner cannula to a Poole suction tip for blunt dissection, but finger dissection is also functional and straightforward. Small vessels that persist during blunt dissection can be electrocauterized and transected. Once freed from the fossa, the gallbladder is attached only by the cystic duct and cystic artery. At this point, different techniques may be selected. Some surgeons create a cholecystotomy incision and remove the inspissated bile and mucous in order to cannulate the cystic and common bile ducts in a normograde fashion (▶Fig. 9-41). The gallbladder incision is made along the fundus and can extend toward the cystic duct. The mucocele is removed using a gall spoon. Typically, a 5-French red rubber catheter is introduced down the cystic duct and into the CBD. The gallbladder can be tractioned to straighten the cystic duct and CBD to facilitate cannulation. Gentle flushing is utilized to flush inspissated bile through the CBD and into the duodenum. Once the CBD is determined to be patent and uninjured, the catheter is removed, and a ligature is placed around the cystic duct. The cystic artery travels parallel to the cystic duct and is ligated concurrently. The authors prefer to place two ligatures, ideally a circumferential and a transfixation ligature, but in some dogs, this is not possible due to a lack of space in the cystic duct.

In some dogs, a catheter cannot be passed in a normograde manner, or the bloodwork and imaging indicate biliary obstruction and/or pathology within the CBD. In these dogs, the surgeon may elect to pass a catheter in a retrograde manner (▶Fig. 9-42). To pass a catheter retrograde, an approximately 2 cm duodenotomy is created on the antimesenteric margin of the duodenum, approximately 2 cm aboral to the pylorus. Stay sutures can be placed on the edges of the duodenotomy to facilitate the identification of the major duodenal papilla. Alternatively, a DeBakey thumb forceps can be placed

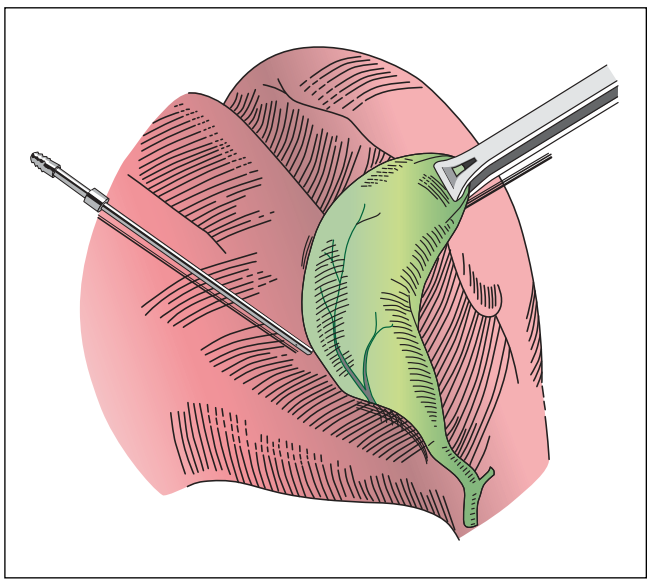


**Fig. 9-40** Blunt dissection of the gallbladder out of the fossa using the inner cannula of a Poole suction tip
(Image produced by VeLisa Bayer, Texas A&M University.)

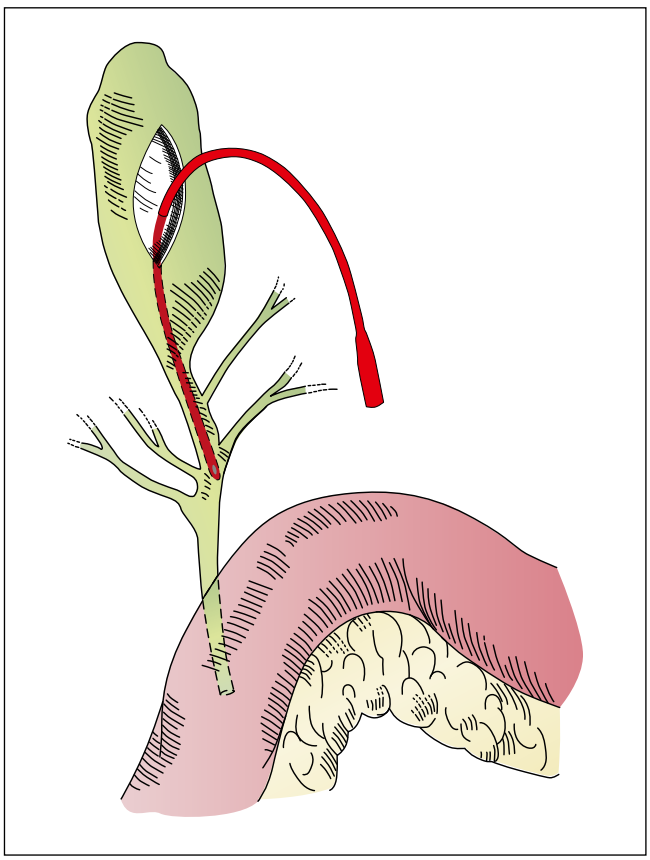


**Fig. 9-41** Normograde cannulation of the common bile duct through a cholecystotomy incision
(Image produced by VeLisa Bayer, Texas A&M University.)

into the incision and allowed to open, holding open the duodenotomy incision. The major duodenal papilla is visualized on the mesenteric luminal surface, and an approximately 3- to 5-French red rubber catheter is introduced. A headlamp and magnification are helpful tools for visualization of the major duodenal papilla. Gentle lavage with sterile saline can help dislodge any inspissated bile and mucous and flush it into the gallbladder. A cholecystotomy incision can be created if not already present, and judicious flushing should be used to prevent over-pressurizing the biliary system. Once the CBD is determined to be patent, the cystic duct is ligated as described above, and the gallbladder is removed. Once the gallbladder is removed, the CBD can be cannulated again to gently leak check the ligated cystic duct.

In some dogs with gallbladder mucocele, the serum total bilirubin concentration is normal, and no biliary obstruction is present. In those dogs, cannulation of the CBD may not need to be performed. In the same subset of dogs, laparoscopic cholecystectomy may be an option.[27]

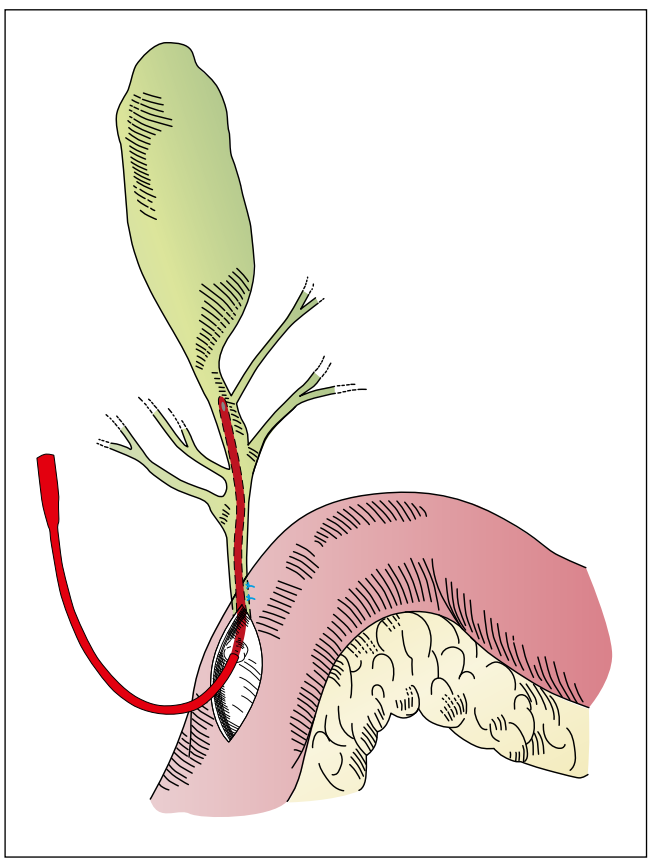


**Fig. 9-42** Retrograde cannulation of the common bile duct through a duodenotomy incision
(Image produced by VeLisa Bayer, Texas A&M University.)

Laparoscopic cholecystectomy is appropriate for dogs with uncomplicated gallbladder mucoceles. This means that the presence of a complicated gallbladder mucocele (e.g., coagulopathy, clinical or laboratory evidence of extrahepatic biliary obstruction or bile peritonitis, or small body size [<4 kg]) is a contraindication.[28] Patient selection is important when attempting laparoscopic cholecystectomy, and the surgeon should be prepared to convert to an open laparotomy if necessary. The dog is placed in dorsal recumbency, and four ports are created.[27,28] Briefly, the first port is subumbilical. The others are triangulated around the position of the gallbladder, with one being on the dog's left cranial quadrant and two being in the right cranial quadrant.[27,28] The cystic duct is dissected using right-angle forceps and ligated with hemoclips or sutures.[27,28] The cystic duct is divided between ligatures, and the gallbladder is dissected out of the fossa. The gallbladder is removed via a specimen retrieval bag.

Regardless of the surgical technique, the excised gallbladder is submitted for histopathologic examination. Bile is collected for aerobic and anaerobic bacterial culture, and a liver biopsy is performed for histopathologic evaluation, copper quantification, and bacterial culture.

### 9.6.2.5 Prognosis

Historically, the mortality rates with gallbladder mucocele in the postoperative period range from 22–40%.[1,2,23,29,30] Other recent studies report mortality rates from 7–15%.[3,8,31] Once dogs undergoing biliary surgery survive the perioperative period, they have a good long-term prognosis.[30]

Specific, reliable predictive factors are challenging to elucidate from the current literature. For example, in one study, vomiting was a predictor of survival,[8] while in a different study,[31] vomiting was a predictor of mortality. Similarly, in one study, dogs with gallbladder rupture and bile peritonitis at the time of surgery were 2.7 times more likely to die.[25] However, in a different study, suspicion of biliary rupture on abdominal ultrasound was correlated with increased survival.[7] Amsellem et al. (2006)[30] did not find bile peritonitis to be a risk factor for death in dogs undergoing biliary surgery.

Several pre-operative factors have been associated with prognosis in dogs with a gallbladder mucocele. In the largest study published on gallbladder mucoceles, which includes over 1,000 dogs, several factors were identified that impacted survival.[8] The study reported that icterus identified by the owner, hyperadrenocorticism, increasing age, increased serum/plasma bilirubin concentration, and Pomeranian breed were all associated with increased odds of death.[8] Older dogs and dogs with a higher white blood cell count (WBC) are also at increased risk of death.[32]

Other postoperative factors have been associated with prognosis. Postoperative hypotension has been shown to indicate a 20 times higher chance of mortality.[3] Further, for each unit increase in lactate postoperatively, the chance of death increases by 30%.[3]

In humans with acute cholecystitis, increasing the duration between the onset of clinical signs and cholecystectomy is associated with worsening outcomes.[33] In dogs, little has been agreed upon concerning the timing of surgery. Interestingly, in the study, including over 1,000 dogs, the duration between the onset of clinical signs and surgery did not affect outcomes.[8] A different study[7] compared the outcomes of three groups of dogs: those managed surgically (with cholecystectomy), those managed medically, and those with medical management followed by cholecystectomy. In that study, they included dogs that survived 14 days after diagnosis and found that median survival times were 1,802 days (surgical management), 1,340 days (medical management), and 203 days (medical then surgical management), leading to the conclusion that cholecystectomy results in the best long-term survival in dogs but that medical management may be appropriate for some dogs.[7] The same group found that gallbladder mucocele type, serum ALP activity, and serum creatinine and phosphorous concentrations were each associated with decreased survival.[7]

Asymptomatic dogs with gallbladder mucocele that undergo an "elective" cholecystectomy have a lower mortality rate (2%) than those undergoing "non-elective" surgery (20%).[31] This finding was supported by Jaffey et al. (2019);[8] they found that in dogs undergoing cholecystectomy, death-in-hospital occurred in 17% of dogs with clinical signs consistent with biliary tract disease at the time of surgery, while only 5% of subclinical dogs died. These findings of lower mortality rates may encourage surgeons to operate on subclinical patients, although, in the subclinical patients, the mortality rate was still 2–5%.[8,31] Therefore, risks of surgery should be considered when discussing cholecystectomy in asymptomatic dogs.

**KEY FACTS**

- Dogs with metabolic abnormalities are predisposed to forming a gallbladder mucocele.
- The treatment of choice for gallbladder mucocele is cholecystectomy.

**References**

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## 9.6.3 Cholecystitis/cholangitis

Jared A. Jaffey

### 9.6.3.1 Cholecystitis

Cholecystitis is defined as inflammation within the gallbladder wall and is further subclassified in humans based on the predominant type of inflammation.[1] A formal classification scheme of cholecystitis subtypes has not been reported for companion animals, but a recent study proposed an adaptation of the system used in humans:

1. Acute: neutrophilic infiltration
2. Acute with necrosis: neutrophilic inflammation with evidence of necrosis
3. Chronic: wall thickening by fibrosis and presence of mixed inflammatory cells without neutrophils
4. Acute-on-chronic: superimposition of neutrophilic infiltration on chronic inflammation.[2]

The majority of dogs and cats with cholecystitis described in the literature have had acute cholecystitis, including its variants (i.e., necrosis and acute-on-chronic).[2–11] However, the reported distribution may not be clinically representative as animals with chronic cholecystitis usually exhibit milder clinical signs and, thus, are less likely to have histopathologic examinations performed of the gallbladder after cholecystectomy or necropsy. Dogs and cats with cholecystitis tend to be older-aged (>9 years), but younger animals can be affected as well.[2,4–10,12–18] There is no clear breed or sex predisposition.

#### 9.6.3.1.1 Etiopathogenesis

Several diseases are reported to occur in conjunction with cholecystitis in companion animals, including bacterial and nonbacterial infections (e.g., *Platynosomum* spp., *Toxoplasma gondii*, *Candida albicans*), mucoid sludge, gallbladder mucocele, lymphoplasmacytic enteritis, cholelithiasis, biliary neoplasia, infarction, and gallbladder torsion.[2–4,6–15,19–26] There is little doubt that some of these disorders directly cause cholecystitis (e.g., nonbacterial infection, neoplasia, and gallbladder torsion); however, a clear cause-and-effect relationship with the remaining diseases cannot be determined.

Cholelithiasis is the most common cause of acute cholecystitis in humans.[27] Here, the primary mechanism by which cholecystitis develops is through cholelith-associated partial or complete extrahepatic bile duct obstruction (EHBO).[27,28] Progressive gallbladder distension secondary to biliary obstruction can impair mural circulation and predispose to infarction, necrosis, inflammation (sterile or

bacterial), and perforation. Moreover, bile stasis reduces the antimicrobial properties of bile. The causal relationship between biliary obstruction and the development of cholecystitis was highlighted in a study that evaluated the sequela of cystic duct ligation in dogs.[29] In that study, gallbladder volume increased over the 2–4 week study period, and all dogs developed severe acute cholecystitis with or without gallbladder rupture.[29] Cholecystitis is also commonly identified in dogs and cats with naturally occurring EHBO caused by cholelithiasis (▶Chap. 9.6.4) and other obstructive biliary disorders.[3,8,10,15,23,24]

Gallbladder hypomotility is postulated to contribute to the development of acute and chronic cholecystitis via pathogenic alterations to bile that can incite inflammation via oxidative damage, lipid peroxidation, and mural ischemia due to vascular thromboses and compression.[28,30–32] Several disorders in dogs, including gallbladder mucocele, mucoid sludge, hypercortisolemia, and hyperlipidemia, can cause gallbladder hypomotility, but their contribution to the eventual development of cholecystitis is unknown.[33–35] A recent study identified a potential link between chronic cholecystitis and lymphoplasmacytic enteritis in dogs.[11] The authors of that study speculated that chronic cholecystitis developed due to duodenal inflammation-induced gallbladder hypomotility.[11] Studies investigating gallbladder kinetics and cholecystitis in cats are lacking.

Bacterial infection is relatively common in dogs and cats with cholecystitis and can either occur as a secondary complication or represent the primary impetus for the development of cholecystitis.[7,8,13] Bacterial infection in humans with cholecystitis is predominately a secondary complication rather than the primary cause of inflammation.[36] The distinction between primary or secondary bacterial infection in companion animals with cholecystitis is less clear, but evidence suggests bacterial infection can occur as a secondary complication to cholecystitis.[37] In this study, bacterial growth from bile was identified in all dogs with experimentally induced acute acalculous cholecystitis.[37]

#### 9.6.3.1.2 Clinical presention

As with most biliary diseases, clinical signs are generally nonspecific and overlap with various other systemic disease processes. These signs include decreased appetite, lethargy, vomiting, diarrhea, abdominal pain, and occasionally pyrexia.[3,6,8,11,13] Jaundice, in addition to the previously mentioned clinical signs should increase the suspicion for biliary disease. The average time clinical signs are observed before veterinary consultation for acute cholecystitis is 3 days in dogs (range 0.5–14 days) and 4 days in cats (range 1–21 days).[3,8] Animals with chronic cholecystitis can have episodic, mild clinical signs.[11]

#### 9.6.3.1.3 Diagnosis

The most common clinicopathologic findings include increased serum alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), and γ-glutamyl transferase (GGT) activities, total bilirubin concentration, and an inflammatory leukogram with or without a left-shift.[3,8,13] Interestingly, the distribution of individual increases in liver enzyme activities differs between dogs and cats.



The serum liver enzyme activity pattern in dogs is generally cholestatic (increased ALP and GGT).[3,13]



Cats tend to have higher hepatocellular liver enzyme activities (ALT and AST).[8,38]

Histopathologic examination of the gallbladder is required to make a definitive diagnosis of cholecystitis. However, ultrasound examination can establish a suspected diagnosis in conjunction with clinical signs, physical examination, and clinicopathologic abnormalities. Acute cholecystitis can have a variety of sonographic appearances, including a thickened (dogs >1–3 mm, cats >1 mm), hypoechoic, or hyperechoic gallbladder wall that can appear smooth or markedly irregular and asymmetric (▶Fig. 9-43a).[39] Other findings can include polypoid masses, cholecystoliths, mucoid sludge, gallbladder mucocele, distended gallbladder and/or common bile duct dilation (dogs >3 mm, cats >4 mm), and/or the Murphy sign (pain detected in the gallbladder region during ultrasound study).[39] Emphysematous cholecystitis (gas within the gallbladder wall or lumen secondary to gas-producing bacteria) can appear sonographically as wall thickening and "dirty" shadowing with gas reverberation.[39] Chronic cholecystitis can appear as smooth or asymmetric gallbladder wall thickening, polypoid masses, wall mineralization, cholecystoliths, mucoid sludge, or gallbladder mucocele (▶Fig. 9-43b and ▶Fig. 9-43c).[39] The gallbladder can be contracted and difficult to identify in some cases because of severe fibrosis of the wall that prevents normal distension.[39]

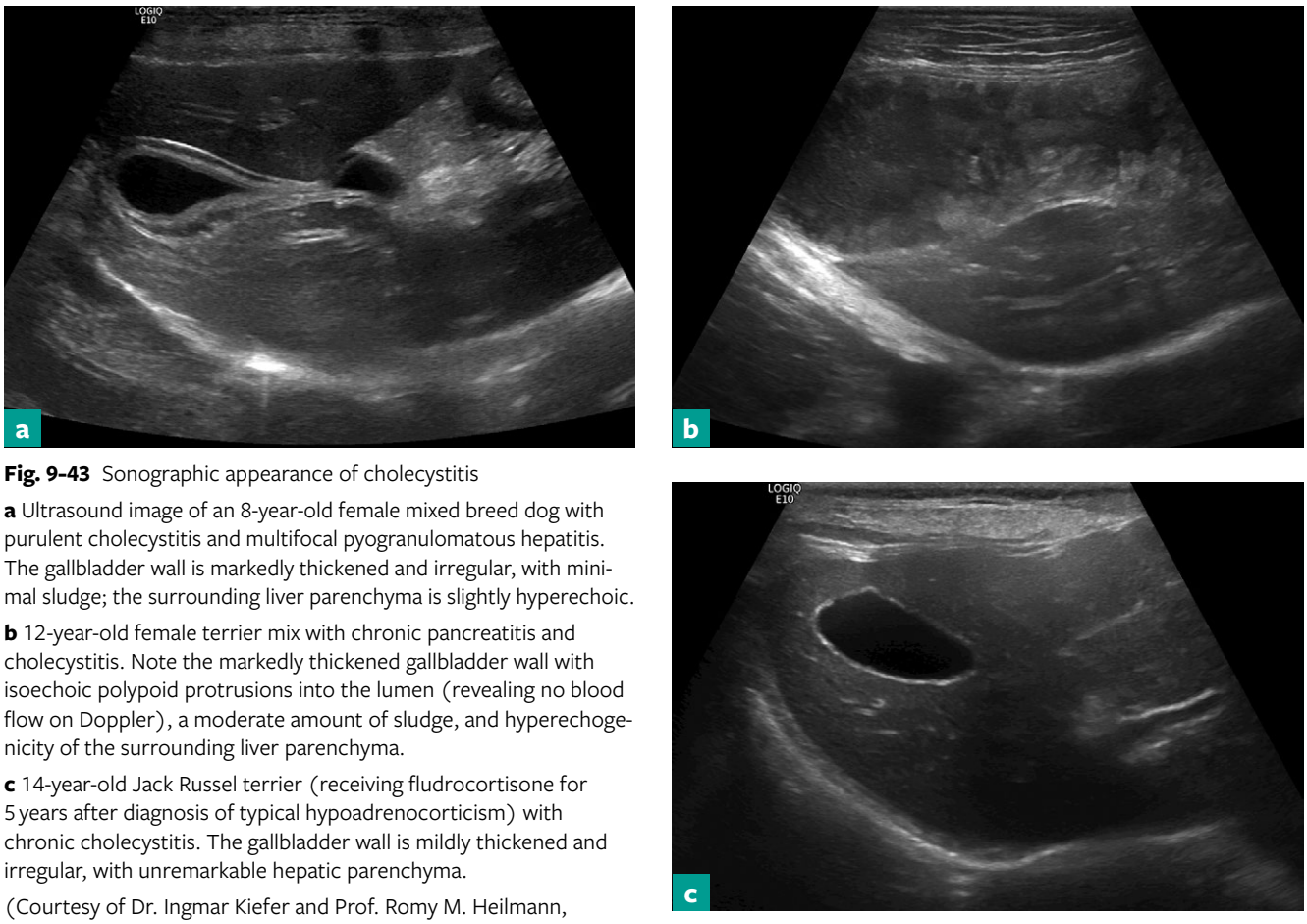



**Fig. 9-43** Sonographic appearance of cholecystitis

**a** Ultrasound image of an 8-year-old female mixed breed dog with purulent cholecystitis and multifocal pyogranulomatous hepatitis. The gallbladder wall is markedly thickened and irregular, with minimal sludge; the surrounding liver parenchyma is slightly hyperechoic.

**b** 12-year-old female terrier mix with chronic pancreatitis and cholecystitis. Note the markedly thickened gallbladder wall with isoechoic polypoid protrusions into the lumen (revealing no blood flow on Doppler), a moderate amount of sludge, and hyperechogenicity of the surrounding liver parenchyma.

**c** 14-year-old Jack Russel terrier (receiving fludrocortisone for 5 years after diagnosis of typical hypoadrenocorticism) with chronic cholecystitis. The gallbladder wall is mildly thickened and irregular, with unremarkable hepatic parenchyma.

(Courtesy of Dr. Ingmar Kiefer and Prof. Romy M. Heilmann, College of Veterinary Medicine, University of Leipzig, Germany.)

#### 9.6.3.1.4 Treatment

### Surgical management

Cholecystectomy is generally recommended for dogs and cats with moderate-to-severe cholecystitis, emphysematous cholecystitis, if there is a concurrent gallbladder mucocele or suspicion for EHBO or gallbladder rupture (▶ Chap. 9.6.2). Surgical intervention in cases with mild cholecystitis is reasonable; however, medical management is often pursued first. Occasionally, biliary enteric diversion procedures are needed in lieu of cholecystectomy in cases where patency of the common bile duct cannot be established. The requisite criteria to classify the severity of cholecystitis (i.e., mild, moderate, severe) is subjective and determined after a collaborative assessment of clinical, clinicopathologic, and sonographic abnormalities. The optimal time from the onset of clinical signs to surgical intervention has not been investigated in companion animals with acute cholecystitis. Cholecystectomy performed in humans with acute cholecystitis within 72 hours of the onset of symptoms reduces the incidence of complications such as intra-operative blood loss, duration of hospitalization, wound infection, and overall morbidity/mortality.[40] Delayed cholecystectomy can lead to gallbladder rupture, bile peritonitis, pericholecystic abscess, and the development of biliary fistulas.[40]

In addition to surgical intervention, animals usually require intensive supportive care that varies on a case-by-case basis, but typically includes IV fluids, electrolyte supplementation, broad-spectrum antibiotics, analgesia, anti-nausea medications (e.g., ondansetron, maropitant), ursodeoxycholic acid, and S-adenosylmethionine. Gallbladder wall tissue and/or contents (e.g., cholelith, mucoid sludge, bile) are obtained intra-operatively and submitted for bacterial culture, and antibiotics are subsequently tailored to the susceptibility panel.

**CLINICAL PEARLS**

The administration of antibiotics should not be delayed for fear it will influence the culture results.

Negative culture results are common and should not necessarily dissuade from continued antibiotic administration if clinical and clinicopathologic improvements are achieved.

Perioperative hypotension and anemia are common in dogs and cats that undergo biliary surgery.[8,41] Therefore, vasopressor medications and blood products should be available onsite in the event they are needed.

Much less is known about chronic cholecystitis compared with its acute counterpart in companion animals. These cases generally exhibit similar but milder clinical signs that are often episodic. Cholecystectomy could be considered in cases that are refractory to medical management or with frequent episodes of relapse.[11]

There is little published information available that describes the outcomes of dogs and cats with cholecystitis undergoing biliary surgery. The presence and severity of comorbid conditions and complications affect prognosis. Generally, animals that survive the immediate postoperative period (7 days) tend to have a good long-term prognosis.[2,3,7–11,13,42]

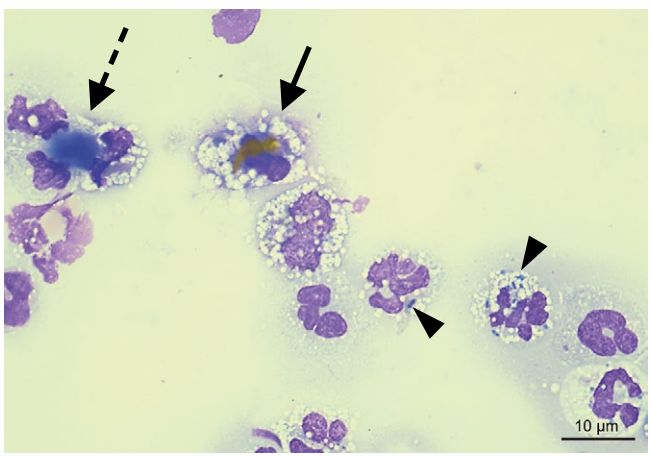



**Fig. 9-44** Septic, bilious effusion

Bile cytology of a 10-year-old male bull terrier with acute cholecystitis and gallbladder rupture. The cells present are variably degenerate neutrophils that contain various intracellular inclusions: blue, amorphous white bile (**dashed arrow**), and irregular to polygonal, yellow bile crystals (**solid arrow**), or short, thin bacterial rods and diplococci (**arrowheads**). 100x; Wright-Giemsa Stain.

(Courtesy of Dr. Mary E. White, Midwestern University, College of Veterinary Medicine, AZ, USA.).

### Medical management

Medical therapy in animals with cholecystitis generally includes ursodeoxycholic acid, S-adenosylmethionine, antibiotic(s), low-fat diet, and other supportive care treatments that vary on a case-by-case basis. Percutaneous ultrasound-guided cholecystocentesis can be performed by trained individuals to obtain bile samples for bacterial culture and cytology (▶Fig. 9-44) in animals suspected to have cholecystitis absent any sonographic changes consistent with emphysematous cholecystitis or gallbladder mucocele. Cytologic examination of bile provides several relevant advantages, including guiding initial antimicrobial treatment, identifying mixed bacterial populations that could be missed due to being overgrown by a single isolate, and identifying nonbacterial pathogens (e.g., *Platynosomum* spp., *Toxoplasma gondii*, *Candida albicans*) or neoplastic cells.[19–22,43] A positive bacterial culture strengthens a diagnosis of cholecystitis and can facilitate targeted antibiotic administration based on the susceptibility panel.

**NOTE**

Cholecystitis cannot be excluded in cases with an unremarkable cytologic examination of bile or negative cultures.

If bile cannot be obtained for cytology and culture, empiric administration of antibiotic(s) is generally recommended. Surgery should be considered in animals that fail to improve (or decline) clinically and clinicopathologically within 7–10 days of initiating medical therapy or those with disease recurrence.

## 9.6.3.2 Cholangitis

Inflammatory disease of the intrahepatic biliary system in dogs and cats frequently occurs in clinical practice.[14,44–46] Cholangitis is defined as inflammatory cell infiltration in the bile duct lumen and/or epithelium.[47] Cholangiohepatitis is characterized by an extension of inflammation from the bile duct beyond the limiting plate into the adjacent periportal region.[47] While these terms are often used interchangeably to describe the same disorder, the World Small Animal Veterinary Association (WSAVA) guidelines recommend that the term "cholangitis" be used preferentially because involvement of the hepatic parenchyma is a rare feature and, if present, is typically an extension of primary cholangitis.[47]

Current guidelines provided by the WSAVA Liver Diseases Standardization Group include four types of cholangitis (▶Chap. 1.8.2).[47]:

1. Neutrophilic
2. Lymphocytic
3. Chronic
4. Destructive

**Neutrophilic cholangitis** is the most common subtype in dogs and vies with lymphocytic cholangitis as the most common form in cats.[44–46,48,49] Histologically, neutrophilic cholangitis is characterized by neutrophils in the bile duct lumen, epithelium, or both.[47] Lesions can have an irregular patchy distribution with variable severity among liver lobes.[47] Neutrophilic cholangitis is further subclassified as acute neutrophilic cholangitis or chronic neutrophilic cholangitis. The acute form is characterized by neutrophils and edema in the portal region and mild bile duct hyperplasia, fibroplasia, or fibrosis.[47,49] The chronic form is characterized by mixed neutrophilic and mononuclear inflammation in portal areas and moderate-to-severe bile duct hyperplasia, fibroplasia, or fibrosis.[47,49] Other than being an indication of disease chronicity, the clinical relevance of this subclassification scheme is currently unknown. Dogs and cats of any age, breed, or sex can be affected. The reported mean age at the time of diagnosis in dogs is 9.7 years (±3 years).[48] Likewise, cats are also generally older-aged at the time of diagnosis (median age: 7–14.5 years; range: 0.8–20 years).[44–46,50–52] There are no known predisposed dog breeds. However, several potential breed associations, but no sex predilection, have been identified in cats. Breeds shown to be at an increased risk in either the United Kingdom or New Zealand include the British shorthair, Burmese, domestic longhair, Persian, Siamese, and Sphynx, while the domestic shorthair has a decreased risk.[45,46]

**Lymphocytic cholangitis** is almost exclusively seen in cats.[44–46,48,49,51,53,54] The WSAVA Liver Diseases Standardization Group describes lymphocytic cholangitis histologically as infiltration of small lymphocytes in the portal region with varying severities of fibrosis and bile duct proliferation. Lymphocytes can also be seen around or within the biliary epithelium.[47] There is a wide spectrum of congruent histologic features within that definition, and it is likely responsible for the varying terminology used to describe the disorder in the literature (i.e., nonsuppurative cholangitis, lymphocytic portal hepatitis, and progressive cholangitis).[51,53,55–59] Currently, it is unclear if the range of histologic features simply reflects disease chronicity or, perhaps, distinct phenotypes. Lymphocytic cholangitis can be seen in cats of any breed, age, or sex. The reported mean/median ages at diagnosis are 4.4–15 years (range 0.4–21 years).[44,45,51,52,56–60] Recent studies identified Siamese, Burmese, and the Norwegian forest cats as predisposed breeds.[46,61] Several studies have also reported Persian breed cats to be overrepresented.[56–58] There is no known sex predisposition.

**Chronic cholangitis** associated with liver fluke infection is observed predominately in cats but occasionally can be found in dogs in endemic regions (▶Chap. 9.6.5). Flukes that cause chronic cholangitis exist worldwide and are endemic in tropical and subtropical areas (e.g., Brazil, British Guyana, Cayman Islands, Colombia, Cuba, Curacao, Bonaire and Aruba, Indonesia, Malaysia, Mexico, Papa New Guinea, Nigeria, Puerto Rico, St. Kitts, Thailand, Venezuela, Trinidad and Tobago, and various regions of the US including Florida, Texas and Hawaii).[62] Histopathologic examination generally shows varying degrees of cholangitis, cholangiectasis, biliary hyperplasia, and fibrosis.[19,47,63–69] The inflammatory infiltrate is variable and influenced by disease chronicity, secondary bacterial cholangitis, and the individual host immune response. Some animals have predominately lymphoplasmacytic inflammation, while others show considerable neutrophilic and/or eosinophilic inflammation.[19,47,63–69] Occasionally, fluke eggs and adults can be identified within the lumen of dilated bile ducts, and concurrent chronic cholecystitis is a common feature.[19,68,69]

**Destructive cholangitis** is extremely rare in companion animals and is characterized by the destruction and loss of bile ducts in the portal region with inflammation and varying degrees of fibrosis.[47] In humans, destruction and loss of ≥50% of interlobular bile ducts in portal tracts is used to define this disorder.[70] Destructive cholangitis is recognized clinically in cats but has not been reported in the literature. Similarly uncommon in dogs, only nine cases have been reported.[71–73]

#### 9.6.3.2.1 Etiopathogenesis

The specific pathomechanism for the development of neutrophilic cholangitis in dogs and cats remains unknown. Two phenomena are speculated to be central to the pathomechanistic underpinnings of this disorder. The first is mechanical or functional biliary obstruction leading to reduced enterohepatic circulation and increased intraductal pressure.[8,48] Decreased circulation of bile results in decreased bile acid concentration, causing a reduction in antimicrobial properties. Increased intraductal pressure increases bacteria

and endotoxin translocation into the biliary epithelium and alters regional host defense mechanisms.[74–76] The second phenomenon is the proliferation of bacteria in bile. Bacteria are frequently identified in animals with neutrophilic cholangitis, and even in their absence, a positive clinical response to antibiotics is noted.[7,9,14,48–50,77–80]

There are two sources of bacteria in animals with neutrophilic cholangitis:

- Ascendant from the duodenum.
- Translocation across the intestinal wall with hematogenous spread via the portal circulation.

Ascension of bacteria from the duodenum occurs mainly in cats because the species has a relatively rich bacterial flora in the proximal duodenum.[81,82]

The hematogenous spread of bacteria from the intestines is further supported by the commonality with which bacteria of enteric origin are isolated in animals with hepatobiliary disease.[7,8,20,77,83] Concurrent gallbladder disease is often recognized in animals with neutrophilic cholangitis; however, it is unknown if cholangitis causes or is caused by gallbladder disease. Primary gallbladder disease has the potential to predispose animals to neutrophilic cholangitis because it contributes to bile stasis, and abnormal tissue or luminal contents are niduses for infection.

Lymphocytic cholangitis is believed to have an immune-mediated pathogenesis. Several histologic and immunohistochemical features corroborate this suspicion[58–60]:

1. A predominance of $CD3^+$ T-lymphocytes that surround bile ductules and infiltrate the portal biliary epithelium.
2. Portal distribution of $CD79^+$ B-lymphocytes
3. Regional major histocompatibility complex II expression
4. Targeted bile duct destruction and ductopenia

In addition, immunosuppressive treatment generally results in clinical and histologic improvement.[58–60]

Liver flukes reported to infect animals include trematode species of the families Opisthorchiidae (*Opisthorchis* spp., *Metorchis* spp., *Amphimerus* spp., and *Clonorchis* spp.) and Dicrocoeliidae (*Platynosomum* spp.). *Platynosomum* spp. is the most common liver fluke to affect animals that become infected after predation of lizards, geckos, marine toads, and possibly mice (▶Chap. 9.6.5).[62,84]

The pathogenesis of destructive cholangitis in animals is unknown. Causal mechanisms suspected in the limited available reports include drug-induced or canine distemper virus.[71–73] In humans, this disorder includes a spectrum of diseases and can be a component of congenital ductal plate malformation or be acquired.[70,85] Acquired diseases resulting in ductopenia in humans include immunologic disorders (small-duct primary sclerosing cholangitis without large duct involvement, primary biliary cholangitis, graft-versus-host reaction), viral infections, neoplasia, and drug-induced.

#### 9.6.3.2.2 Clinical presentation

The presence, type, and severity of clinical signs depend on the subtype of cholangitis, chronicity, presence of comorbidities, and potential complications. Clinical signs can include decreased appetite, weight loss, lethargy, vomiting, diarrhea, abdominal pain, abdominal distension with ascites, pyrexia, obtunded mentation, and jaundice. Most animals with neutrophilic cholangitis are presented for evaluation within 7–10 days of the onset of clinical signs; but some cases demonstrate clinical signs for several months before diagnosis.[7,48,50] Occasionally, cats with lymphocytic cholangitis can be subclinical, with the diagnostic investigation initiated after an incidental detection of serum liver enzymopathy. Most cats with lymphocytic cholangitis exhibiting clinical signs have a protracted history of slow progression over weeks to years, with owners recognizing clinical signs for several months before evaluation.[58,86] Animals with platynosomosis in endemic regions are often subclinical.[63,64,87] The presence and severity of clinical signs appear to be associated with fluke burden, chronicity of infection, and the host immune response.[62]



Most dogs with neutrophilic cholangitis have increased liver enzyme activities (ALP >> ALT), often combined with hyperbilirubinemia and hypercholesterolemia.[48]



Cats with any of the reported subtypes of cholangitis generally, but not always, show an increase of at least one liver enzyme (ALT, AST, ALP, and/or GGT) activity, usually along with hyperbilirubinemia.[7,49,51,57] In contrast to dogs, increased serum AST and ALT activities are identified more consistently than cholestatic liver enzymes in cats with cholangitis.[7,49,51]

Inflammatory leukograms with or without band neutrophils are common in dogs and cats with neutrophilic cholangitis.[14,48] Hematology results vary but are commonly unremarkable in cats with lymphocytic cholangitis.[49,51,56,57] Clinicopathologic abnormalities can be affected by comorbid

conditions and disease complications such as cholecystitis, EHBO, sepsis, pancreatitis, gallbladder mucocele, chronic intestinal inflammation, biliary rupture, hepatic lipidosis, and coagulopathy.

#### 9.6.3.2.3 Diagnosis

**Histopathology** is required for a definitive diagnosis of cholangitis. However, liver biopsies are often not obtained due to the high risk to an unstable patient or lack of owner consent. In the absence of histopathology, clinicians are often forced to use a combination of clinical signs, physical examination findings, clinicopathology results, diagnostic imaging, bile/liver cytological examination, bacterial culture, and response to therapy to establish suspected diagnoses of neutrophilic or lymphocytic cholangitis. Similar empirical evidence cannot be used to develop a suspected diagnosis of destructive cholangitis as there is too little information about this disorder in dogs and cats. Chronic cholangitis caused by *Platynosomum* spp. can be diagnosed via the detection of eggs in feces or bile.[19] Double centrifugation with Sheather's sugar flotation solution is most sensitive to detect eggs in feces.[88] Eggs can be missed during fecal analysis because of variable shedding, inconsistent egg morphology, and sporadic egg passage (especially in cases with EHBO). Serial fecal analyses or cytological examination of bile should be considered in animals with initial negative fecal results but clinical suspicion for liver flukes.[19]

The **sonographic appearance** of the liver is variable in cases with cholangitis. Hepatic parenchymal abnormalities that can be found include any of the following: hepatomegaly, diffuse or mixed echogenicity changes, and focal or multifocal nodules.[14,19,48,49,51,52,89] Biliary tract dilation or identifying an obvious obstruction is an essential diagnostic component of acute cholangitis in humans and could be of similar importance to diagnosing neutrophilic cholangitis in animals.[8,9,14,48,90] Bile duct dilation can also be seen in liver fluke-associated chronic cholangitis cases and must be considered in endemic regions.[19] Biliary tract dilation is not a common feature of lymphocytic cholangitis unless a secondary complication occurs. A recent study found the sonographic appearance of the gallbladder in cats, but not dogs, with suspected hepatobiliary disease to be useful in predicting bile culture positivity.[83] Specific abnormalities associated with increased odds of culture positivity in cats included a thickened gallbladder wall (OR 6.7, 95% CI: 2.2–20.5) or the presence of sludge (OR 3.2, 95% CI: 1.1–9.3).[83] Negative and positive predictive values for sonographic gallbladder features to predict bile culture positivity in cats were 96% (95% CI: 77–99%) and 48% (95% CI: 41–55%), respectively.[83] This suggests that cats with a normal appearing gallbladder on ultrasound examination are unlikely to have a positive bile culture and that sonographic gallbladder abnormalities are unreliable in predicting culture-positive results. Bactibilia is most commonly identified in animals with acute cholecystitis (with or without neutrophilic cholangitis) but can also be a secondary complication with other hepatobiliary disorders (e.g., lymphocytic cholangitis, chronic cholangitis, hepatic lipidosis, gallbladder mucocele, or neoplasia).[20,91] Overall, the sonographic appearance of the liver in animals with cholangitis can be unremarkable, or if abnormalities are present, they are usually nonspecific. Therefore, ultrasound examination alone cannot be used to exclude or definitively diagnose cholangitis.

Bile collection and submission for **cytological examination and bacterial culture** can provide integral diagnostic and actionable information and should be performed in animals with suspected cholangitis. Bile can be procured via ultrasound-guided percutaneous cholecystocentesis, or gallbladder tissue and contents can be obtained intra-operatively. Cytological examination of the liver via ultrasound-guided fine-needle aspiration could be considered in animals that are not stable or when owners are averse to liver biopsy acquisition. Cytology can identify infiltrative diseases (e.g., fungal infections, lymphoma, other neoplasms) in dogs and cats or concurrent hepatic lipidosis in cats (▶Chap. 1.7).[92,93] However, clinicians cannot exclude infiltrative or inflammatory hepatobiliary disease in cats when cytological examination of the liver detects hepatic lipidosis alone.[94] Peritoneal effusion is occasionally present in animals with cholangitis. This fluid should be sampled and submitted for fluid analysis, cytological evaluation, and possibly culture.

#### 9.6.3.2.4 Therapy and prognosis

##### Neutrophilic cholangitis

Animals with suspected neutrophilic cholangitis should be admitted to the hospital, but outpatient therapy can be considered in stable animals with mild disease. Treatment recommendations are dictated by disease severity and the presence of complications that could require surgical intervention (e.g., cholecystitis, cholelithiasis, biliary tract neoplasia, gallbladder mucocele, EHBO, biliary rupture).

**Antibiotics** are one of the most important treatment components, and drug selection should be tailored to culture and susceptibility results. Broad-spectrum coverage (Gram-negative, Gram-positive, and anaerobes) should be considered while culture results are pending or in cases that do not have cultures performed. A single antibiotic can be used

initially in mild cases without cultures performed and alterations made, if needed, based on clinical and clinicopathologic response. The most commonly isolated bacteria from the hepatobiliary system are aerobic and anaerobic bacteria of enteric origin, including *E. coli, Enterococcus* spp., and *Clostridium* spp.[7,8,20,48,77,83,91,95] Other therapeutic interventions will vary on a case-by-case basis but are similar to previously mentioned strategies for biliary disorders. Clinicians should consider supplemental nutrition in animals not consuming at least 75% of their resting energy requirements (▶Chap. 3.2), especially in cats, to prevent the development of hepatic lipidosis.

**Therapeutic bile drainage** is performed in humans with moderate-to-severe acute cholangitis within 24–48 hours.[96,97] Bile drainage aims to control the bacterial source, reduce intraductal pressures, and promote bile flow. In one study, multivariable survival analysis found early biliary drainage to significantly improve 30-day survival in human acute cholangitis.[90] Therapeutic bile drainage has shown benefits in experimental studies, and case reports in companion animals, but there is insufficient evidence to recommend it as the standard of care in neutrophilic cholangitis cases at this time. However, it could prove useful in some cases, especially those with an EHBO, as a temporary bridge to surgery or if surgery is not an option.[38,98,99] Given the high frequency of concurrent gallbladder disease in dogs and cats with neutrophilic cholangitis, a thorough intra-operative assessment of the gallbladder is warranted, and a cholecystectomy is performed if indicated. A recent study found dogs with neutrophilic cholangitis after cholecystectomy to be twice as likely to survive as dogs that did not undergo that procedure.[48] Similar investigations have not been performed in cats, and further evidence is needed before cholecystectomy can be recommended as the standard of care in cats with neutrophilic cholangitis.

**Short-term corticosteroid administration** at an anti-inflammatory dose (prednisolone, 1.0–1.5 mg/kg PO per day) may be considered in some cats with neutrophilic cholangitis that do not substantially improve clinically within 2 weeks of antibiotic administration and other supportive care, or if the cat deteriorates during that time. Comorbidities and disease complications that could require surgical intervention must be considered or excluded before initiating corticosteroids. The reason some cats with neutrophilic cholangitis benefit from corticosteroids is unknown but is speculated to be related to concurrent chronic pancreatitis and/or intestinal disease and the improvement of bile flow from decreased tissue edema.

The prognosis for dogs and cats with neutrophilic cholangitis is generally good but can be affected by concurrent disorders (e.g., necrotizing pancreatitis, EHBO, hepatic lipidosis, biliary neoplasia, and biliary rupture). The mean reported survival time for cats with neutrophilic cholangitis in one study was 29.3 months, with 47% (7/15), 40% (6/15), and 13% (2/15) of cats surviving <1 year, 1–5 years, and >5 years, respectively.[51] The median survival time for dogs with neutrophilic cholangitis in one study was 671 days (95% CI: 114–1,426 days).[48]

### Lymphocytic cholangitis

Long-term therapy of cats with lymphocytic cholangitis requires immunomodulation. Immunosuppressive dosages of corticosteroids (prednisolone, 2–3 mg/kg PO per day) are recommended initially in cats with negative culture results. Anti-inflammatory dosages (0.7–1.0 mg/kg PO per day, but some cats might require up to 1.5 mg/kg PO per day) are generally used in cats during treatment for concurrent bacterial infections. Ursodeoxycholic acid (10–15 mg/kg PO q24h or 5–7.5 mg/kg PO q12h) and S-adenosylmethionine (10–20 mg/kg PO q24h) are included in the treatment regimen. Clinical signs and serum biochemical parameters are used as markers of response to therapy. A complete response is defined as the resolution of clinical signs and normalization of serum liver enzyme abnormalities and total bilirubin concentration. The dosage of prednisolone is gradually decreased over 4–6 months until the lowest effective dose that prevents disease relapse is identified. Chlorambucil can be considered in cases in which prednisolone monotherapy fails to achieve a complete response or when corticosteroid administration is contraindicated (e.g., diabetes mellitus, underlying cardiac disease). In one study, the median survival time of cats with lymphocytic cholangitis treated with either prednisolone or ursodeoxycholic acid was 795 days, and the 1-, 2-, and 3-year survival rates were 74%, 56%, and 35%.[61] Even cats with severe clinical signs (e.g., jaundice, ascites) and histologic abnormalities (e.g., bile duct destruction, ductopenia, and fibrosis) can respond to therapy and live for many years.[56,57]

### Liver fluke-associated cholangitis

Treatment of liver flukes is the foundation of therapy in animals with chronic cholangitis in endemic areas. Praziquantel, administered at a dose of 20 mg/kg IM q24h for three consecutive days, is recommended to treat cats with platynosomosis.[100] A repeat treatment 12 weeks later is recommended to provide sufficient time for metacercariae ingested near the initial treatment to mature. Adjunctive therapy, as already mentioned for biliary disorders, is typically needed in clini-

cally unwell animals with liver flukes. Concurrent bacterial infections have been identified in cats with platynosomosis. Thus, antibiotic administration should be considered.[19] Prognosis depends on the severity of clinical illness of the infected animal at the time of diagnosis.[65–67]

Treatment options in humans for destructive cholangitis depend on the underlying cause and include cessation of the responsible drug, ursodeoxycholic acid administration, and immunosuppression. However, most cases are idiopathic, and targeted therapy is not possible. Immunosuppression, high-dose ursodeoxycholic acid, or both have been used with varying success in humans with idiopathic destructive cholangitis.[101,102] Prognosis is variable in humans but tends to be worse in idiopathic cases, with up to 50% of patients progressing to liver failure.[85,103] Treatment and outcome cannot be ascertained from the limited reports on this disease in dogs. One dog was reported to have clinical, clinicopathologic, and histologic improvement after administering high-dose ursodeoxycholic acid (50–74 mg/kg per day) and prednisolone (2 mg/kg per day initially and gradually decreased to 0.5 mg/kg per day).[73]

**KEY FACTS**

- Cholecystitis is defined as inflammation within the gallbladder wall. In addition to cholecystectomy, animals usually require intensive supportive care that varies on a case-by-case basis but typically includes IV fluids, electrolyte supplementation, antibiotics, analgesia, anti-nausea medications, ursodeoxycholic acid, and S-adenosylmethionine.
- Medical therapy in animals with cholecystitis generally includes ursodeoxycholic acid, S-adenosylmethionine, antibiotic(s), low-fat diet, and other supportive care treatments that vary on a case-by-case basis. Percutaneous ultrasound-guided cholecystocentesis can be performed by trained individuals to obtain bile samples for bacterial culture and cytology.
- Cholangitis is defined as inflammatory cell infiltration in the bile duct lumen and/or epithelium and can be neutrophilic, lymphocytic, chronic or destructive.
- Antibiotics are one of the most important treatment components of cholecystitis and neutrophilic cholangitis.

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
svg.to/9842-09-06-03

## 9.6.4 Cholelithiasis/choleductolithiasis

Jared Jaffey

Cholelithiasis is relatively uncommon in dogs and cats compared with humans.[1–4] The prevalence of cholelithiasis in dogs is estimated to be between 0.97–13%.[1,2] Prevalence studies have not been performed in cats, but the frequency of occurrence is believed to be similarly low. Choleliths are predominately formed in the gallbladder but can occasionally develop in the bile ducts. The accumulation of choleliths in the gallbladder and bile ducts is referred to as cholecystolithiasis and choleductolithiasis, respectively. Cholecystoliths occur most commonly but can also occasionally include choleliths in the cystic and common bile ducts.[1,2,4–13] Intrahepatic choleductolithiasis in dogs and cats is rare.[2,14] Cholelithiasis generally occurs in older (>9 years) dogs and cats but can occur in younger animals.[2,5–7,9,12–16] There are no reported breed or sex predilections.

### 9.6.4.1 Etiopathogenesis

Choleliths in companion animals differ from those in humans, which are predominately comprised of cholesterol.[17,18] The majority of choleliths in dogs and cats are pigment stones, which can be further categorized as black or brown pigment based on their outward appearance, firmness, and composition.[1,2,5,11–13] Black-pigment choleliths are hard, black in color, and composed mainly of calcium bilirubinate as well as variable fractions of calcium salts of carbonate, phosphate, and free-fatty acids, and generally contain minimal cholesterol.[19] Hydrolyzed bilirubin conjugates bind with free $Ca^{2+}$ ions in bile to form precipitated salts that cause mucosal inflammation, mucus hypersecretion, and gallbladder dysmotility, which imparts a self-perpetuating cycle of cholelith aggregation, inflammation, mucus production, and biliary dysmotility.[19] Brown-pigment choleliths are soft, brown in color, and have an overlapping composition with black-pigment choleliths but generally contain more cholesterol.[19] Brown-pigment choleliths are associated with chronic bile stasis and/or bacterial infection.[19] The majority of dogs and cats have black-pigment choleliths, but the clinical relevance of this distinction is unknown.[1,6,11,13,16]

The specific pathogenesis of cholelith formation in dogs and cats is unknown. Proposed mechanisms are inferred from humans or based on findings from experimental dog studies and include gallbladder hypomotility, bacterial infection, sterile inflammation, mucus hypersecretion, and altered bile composition.[19–21] While cholecystitis, gallbladder hypomotility, altered bile acid composition, and excess mucus are commonly identified in companion animals with

cholelithiasis, a clear cause-and-effect relationship cannot be deduced.[1,2,4–7,13,20]

Bilirubin cholelithiasis can occasionally be identified in cats with pyruvate kinase deficiency-induced chronic hemolysis but has not been reported in dogs with the same erythrocytic enzymopathy.[4,7]

#### 9.6.4.2 Clinical presentation

Similary to humans, dogs tend to be subclinical at the time of cholelith identification.[2,14,22] Anecdotally, the same is likely true for cats, but studies investigating this are lacking. Choleliths are most commonly diagnosed as an incidental finding during screening for unrelated conditions. The presence and magnitude of signs (e.g., vomiting, diarrhea, decreased appetite, lethargy, weight loss, painful abdomen, icterus, pyrexia) are usually related to complications of cholelithiasis that include partial or complete extrahepatic bile duct obstruction (EHBO), cholecystitis, cholangitis/cholangiohepatitis, pancreatitis (mainly in cats because of the species-specific common pancreaticobiliary duct), gallbladder rupture, and bile peritonitis.[1,2,5,8,9,12,13,16,23–29] Biliary colic is a syndrome of episodic abdominal pain associated with cholecystolithiasis in humans. The pain results from increased intraluminal gallbladder pressure following contraction against a transient cystic duct obstruction (e.g., cholelith or mucoid debris).[30] Biliary colic has not been formally investigated in companion animals, but it is reasonable to suspect it could be a contributing cause for episodic clinical signs in dogs and cats with cholecystolithiasis.

#### 9.6.4.3 Diagnosis

Abdominal ultrasonography is the imaging modality of choice to diagnose cholecystolithiasis and choledocholithiasis in humans.[3] The reported sensitivity and specificity of ultrasonography to detect cholecystoliths in humans is 97% and 95%, respectively.[31] Choleliths display distal acoustic shadowing on ultrasound examination that intensifies as size and mineral content increase.[32] Extrahepatic choledocholithiasis can be more difficult to characterize in the absence of concurrent bile duct dilation because of interference from intestinal gas.[32] Intrahepatic choledocholiths appear on ultrasound imaging as hyperechoic branched linear structures or multiple discrete hyperechoic foci with varying amounts of distal acoustic shadowing.[14] Radiography has poor sensitivity (50–59%) for identifying choleliths in dogs.[2,5] Several variables, such as small size, limited mineral content, or interference with intestinal gas, affect the detection of choleliths with radiography.

#### 9.6.4.4 Treatment

##### 9.6.4.4.1 Surgical management

Surgical intervention is recommended in humans that exhibit clinical signs and clinicopathologic abnormalities associated with cholecystolithiasis or extrahepatic choledocholithiasis related complications.[3] Generally, surgery is also advised in dogs and cats under these conditions, but evidence to support this recommendation is lacking. The specific surgical technique(s) is heavily influenced by intra-operative findings, but cholecystectomy is recommended, assuming the common bile duct is patent, in animals with cholecystolithiasis, extrahepatic choledocholithiasis, or both.[16,33] Cholecystotomy to remove cholecystoliths is not recommended because of the risk for recrudescence as well unmitigated short- and long-term complications (e.g., cholecystitis, EHBO, pancreatitis, gallbladder rupture, bile peritonitis).[33] Dogs and cats that undergo biliary surgery also require concurrent medical therapy that will vary on a case-by-case basis, but generally includes IV fluids, electrolytes, ursodeoxycholic acid, S-adenosylmethionine, analgesia, and anti-emetics. Bile stasis and increased intraductal pressure predispose to bacterial infection; therefore, empiric broad-spectrum (e.g., Gram-negative and Gram-positive aerobes and anaerobes) antibiotics are recommended before surgery. Intra-operative samples (e.g., bile and gallbladder wall) are procured and submitted for aerobic and anaerobic bacterial culture, and antibiotic administration is tailored accordingly. Outcomes in systemically ill dogs and cats that undergo biliary surgery is influenced by the type and severity of cholelith-associated complications as well as the type of required surgical interventions. Generally, animals that survive the immediate postoperative period (<7 days) tend to have a good long-term prognosis.[2,4–6,8,12,13,16,25]

##### 9.6.4.4.2 Medical management

Medical therapy without surgery could be considered in dogs and cats with mild-to-moderate clinical and clinicopathologic abnormalities that do not have evidence of partial or complete EHBO, gallbladder rupture, or emphysematous cholecystitis. Medical interventions aimed at treating the complications of cholelithiasis will vary on a case-by-case basis (see above

for medical therapies). Ideally, bile should be obtained for cytology and bacterial culture to guide antibiotic administration decisions.

**NOTE**
Negative culture results do not preclude bacterial infection of the biliary tract. If bile cannot be procured, empiric administration of antibiotics is generally recommended.

Surgery should be considered in animals that do not improve, those that decline clinically and clinicopathologically within 7–10 days of initiating medical therapy, or those with recurrent disease.

There is no consensus on the management of incidental cholelithiasis in dogs and cats. Pigment choleliths cannot be dissolved with medical therapy.[34] Therefore, treatment is focused on correcting suspected contributory disorders that can cause gallbladder hypomotility or altered bile acid composition to reduce the risk of additional cholelith formation and the development of complications. Ursodeoxycholic acid cannot dissolve pigment choleliths, but evidence in humans suggests it could still have clinical value as it has been shown to improve gallbladder muscle function and neutralize lithogenic microenvironments, both of which contribute to pigment cholelith formation.[35] Moreover, long-term administration of ursodeoxycholic acid in humans with cholelithiasis is associated with decreased risk of biliary pain and acute cholecystitis, irrespective of cholelith dissolution.[36] There is a lack of information regarding the risk for a dog or cat to eventually develop a cholelithiasis-associated complication after the initial incidental diagnosis. Investigators from one study found that only 3% (1/33) of dogs that were subclinical at the time of cholelith identification eventually developed complications in the follow-up period (median: 145 days, range: 10–1688 days).[2] A recent study in humans found that 20% (130/664) of individuals went on to develop complications related to cholelithiasis in the 20-year follow-up period.[37]

**References**
The complete list of references for this chapter can be downloaded from vetline.de:
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## 9.6.5 Parasitic diseases of the biliary system

Jenny Stiller

Parasites residing within the biliary tract of cats or dogs can cause acute or chronic disease. Biliary helminthiases are mainly caused by species of the trematode family, mostly affecting cats.[1] Biliary coccidioses are rare in cats and dogs.[2–4] This chapter focuses on trematode infections in cats and dogs.

### 9.6.5.1 Etiology

Chronic cholangitis due to liver fluke infestation is caused by Opisthorchiidae (cats, dogs) and Dicrocoeliidae (cats). The most common species in North America include the opisthorchid *Amphimerus pseudofelineus* and the dicrocoelid *Platynosomum fastosum*. The latter causes lizard poisoning in cats and may be synonymous with *P. concinnum*, *P. illiciens*, and other dicrocoelids. Opisthorchiidae (including *Opisthorchis* spp., *Clonorchis* spp., *Metorchis* spp., and *Amphimerus spp.*) are mainly found in North and South America, Europe, and Asia. Infections with *Opisthorchis felineus* are reported in cats and dogs in Central and Southeast Europe and Asia. In endemic areas in Italy, *O. felineus* prevalence in stray cats was 73%.[5] Infections with *O. viverrini* in Southeast Asia have a prevalence of 31% in cats.[6] In endemic regions in China, infections with the Oriental liver fluke of people (*C. sinensis*) affect up to 70% of cats and dogs.[7] Prevalences of *Amphimerus* spp. infections in endemic regions in Ecuador were 71% in domestic cats and 39% in dogs.[8] *Platynosomum fastosum* is endemic in tropical and subtropical areas, including the Southeast USA, Hawaii, and the Bahamas, with prevalences in cats ranging from 10–80%.[1,9]

The lifecycle of opisthorchids requires two intermediate hosts, the first one being aquatic snails infected by the ingestion of eggs. Within that host, cercariae develop. These escape the snail and search for freshwater fish, the second intermediate host, where infectious metacercariae develop. The definitive vertebrate hosts (e.g., cats, dogs, and humans) acquire the infection by ingesting raw fish. Larvae inside the metacercarial cysts escape and migrate from the intestine to the gallbladder and bile ducts, developing into adults, and eggs are shed via feces.[1,10,11]

The lifecycle of *P. fastosum* entails two intermediate hosts and a paratenic host. The first intermediate host, terrestrial snails, is infected by ingesting the eggs. Sporocysts con-

taining cercariae are released from the snail and ingested by terrestrial isopods, the second intermediate host. Here, cercariae develop into infective metacercariae. Lizards and amphibian species are the paratenic hosts infected by eating isopods. Cats and other mammals (e.g., opossums, skunks) acquire the infection by ingesting lizards. In the final host, the metacercariae excyst and migrate through the intestine into the biliary system.[9] Residing in the gallbladder and biliary ducts, liver flukes can cause inflammation and biliary obstruction.[9,12]

### 9.6.5.2 Signalment and risk factors

Cats have a higher prevalence of liver fluke infestation than dogs.[1,6,8] Risk factors for *P. fastosum* infection include living outdoors or having outdoor access and being >2 years old.[13,14,15] Both female and male predominance have been reported for *P. fastosum*-infected cats.[13–15] Risk factors for feline opisthorchid infections include eating raw fish and being >3 years of age.[6,16] Consuming raw fish is also a risk factor for trematode infections, including *C. sinensis*, in dogs.[16]

### 9.6.5.3 Clinical presentation

Clinical signs depend on the parasite burden, time of infection, and individual reaction to parasites.[17,18]

Cats with mild infections can be asymptomatic, whereas a higher parasite burden often causes clinical signs.[19] First clinical signs develop 7–16 weeks after infection.[17,20] These include acute or chronic anorexia, lethargy, vomiting, mucoid diarrhea, weight loss, fever, icterus, and abdominal distension.[9,12,19,21,22] In severe cases, cats may present with acute clinical signs, including icterus and acholic feces, due to extrahepatic bile duct obstruction (EHBO).[18,22,23] Neurological signs due to hepatic encephalopathy (▶ Chap. 9.4.4) have also been reported in affected cats.[24] On physical examination, findings include poor body condition, jaundice, fever, abdominal distension, hepatomegaly, evidence of ascites, and abdominal pain.[19,21,22]

In dogs, clinical signs and physical examination findings of opisthorchid infections include anorexia, lethargy, vomiting, weight loss, abdominal distension, jaundice, and fever.[25,26]

### 9.6.5.4 Diagnosis

#### 9.6.5.4.1 Routine hematology and biochemical parameters

In infected cats, hematology and serum biochemistry results can be normal or reveal unspecific changes. Hematologic abnormalities include a mild nonregenerative anemia and leukocytosis with eosinophilia.[12,19,24,27,28] Experimentally infected cats with *P. fastosum* consistently developed eosinophilia peaking at 4–5 months post-infection, independent of the parasite burden.[19] Biochemical changes include hyperbilirubinemia and a mild to moderate increase in serum liver enzyme activities.[12,19,21,22,24,29] The pattern of liver enzyme increases in cats with biliary trematodiases consists of a mild to moderate increase in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activity, whereas that of alkaline phosphatase (ALP) usually remains within normal limits.[19,27–29]

In dogs infected with *Opisthorchis felineus* and *Metorchis bilis,* increases in glutamate dehydrogenase (GLDH) activity are seen, while ALT and ALP are increased in only some animals; AST activity was reportedly normal.[30]

#### 9.6.5.4.2 Diagnostic imaging

Abdominal radiographs are often unremarkable or may reveal hepatomegaly in affected cats.[12] Abdominal ultrasound findings are variable, with evidence of EHBO (▶ Chap. 9.6.1) in 59% of *P. fastosum*-infected cats.[15] Sonographic abnormalities include distended and tortuous intrahepatic and common bile ducts, periductal hyperechogenicity, dilation of the gallbladder, hyperechoic and thickened gallbladder walls, gallbladder sludge, hepatomegaly, irregular liver margins, hyperechoic and heterogeneous hepatic parenchyma, and/or diffuse cystic hepatic lesions.[12,13,15,21,22,31] The latter is consistent with intrahepatic bile duct dilation.[31] Sonographic visualization of flukes within the bile ducts or gallbladder has not been reported in cats. In people examined by with high-resolution abdominal ultrasonography, biliary flukes can be identified as non-shadowing hyperechoic spots or casts within the bile ducts or floating/dependent, discrete, non-shadowing hyperechoic foci within the gallbladder.[32] In a dog from Canada with an opisthorchid infection, sonographic findings, noted

after 2–5 weeks, included distension of the gallbladder, intrahepatic and common bile ducts, and echogenic debris within the biliary tract.[25] Abdominal computed tomography (CT) findings in dogs with *C. sinensis* were dilation of intrahepatic bile ducts, contrast-enhancing bile duct walls, transient aberrant attenuation of hepatic parenchyma adjacent to dilated bile ducts, and visualization of flukes within the biliary tree. After successful treatment, these abnormalities resolved or decreased in severity, by small nodular calcifications along the portal tract remained.[33]

#### 9.6.5.4.3 Identification of trematode eggs

The antemortem diagnosis of biliary helminthiases relies on a combination of clinical and ultrasonographic findings and confirmation of infection by detection of eggs in feces, bile, or adult flukes or eggs in liver biopsies.

**CLINICAL PEARLS**

Diagnostic sensitivity of fecal analysis can be limited due to intermittent shedding of eggs, small size and number of eggs being shed (2–10 eggs/g feces with low burden and 10–100 eggs/g feces with higher burdens), and varying egg morphology at different developmental stages. Also, bile duct obstruction and fibrosis might impede the passage of eggs into the duodenum.[9,12,34] Therefore, a negative fecal analysis does not rule out infection, and analysis of fecal samples collected from at least 3 different days is recommended to increase the diagnostic yield.[5,12]

For *P. fastosum* infections in cats, studies evaluating the diagnostic accuracy of different fecal analysis methods revealed contradictory results. Formalin-ether sedimentation was the most sensitive technique in some studies,[34,35] whereas other studies showed centrifugation techniques with Sheather's sugar flotation solution to be superior to formalin-ether sedimentation and other methods.[36–38] Possible reasons for these discrepancies include operator experience and differences in methods, including the volume of examined fecal material. Because formalin-ether sedimentation is not routinely performed in most veterinary diagnostic laboratories, double centrifugation with Sheather's sugar flotation solution and zinc sulfate flotation methods can be used to identify *P. fastosum* eggs during a routine fecal examination.[36–39] Formalin-ether sedimentation can also detect eggs shed by Opisthorchiidae in the feces of cats and dogs.[8] Recently, fecal molecular (PCR), immunological (ELISA), and other techniques have been developed and are mainly used in human patients and epidemiological studies.[40–42]

Trematode eggs can also be identified on bile analysis. In cats with *P. fastosum* infection, percutaneous ultrasound-guided cholecystocentesis with bile fluid cytology revealed significantly higher egg counts than fecal analysis by double centrifugation.[15] Therefore, bile egg count appears to be more sensitive than fecal analysis and should be considered in cats with negative fecal analysis and suspicion of trematode infection (e.g., signs of chronic cholangitis). Adult liver flukes or eggs can also be identified on liver biopsy specimens.[1,22]

#### 9.6.5.4.4 Histopathology

Histologic abnormalities of the liver include dilation of intrahepatic bile ducts, periductal to portal fibrosis, and adenomatous hyperplasia of the biliary epithelium. Inflammatory cells can be identified within the ducts, and in the periductal and portal areas. Inflammatory cellular infiltrates include lymphocytes, plasma cells, macrophages, neutrophils, and eosinophils; the latter are usually limited in number. In severe cases, inflammation within the portal triads can extend into the hepatic parenchyma leading to periportal interface hepatitis. Hyperplastic adenomatous or ulcerative cholecystitis may be detected.[1,9,12,15,21,29] The absence of adult liver flukes, or eggs, does not rule out infection.[1,12,29]

### 9.6.5.5 Treatment

Praziquantel is the treatment of choice.

Praziquantel at a dose of 10–25 mg/kg PO, SC, or IM q24h for 3–5 days seems to effectively eliminate *P. fastosum* in most cats.[9,12,17,22,43] A single dose of 40 mg/kg praziquantel PO was highly effective and safe in *O. viverrini*-infected cats.[27] 40 mg/kg of praziquantel q24h IM for 3 days is reported for *A. pseudofelineus* infection.[23]

In dogs, a single dose of 20 mg/kg praziquantel effectively treats *O. felineus*.[30]

Supportive treatment is also recommended, but controlled clinical trials are lacking. Ursodeoxycholic acid (10–15 mg/kg PO q24h) is used as a choleretic and anti-inflammatory drug,

and prednisolone (1 mg/kg PO q24h, tapering course) to reduce fluke-associated inflammation.[12,22,44] Antimicrobials are indicated to treat secondary bacterial infections associated with parasitic cholangitis.[22,45] Vitamin $K_1$ (0.5–1.5 mg/kg SQ q12h for 2–3 doses) should be supplemented in cases of biliary obstruction causing decreased intestinal absorption. S-adenosylmethionine (20 mg/kg PO q24h) can be given as an antioxidant hepatoprotectant.[44] Patients with EHBO frequently require surgical decompression (▶Chap. 9.6.1).[22,45]

#### 9.6.5.6 Prognosis

Besides developing EHBO and intrahepatic cysts, complications of biliary helminthiasis in cats and dogs include secondary bacterial infections with cholangitis or cholangiohepatitis and liver abscess formation,[15,22,25] multi-organ failure,[26] development of cholangiocarcinoma,[46,47] and pancreatitis.[48] Neoplastic transformation may be caused by physical (movement) and/or biochemical (metabolites leading to cytotoxic and mutagenic damages) stimuli of trematode presence.[46,47,49]

Pancreatitis in cats be caused by liver flukes migrating into the pancreas because of the common bile duct joining the pancreatic duct at the major duodenal papilla.[20]

A recent study showed pancreatitis caused by platynosomosis to be rare (5%).[48]

Most *P. fastosum*-infected cats are asymptomatic, and their long-term outcomes are unknown. Animals with biliary trematodiases developing complications (e.g., EHBO) or extensive hepatic involvement have a guarded prognosis.[21,22,24,26,46]

**KEY FACTS**

- Biliary trematodiases should be considered in animals with biliary disease that have access to raw freshwater fish (cats, dogs) or eating lizards (cats).
- Biliary trematodiases can lead to extrahepatic bile duct obstruction and, rarely, to cholangiocarcinoma and pancreatitis.
- The diagnosis of biliary trematodiasis requires the detection of eggs in feces, bile, or adult flukes or eggs in liver biopsies.
- Praziquantel is the treatment of choice for biliary trematodiases.

**References**

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## 9.6.6 Neoplasms of the biliary system

Brandan Wustefeld-Janssens

### 9.6.6.1 Introduction

Biliary neoplasms arise from the bile duct epithelium, most frequently within the liver parenchyma, but can also arise from extrahepatic biliary structures. Benign tumors, namely biliary adenomas, biliary cystadenomas, or cholangiocellular adenomas, are common in cats, and, in some studies, comprise >50% of all hepatobiliary tumors.[1,2] The true incidence of benign biliary neoplasms is difficult to discern because of a wide overlap with congenital biliary disorders (▶Chap. 9.5.6). Many previously diagnosed benign tumors have been reclassified as non-neoplastic.[3–6] A key difference between cholangiocellular adenoma and carcinoma is the degree of differentiation of the lining epithelium, presence or absence of mitotic figures, and presence of tumor invasion. Cholangiocellular or biliary carcinomas are rare and comprise <1% of all neoplasms in dogs and cats.

In dogs, malignant tumors are more common than benign neoplasias, and most affected dogs (65%) are >10 years of age.[7]

In cats with malignant tumors, most are >9 years of age, and females tend to have a higher risk of developing tumors in some studies.[8,9]

Gallbladder adenomas and carcinomas are very rare in all species apart from cattle.[3]

No known etiology has been strongly linked to the development of biliary neoplasia in dogs and cats. Parasitism in people with the liver fluke *Clonorchis sinensis* is linked to hepatocellular carcinoma (HCC) and cholangiocellular carcinoma.[10] A small study in dogs and cats with cholangiocellular carcinoma identified the same parasite, but the presence of the fluke as a predisposing factor is still to be elucidated.[11]

### 9.6.6.2 Clinical presentation

Benign tumors tend to be asymptomatic and clinical signs arise when the mass compresses adjacent structures. In contrast, 75% of dogs with malignant disease are clinically symptomatic on presentation.[8,9,12–17] In dogs and cats with malignant biliary tumors, clinical signs tend to be nonspecific and have considerable overlap with HCC.[9,12,14] Polyuria and polydipsia can be found in some cats. Icterus is common in dogs with extrahepatic bile duct carcinoma and is an important differential diagnosis with diffuse morphology neuroendocrine tumors.[14,16]

### 9.6.6.3 Diagnosis

Hematologic and serum biochemistry changes tend to be nonspecific. Raised serum liver enzyme activities are common and likely reflect hepatocellular injury or biliary stasis (▶ Chap. 1.3.3). Liver enzyme activity changes are nonspecific for neoplasia, and no correlation with the degree of disease progression has been found.[18] However, increases in specific serum liver enzymes may help discern the type of neoplasia and differentiate primary from metastatic disease.[12] For example, increases in ALP and AST activities are more common in primary tumors, whereas increases in AST activity and bilirubin concentration are more common with metastatic disease. In one study, a ratio of AST:ALT >1 was more sarcomas likely to be associated with neuroendocrine tumors or sarcoma compared with an AST:ALT ratio <1, which was more likely seen with HCC or biliary tumors.[14] However, in general, liver enzyme activities should not be used independently to make clinical decisions. In cats, serum ALP elevation is rare, likely due to its short half-life. Increases in serum ALT, AST, and bilirubin are common. In some cats with hepatobiliary neoplasia, the only biochemical abnormality is azotemia.[8,9,14]

Diagnostic imaging consisting of radiographs, abdominal ultrasound, and CT is commonly used for clinical staging and treatment planning. Mineralization of the biliary tree is a rare finding in dogs with bile duct carcinoma.[18] Tumors can appear cystic or solid on diagnostic imaging, which does not impact prognosis nor predict biological behavior. Morphologic forms are similarly described as for HCC as either massive, nodular, or diffuse. Massive and nodular forms predominate but, unlike HCC, rarely affect a single liver lobe. Larger tumors and those with massive morphology are frequently lobulated with a distinct margin with the normal liver parenchyma. Nodular morphology is the most common presentation with cholangiocellular carcinoma. Nodules can range from 5–40 mm in diameter and are scattered throughout the lobes. Different from HCC is an abundant amount of connective tissue stroma within the biliary tumors that gives them a firm consistency compared with HCC, which is softer and more friable.[19]

### 9.6.6.4 Staging

Clinical staging is important with cholangiocellular carcinoma as these tumors have a highly invasive growth pattern and frequently metastasize. The metastatic rate to extrahepatic sites in dogs is reported to be as high as 60–88%.[7,16,20] Typical sites are regional and distant lymph nodes, lungs, and peritoneum. Similarly, the metastatic rate in cats has been reported as 78%, and metastasis most commonly occurs in the lungs, lymph nodes, and serosa of abdominal organs.

Benign gallbladder adenomas are frequently pedunculated or papillary and often are attached at the fundic region by a thick stalk. The tumor is often not apparent from the outside of the gallbladder and rarely obstructs flow.

Conversely, gallbladder carcinomas are highly invasive and can invade through the gallbladder wall into the surrounding liver parenchyma, and metastatic disease is common.[1,3,20]

### 9.6.6.5 Treatment and prognosis

The recommended first-line treatment for massive or nodular morphology cholangiocellular adenoma affecting single or two liver lobes is surgical resection.[1,2,8,9,15,21] The prognosis is excellent, with no local recurrence or malignant transformation being reported.[1,8,21]

Surgery is also indicated for massive morphology cholangiocellular carcinoma in dogs, but the outcomes are poor compared with the same morphologic subtype of HCC. Most dogs will experience tumor recurrence and succumb to metastatic disease in the first 6 months following surgery.[8,18] In cats with malignant disease, intraperitoneal metastasis and carcinomatosis are noted in 67–80% and are associated with a poor prognosis.[8,9,15] There is no known effective therapy for nodular or diffuse cholangiocellular carcinoma, and the prognosis is very poor.

## References

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# 10 Exocrine pancreas

## 10.1 Anatomy

Jörg M. Steiner

The pancreas in dogs and cats is a long narrow structure that can be divided into a right and a left limb. In between these two limbs is the head of the pancreas, which, in contrast to humans, is not an easily discernible structure in dogs (▶Fig. 10-1) and cats. The right limb of the pancreas lies directly next to the duodenum, while the left limb is situated next to the spleen. The pancreas is made up of lobules of pancreatic tissue, which in turn are made up of acinar cells (▶Fig. 10-2). In between the lobules there are islets of Langerhans (▶Fig. 10-2), which are collections of neuroendocrine cells. These neuroendocrine cells make up the endocrine portion of the pancreas and synthesize and secrete a variety of regulatory polypeptides, most importantly insulin and glucagon. The acinar cells produce digestive enzymes and zymogens, which are released into the duct system that leads to the duodenum.

Dogs usually have two pancreatic ducts. The main pancreatic duct (ductus pancreaticus) empties into the duodenum on the major duodenal papilla together with the common bile duct. The lumen of the pancreatic duct is separated from the duodenum by the sphincter of Oddi, which is a muscular sphincter that is essential in preventing duodenal contents from entering the pancreatic duct. Dogs and approximately 20% of cats have a second pancreatic duct, the accessory pancreatic duct (ductus pancreaticus accessorius), that empties on the minor duodenal papilla, approximately 1–3 cm distal to the major duodenal papilla into the duodenum.[1]

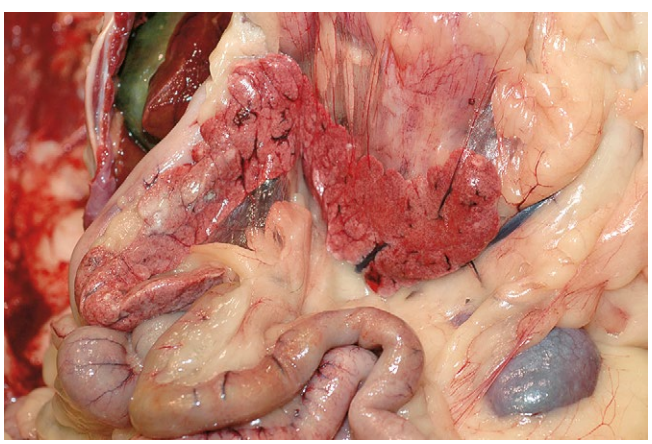


**Fig. 10-1** Normal canine pancreas

This figure shows a normal canine pancreas during necropsy. Note the right and left limbs on either side of the head of the pancreas. In dogs and cats, the head of the pancreas is not as clearly demarcated as is the case in humans, but it can be identified by the pancreatic artery, vein, and duct that enter the pancreas in this area. (Courtesy of Dr. Shelley Newman, Newman Specialty VetPath; Hicksville, NY, USA.)

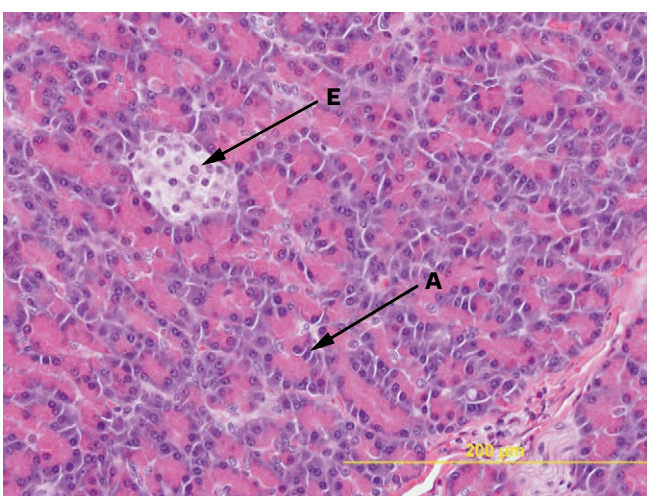



**Fig. 10-2** Histological view of the pancreas

This figure shows a histological view of a normal dog pancreas. The majority of the cells are exocrine pancreatic cells (**A**) arranged in a network of interconnecting tubules that histologically appear as acini that form pancreatic lobules. The islets of Langerhans are composed of clusters of endocrine cells (**E**), which have smaller nuclei and a more vacuolated cytoplasm. (H&E stain, 40x) (Courtesy of Dr. Shelley Newman, Newman Specialty VetPath; Hicksville, NY, USA.)

## 10.2 Physiology

Jörg M. Steiner

The exocrine pancreas has several important functions. Most importantly, the acinar cells, which make up the bulk of the exocrine pancreas, synthesize and secrete many digestive enzymes and zymogens of digestive enzymes (▶Tab. 10-1).[2] These digestive enzymes produced by the pancreas are required for digestion of the macronutrients in the diet. While the digestive tract is characterized by redundancy (i.e., the digestion of each dietary component is facilitated by more than one digestive process), most dogs and cats require at least some pancreatic function to digest dietary macronutrients. However, there are isolated cases of dogs or cats that have virtually no residual exocrine pancreatic function and that do not have any clinical signs of maldigestion. In addition to the synthesis and secretion of pancreatic digestive zymogens and enzymes, the exocrine pancreas also synthesizes and secretes a variety of other molecules (▶Tab. 10-1), such as intrinsic factor, which is crucial for cobalamin absorption; colipase, which is needed to reverse the inhibition of pancreatic lipase by bile salts; pancreatic secretory trypsin inhibitor (PSTI, the product of the *SPINK1* gene); antibacterial factors; pancreatic lipase-related proteins 1 and 2 (PLRP1 and PLRP2); and probably certain trophic factors that have been hypothesized to affect intestinal mucosal thickness.[2,3]

Some digestive enzymes are synthesized and secreted as active enzymes, while others are synthesized and secreted as inactive proforms or zymogens.[2] In general, any enzyme that is capable of digesting components of the cellular membrane, such as proteins and phospholipids, is secreted as a zymogen, while those enzymes that digest components that are normally located inside of organelles or the nucleus are secreted as active enzymes.

Pancreatic enzymes and zymogens of pancreatic enzymes are synthesized by protein synthesis; that is, DNA is transcribed to mRNA during transcription in the nucleus of the acinar cells, and the mRNA, in turn, is read at the ribosomes of the rough endoplasmatic reticulum (rER). As the protein strand is being elongated, it is internalized into the rER, and a small signal peptide is cleaved. The zymogens and enzymes are then processed by the Golgi apparatus, where they undergo glycosylation and other post-translational changes. At the distal end of the Golgi apparatus, the zymogens and enzymes are packaged into zymogen granules. These zymogen granules are then released into the duct lumen by exocytosis.

It is interesting to note that pancreatic secretions are regulated at multiple levels. Peptides, amino acids, and fatty acids containing eight or more carbon atoms or their monoglycerides all stimulate the release of cholecystokinin (CCK) from the neuroendocrine cells in the duodenum and jejunum. CCK stimulates gall bladder contraction and also leads to the secretion of zymogen granules from the acinar cells into the pancreatic duct system. A small amount of zymogen granules are also released into the vascular space. However, CCK, in addition to stimulating the secretion of stored zymogen granules and insulin, also stimulates the protein synthesis of pancreatic zymogens and enzymes.[4]

Hydrolysis of pancreatic trypsinogen to active trypsin is catalyzed by enteropeptidase, a serine protease that is secreted by the duodenal mucosa. In turn, activated trypsin then activates more trypsinogen molecules and other zymogens.[2] Pancreatic digestive enzymes are crucial for the digestion of most dietary components but oral, gastric, and brush border enzymes also contribute to this process. This contribution can be quite significant; for example, under physiological conditions, a significant portion of dietary fat is digested by gastric lipase.[5]

**Tab. 10-1** Secretory products of the exocrine pancreas

This table shows a list of secretory products of the exocrine pancreas. There are three types of secretory products: zymogens of pancreatic digestive enzymes, pancreatic enzymes, and other molecules that are neither.

| Enzymes secreted as zymogens | Enzymes secreted in an active form | Other secretory products |
|---|---|---|
| • Trypsinogen<br>• Chymotrypsinogen<br>• Proelastase<br>• Prophospholipase<br>• Kallikreinogen<br>• Procarboxypeptidase | • Lipase<br>• Amylase<br>• Carboxylesterase<br>• Desoxyribonuclease<br>• Ribonuclease<br>• Pancreatic lipase-related protein 2 | • Water<br>• Bicarbonate<br>• Procolipase<br>• Intrinsic factor<br>• Antimicrobial factors<br>• Pancreatic secretory trypsin inhibitor (PSTI)<br>• Pancreatic lipase-related protein 1<br>• Trophic factors for the intestinal tract |

The main function of the exocrine pancreas is to digest dietary components. One important dietary component in carnivores and omnivores is meat, including pancreatic tissue; thus, the pancreas is always in danger of digesting itself. However, there are several mechanisms in place to prevent autodigestion:[6]

1. The pancreas synthesizes and secretes all the enzymes that can be dangerous to itself as inactive preforms or zymogens.[2]
2. These zymogens are stored in zymogen granules within the acinar cells and are kept strictly separate from the lysosomes. This separation is important to prevent autodigestion, as lysosomal enzymes are capable of activating zymogens.[2]
3. Pancreatic zymogens are inhibited from autoactivation by adverse conditions (e.g., pH) within the zymogen granules. This may not completely abolish autoactivation, but certainly decreases its likelihood.
4. A small inhibitory molecule, PSTI, is co-synthesized, co-transported, and co-stored with pancreatic zymogens.[7] PSTI inhibits prematurely activated trypsin molecules, thereby preventing the cascade of pancreatic enzyme activation. PSTI probably plays a crucial role in preventing pancreatitis in normal individuals. In humans, hereditary pancreatitis is caused by mutations of the genes encoding trypsinogen or, less frequently, PSTI (i.e., *SPINK1* gene).[8] These mutations either lead to the production of non-functional PSTI or a trypsin that cannot effectively be inhibited by PSTI.[8] Mutations in the *SPINK1* gene have also been identified in miniature schnauzers with pancreatitis.[9]
5. There is a unidirectional flow of pancreatic juice in the pancreatic duct. Pancreatic zymogens are activated in the small intestine, and it is crucial that these activated enzymes cannot return to the pancreas, where they could lead to pancreatic autodigestion and pancreatitis.
6. Finally, if all of these safety mechanisms are overcome and activated pancreatic enzymes escape into the vascular space, they are quite effectively inhibited by proteinase inhibitors, such as $\alpha_1$-proteinase inhibitor ($\alpha_1$-PI) and $\alpha_2$-macroglobulin. Trypsin bound to $\alpha_1$-PI is quickly transferred to $\alpha_2$-macroglobulin, which is then trapped in the reticuloendothelial system of the spleen and thus removed from circulation.

There may be other protective mechanisms that are as yet unknown, but it is still quite impressive how many such mechanisms are in place to prevent the pancreas from damaging itself.

Historically, the exocrine pancreas has been considered as having little to no regenerative capacity. However, more recently, it has been shown that the exocrine pancreas can undergo adaptive growth as well as regenerative growth.[4] Adaptive growth is in response to exposure to a high-protein diet and hyperphagia and essentially is a process that compensates for increased food intake. This process is believed to be mediated by CCK. Regenerative growth occurs in response to acinar cell damage. CCK, insulin, and insulin-like growth factor 1 are believed to play an important role in stimulating regenerative growth.[4] It is believed that tubular cells de-differentiate and then differentiate into mature acinar cells.[10] The capacity for regeneration is important in dogs and cats with acinar cell damage due to acute or chronic pancreatitis and may explain the relatively low rate of exocrine pancreatic insufficiency (EPI) in these animals.

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
svg.to/9842-10-01-02

## 10.3 Diseases of the exocrine pancreas

The true incidence of exocrine pancreatic disease in dogs and cats is unknown. However, over the last two decades, diagnosis of exocrine pancreatic diseases has increased dramatically in both dogs and cats.

### 10.3.1 Pancreatitis

Jörg M. Steiner

#### 10.3.1.1 Introduction and definitions

Pancreatitis describes pancreatic inflammation, which, as is the case in humans, is considered to be quite common in both dogs and cats.[1,2] In one study, more than 11% of 208 dogs undergoing necropsy at the Animal Medical Center in New York City had macroscopic lesions suggesting pancreatitis. Pancreata from all 208 dogs were sectioned every 2 cm, and a total of 64% had histological lesions consistent with acute and/or chronic pancreatitis. A subset of 101 of these dogs was described in detail in the literature (▶ Fig. 10-3).[3] In another study, 26% of dogs submitted to necropsy for all

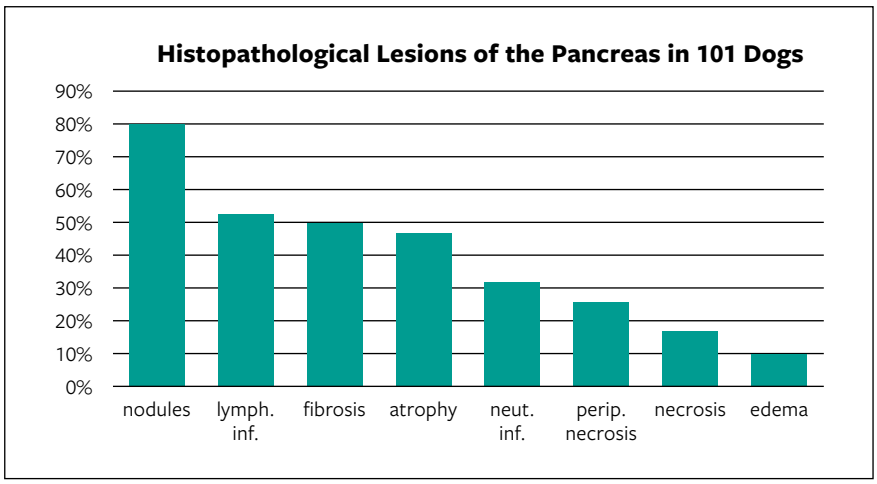



**Fig. 10-3** Frequency of histopathological lesions of the pancreas in 101 dogs

This figure shows the frequencies of histopathological lesions of the pancreas of 101 dogs presented for necropsy to the Department of Pathology at the Animal Medical Center in New York.[6] The dogs evaluated were affected by a wide variety of diseases and died of various causes. Each pancreas was sectioned every 2 cm, and each section was evaluated for hyperplastic pancreatic nodules (**nodules**), lymphocytic infiltration (**lymph. inf.**), pancreatic fibrosis (**fibrosis**), pancreatic atrophy (**atrophy**), neutrophilic infiltration (**neut. inf.**), peripancreatic fat necrosis (**perip. necrosis**), pancreatic necrosis (**necrosis**), and pancreatic edema (**edema**). With the exception of hyperplastic nodules, all other lesions are considered to be evidence of current or previous pancreatitis.

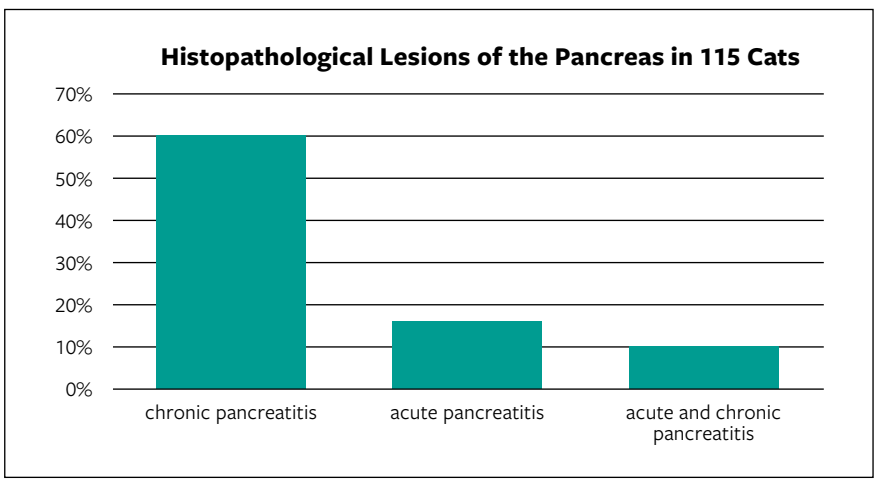



**Fig. 10-4** Frequency of histopathological lesions of the pancreas in 115 cats

This figure shows the frequencies of histopathological lesions of the pancreas in 115 cats presented for necropsy to the Department of Pathology at the University of California, Davis.[5] The cats were affected by a wide variety of diseases and died of various causes. Three biopsies were taken from each pancreas (left limb, right limb, and pancreatic head), and each section was evaluated separately for evidence of either acute or chronic pancreatitis. Lesions considered suggestive of acute pancreatitis were interstitial edema, pancreatic necrosis, peripancreatic fat necrosis, or neutrophilic infiltration of the pancreas. Lesions considered suggestive of chronic pancreatitis were lymphocytic infiltration, interstitial fibrosis, and acinar degeneration.

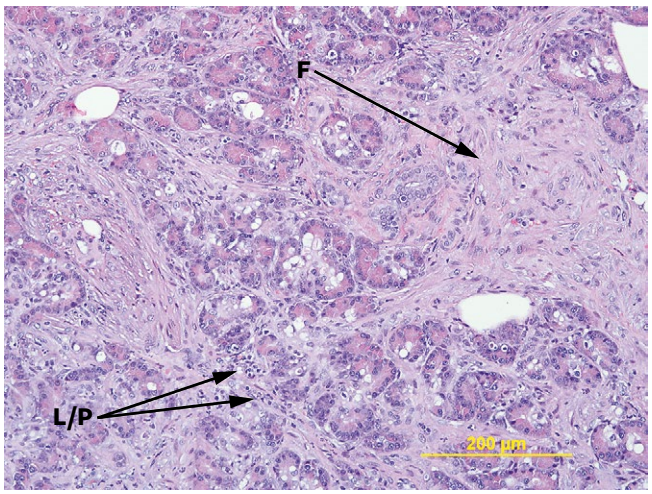



**Fig. 10-5** Chronic pancreatitis: This image shows a section of pancreas from a dog with chronic pancreatitis.

Notably, there is pancreatic acinar atrophy, evidenced by the lack of pancreatic acinar cells and abundant infiltrative fibrosis (**F**). Scattered infiltrates of lymphocytes, and plasma cells (**L/P**) are also seen. (H&E, 20x)
(Courtesy of Dr. Shelley Newman, Newman Specialty VetPath; Hicksville, NY, USA.)

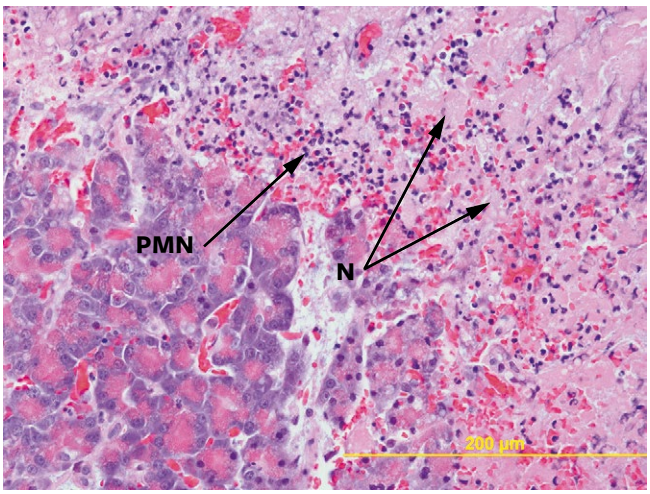



**Fig. 10-6** Acute pancreatitis: This image shows a section of pancreas from a dog with acute pancreatitis.

Note the marked necrosis (**N**) of acinar cells and the infiltration with neutrophils (**PMN**). (H&E, 40x)
(Courtesy of Dr. Shelley Newman, Newman Specialty VetPath; Hicksville, NY, USA.)

causes through a group of first-opinion practices in the UK showed evidence of chronic pancreatitis and 2% evidence of acute pancreatitis.[4] Also, in a study of 115 cats that underwent necropsy and had three pancreatic biopsies collected, the overall histopathological prevalence of pancreatitis was 66% (▶Fig. 10-4), while the prevalence was 45% in apparently healthy cats.[5] These data suggest that pancreatitis is far more common in dogs and cats than previously suspected. These data also suggest that infiltration of the pancreas with inflammatory cells is not always associated with clinical signs; whether such subclinical pancreatic inflammation is clinically significant in all animals remains to be determined.

As with other organs, pancreatic inflammation can be classified based on different parameters. In human medicine, several international conferences have been held to arrive at a universally agreed upon multi-disciplinary classification system for pancreatitis, last updated in 2012.[7] Because a similar classification system is not available for veterinary medicine, the author generally adheres to this human classification system. In general, pancreatitis is divided into acute or chronic disease.[8] This classification is solely based on histopathological findings, with chronic pancreatitis being associated with permanent histopathological changes (▶Fig. 10-5), pancreatic atrophy, and pancreatic fibrosis, while acute pancreatitis is not associated with such permanent changes (▶Fig. 10-6).[8]

Both acute and chronic pancreatitis can be associated with a wide variety of complications. Local complications of acute pancreatitis include pancreatic necrosis and pancreatic and peripancreatic fluid accumulations. Systemic complications of acute pancreatitis include electrolyte imbalances, acid-base imbalances, disseminated intravascular coagulopathy (DIC), acute kidney injury, acute lung injury/acute respiratory distress syndrome, myocarditis, neurological signs, and multi-organ failure. Complications of chronic pancreatitis are related to pancreatic atrophy, leading to exocrine pancreatic insufficiency (EPI; ▶Chap. 10.3.2), diabetes mellitus, or an acute exacerbation of the disease. The severity and prognosis of pancreatitis are dependent on the presence of these local and systemic complications.

### 10.3.1.2 Etiology

The etiology and pathogenesis of pancreatitis are not entirely understood, but there are many risk factors that have been implicated. Miniature schnauzers have long been recognized as being at an increased risk for pancreatitis, but only recently has a mutation been identified that may be responsible for this increased risk.[9,10] Three mutations of the *SPINK1* gene (i.e., the gene encoding pancreatic secretory trypsin inhibitor, PSTI) have been identified.[9] It is interesting to note that

**mutations of the *SPINK1* gene**, though not the same as the ones that have been identified in the miniature schnauzer, are also associated with hereditary pancreatitis in humans.[11,12] There are some other dog breeds that have also been suggested to be at an increased risk for pancreatitis, including boxers, cavalier King Charles spaniels, cocker spaniels, collies, and Yorkshire terriers.[4]

**Dietary indiscretion**, mainly of fatty foods, has anecdotally been blamed for many cases of canine pancreatitis. One study demonstrated that dogs diagnosed with pancreatitis more commonly have a history of dietary indiscretion than dogs diagnosed with acute renal failure, supporting this suspicion.[13]

**Hypertriglyceridemia** is considered a risk factor for pancreatitis in dogs but not in cats. In humans, it has been suggested that the risk for pancreatitis is dramatically increased when serum triglyceride concentrations exceed 1,000 mg/dL (11.3 mmol/L).[14] Similarly, a study in dogs suggested an increased risk for pancreatitis in dogs with a serum triglyceride concentration above 900 mg/dL (10.2 mmol/L).[15,16] However, the pathogenesis of hypertriglyceridemia-induced pancreatitis is poorly understood.[17] Also, hypertriglyceridemia-induced acute pancreatitis in humans is associated with the highest number of complications for any etiology, with one study suggesting a dose-dependent impact on severity.[18,19]

**Hypotension and pancreatic hypoperfusion** have also been identified as risk factors for pancreatitis, and in fact, it has now been speculated that the increased incidence of pancreatitis in human patients undergoing surgery may be caused by pancreatic hypoperfusion rather than pancreatic surgical trauma. Thus, proper fluid support during anesthesia is crucial in maintaining exocrine pancreatic health. Notwithstanding this, pancreatic trauma (surgical or other) can lead to pancreatitis.[20] As a consequence, extreme care should be taken when handling the pancreas during a surgical procedure.

Certain **infections** have also been implicated in causing pancreatitis; however, they are extremely rare in either dogs or cats. Isolated cases of fungal infiltration of the pancreas leading to pancreatitis have anecdotally been reported (Newman SJ, personal communication, 2007). In addition, there are two reports of bacterial infection of the pancreas in dogs.[21,22] In the first, pancreatic abscess (now referred to as walled-off pancreatic necrosis) was diagnosed in six dogs. *Klebsiella pneumoniae* was cultured from the area of the pancreas in one dog, and *Pseudomonas aeruginosa* was cultured in a second dog.[21] The bacterial cultures were negative in the remaining four dogs.[21] In the second report, only two of nine dogs with a pancreatic abscess had a positive bacterial culture.[22] Bacterial infections of the pancreas are also extremely rare in cats and have only been associated with a pancreatic abscess in a single cat.[23] It should, however, be noted that the evaluation of feline pancreatic tissue by fluorescence *in situ* hybridization (FISH) has shown the presence of bacterial DNA in many cats with pancreatitis, but the clinical relevance of this finding is unclear at this point.[24] Besides bacteria, other infectious organisms have also been reported in dogs and cats with pancreatitis. For example, *Toxoplasma gondii* can infect the feline pancreas. In one study, 38 of 45 cats (84.4%) with toxoplasmosis had organisms in the pancreas, but the organism was limited to the pancreas in only a single cat.[25] The hepatic fluke, *Amphimerus pseudofelineus*, can also infest the pancreas of cats and lead to pancreatitis.[26] Other infections, including FIP, feline parvovirus, FIV, or FeLV, have all been implicated in causing pancreatitis, but the evidence is limited. In dogs, infections with *Babesia canis*, *Leishmania infantis*, or *Heterobilharzia americana* have been shown to cause pancreatitis.[27,28] Primary infectious acute pancreatitis is also considered rare in people, with most cases being due to viral infections, helminths, or salmonellosis.[29,30]

**Drugs** can also cause pancreatitis in rare cases, but in humans, more than 500 drugs have been implicated.[1,31] However, demonstration of a cause-and-effect relationship is difficult, and proof of such a relationship has only been demonstrated for a very limited number of agents.[1] In dogs, several agents have been implicated, including calcium, L-asparaginase, potassium bromide, phenobarbital, and antimonial drugs used for the treatment of leishmaniasis.[32–34] In cats, calcium and the topical organophosphate fenthion have been implicated in causing pancreatitis.[35] In humans, many more drugs have been implicated, including azathioprine and didanosine, for which the strongest associations have been reported, as well as vinca alkaloids, diuretics, propofol, and several non-steroidal anti-inflammatory drugs (NSAIDs) and antibacterial agents.[31,36–39] Some of these drugs may cause pancreatitis by causing hypertriglyceridemia, while most others may cause pancreatitis as an idiosyncratic reaction that is both unpredictable and not dose-dependent.[31] Steroid administration is currently not considered a risk factor for pancreatitis by most authors, and the treatment of patients with pancreatitis with steroids is not considered to be contraindicated.



**NOTE**

In addition to calcium administration, hypercalcemia can also be associated with acute pancreatitis.

While uncommon, hypercalcemia of malignancy, most commonly due to parathyroid carcinoma, multiple myeloma, or adult T-cell lymphoma, has been reported in humans with pancreatitis and carries a poor prognosis.[40]

Recently, a dog was reported to develop acute pancreatitis after honeybee envenomation.[41]

Finally, several **endocrine disorders**, including hyperadrenocorticism, diabetes mellitus, and hypothyroidism, have all been identified as risk factors for pancreatitis in dogs.[42] The relationship between diabetes mellitus and pancreatitis is complex, as dogs and cats with either acute or chronic pancreatitis can develop diabetes mellitus.[43] At the same time, experimental hyperglycemia in cats has been shown to lead to inflammatory infiltration of the pancreas.[44] Also, serum concentrations of amylin, a pancreatic hormone, have recently been shown to be increased in both humans and cats with diabetes mellitus or pancreatitis, further linking diabetes mellitus and pancreatitis pathophysiologically.[45]

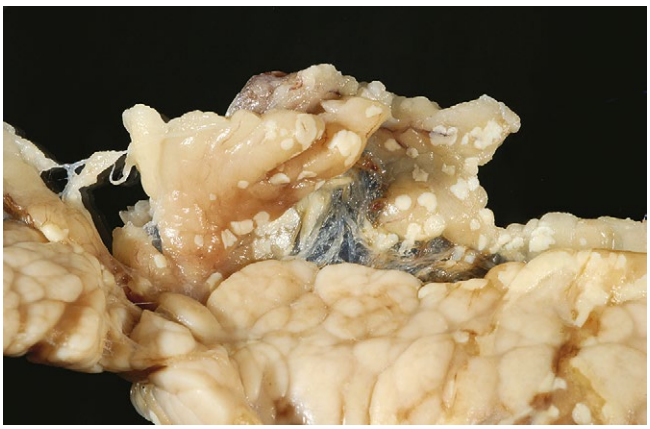


**Fig. 10-7** Peripancreatic fat necrosis

This picture shows a canine pancreas with many white nodules consistent with peripancreatic fat necrosis. Triglycerides in the tissue surrounding the pancreas are hydrolyzed, with the resulting fatty acids forming calcium soaps (saponification).
(Courtesy of Dr. Shelley Newman, Newman Specialty VetPath; Hicksville, NY, USA.)

### 10.3.1.3 Pathogenesis

Pancreatitis is a complex disease, and its pathogenesis is not completely understood. As indicated above, there are many risk factors for pancreatitis. These risk factors ultimately lead to pancreatic inflammation, and it has long been held that they do so by leading to premature activation of trypsinogen and other zymogens within the acinar cells, which in turn leads to local damage and an inflammatory response.[46] However, there are some doubts about this **trypsinogen-centric pathogenesis** hypothesis.[47] In one study, premature activation of trypsinogen within acinar cells was induced in vivo in genetically modified mice, but the mice did not develop pancreatitis. Also, exactly how the enzyme cascade is activated is poorly understood. There is little doubt that in some experimental models of pancreatitis, one of the first indicators of ensuing pancreatitis is a decreased secretion of pancreatic enzymes and co-localization of zymogen granules and lysosomes.[48] Co-localization of these cellular compartments then leads to the activation of trypsinogen by cathepsin B, one of the lysosomal enzymes.[12,47] Trypsin, if not immediately scavenged, in turn, activates more trypsinogen molecules and other zymogens. The prematurely activated digestive enzymes then lead to local damage, including pancreatic necrosis, peripancreatic fat necrosis, pancreatic hyperperfusion, and bleeding (▶Fig. 10-7). The local damage then leads to the release of cytokines and recruitment of inflammatory cells.

However, there is now a significant body of evidence showing that there are **trypsin-independent factors** that are crucial in the pathogenesis of both acute and chronic pancreatitis.[47] Nuclear factor-kappa B (NF-κB) activation is independent of protease activation but plays an early and central role in local and systemic inflammation that involves a large number of cytokines and chemokines.[12,47] Interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNFα) appear to play a more central role in mediating the effects of NF-κB, leading to the recruitment and activation of immune cells.[12] There is not much data related to these events in dogs or cats, but one study reported increased serum concentrations of IL-8, monocyte chemoattractant protein-1 (MCP-1), receptor for advanced glycation endproducts (RAGE), and stem cell factor (SCF) in dogs with suspected pancreatitis, but further studies in dogs and cats are needed to better understand cytokine recruitment in small animal patients.[49] This inflammatory reaction not only leads to further local damage but also leads to systemic complications, such as hypotension, acid-base abnormalities, DIC, renal failure, acute lung injury/acute respiratory distress syndrome, gastrointestinal failure, or multi-organ failure.[50,51] In rodent models of experimental pancreatitis, massive numbers of neutrophils extravasate from the pulmonary capillaries, leading to the formation of neutrophilic extravascular traps and acute respiratory distress syndrome. Also, a model of two critical thresholds has been described.[52] This model suggests that there are stressors and protectors of pancreatic acinar cells.[52] When more stressors than protectors act on pancreatic acinar cells, the first critical threshold is met, and pancreatitis ensues.[52] Amplification loops on one side and management strategies on the other side act on the patient.[52] When the stressors and

amplification loops outweigh the protectors and effects of the management strategies, the second critical threshold is met, and severe acute pancreatitis ensues.[52] This model is of great interest as it would suggest that different management strategies might be efficacious when patients reach one or the other critical threshold.

However, it is unclear how relevant these observations from animal models of acute pancreatitis are for spontaneous disease in dogs and cats. Various studies have shown acinar cell death by necrosis, apoptosis, necroptosis, or pyroptosis, but further studies are needed to elucidate which processes play crucial roles in which patient and whether premature protease activation and/or inflammation drive cell death or whether cell death drives inflammation.[12]

The pathogenesis of **chronic pancreatitis** is even more obscure than that of acute pancreatitis as there is rarely any evidence of pancreatic necrosis, and thus premature activation of trypsinogen and an ensuing enzymatic cascade can hardly be suspected of eliciting the inflammatory reaction. It is also interesting to note that chronic pancreatitis is not simply a progression of acute pancreatitis. While 50–70% of humans with chronic pancreatitis have a history of one or multiple episodes of acute pancreatitis, the remainder do not.[53] Thus, while the so-called "two-hit model" of acute pancreatitis leading to activation of pancreatic stellate cells, which lead to further injury, inflammation, and fibrosis may play a role in some cases, there are clearly acute-pancreatitis-independent factors leading to chronic disease.[54]

#### 10.3.1.4 Clinical presentation

It should be noted that studies reporting the clinical signs of dogs and cats with pancreatitis may be misleading as many studies only included dogs or cats with severe or even fatal disease, which does not accurately mirror the population of dogs and cats seen in a typical clinical setting. For example, one study of 70 dogs with fatal pancreatitis (i.e., dogs that either died of their disease or were euthanized because of the severity of their disease) reported the most common clinical signs to be anorexia (91%), vomiting (90%), weakness (79%), abdominal pain (58%), dehydration (46%), diarrhea (33%), and fever (21%).[55] Similarly, a compilation of 159 feline pancreatitis cases reported anorexia (87%), lethargy (81%), dehydration (54%), weight loss (47%), hypothermia (46%), vomiting (46%), icterus (37%), fever (25%), abdominal pain (19%), and diarrhea (12%) as the most common clinical signs.[56]

**CLINICAL PEARLS**

While these clinical signs reported for either dogs or cats with severe pancreatitis are fairly nonspecific, many patients will present with less severe forms of pancreatitis associated with even fewer clinical signs. Thus, it is important to also consider pancreatitis in dogs and cats that present with signs such as hyporexia, lethargy, or behavioral changes. Of note, abdominal pain, one of the key clinical signs of pancreatitis in humans, is reported much less frequently in dogs and cats than in humans. While one could stipulate that dogs and cats with pancreatitis are less commonly affected by abdominal pain than are humans, the author believes that it is far more likely that abdominal pain is not accurately identified in small animals. As a consequence, abdominal pain should be suspected in all small animal patients diagnosed with pancreatitis.

Some patients may not show any obvious evidence of abdominal pain, but others may show classical signs of severe abdominal pain. One such example in dogs is the so-called prayer position (▶Fig. 1-9). As stated above, diarrhea has been reported in a significant portion of both dogs and cats with pancreatitis, and pancreatitis should be considered as a differential diagnosis in dogs and cats presenting with diarrhea.[55,56]

#### 10.3.1.5 Diagnosis

##### 10.3.1.5.1 Routine clinical pathology

A minimum database consisting of a complete blood count (CBC), serum/plasma chemistry profile, and urinalysis often shows nonspecific changes, and routine blood work is generally not useful for diagnosing pancreatitis.[35,55] However, findings on a minimum database are crucial for ruling in or ruling out other differential diagnoses and assessing the overall health status of the patient, including any evidence of systemic complications from pancreatitis.

**CBC** changes reported in dogs and cats with pancreatitis include thrombocytopenia, neutrophilia with a left shift, but also neutropenia, anemia, but also hemoconcentration.[35,55]

**Changes in serum/plasma biochemistry profiles** may include increases in hepatic enzyme activities, electrolyte abnormalities, azotemia, hypoalbuminemia, hyperbilirubinemia, hyperglycemia or hypoglycemia, as well as hypocalcemia or hypercalcemia. As the blood from the exocrine

pancreas drains into the portal vein, inflammation of the pancreas can have a direct impact on hepatocytes. Electrolyte and fluid loss, as well as third-spacing, can lead to dramatic electrolyte imbalances. Dehydration can lead to prerenal azotemia, but acute renal injury is also one of the most important complications of severe acute pancreatitis in humans, and renal azotemia is common in these patients. Albumin is considered a negative acute phase reactant. Sepsis may be associated with hypoglycemia, but pancreatic necrosis may lead to hyperglycemia due to a lack of insulin secretion. Calcium can be utilized during the formation of peripancreatic fat necrosis as calcium is needed to form calcium soaps with free fatty acids, but hypercalcemia may be present as an indicator of an underlying cause of pancreatitis. Hyperbilirubinemia can occur secondary to extrahepatic bile duct obstruction that is suspected to be due to regional inflammation.

**Urinalysis** initially often reveals an elevated urine-specific gravity secondary to dehydration. However, in severe cases, acute kidney injury may ensue, and the urine specific gravity may drop, and casts may be seen in the sediment.

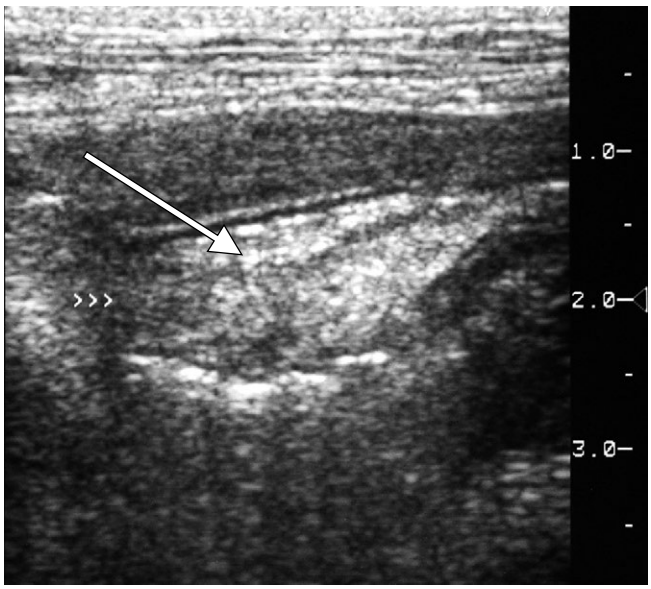



**Fig. 10-8** Pancreatic fibrosis: This ultrasonographic image was taken in a cat.

The pancreas is markedly hyperechoic (**arrow**), suggesting pancreatic fibrosis. However, pancreatic fibrosis often is not severe enough to be identified during ultrasound examination. (Courtesy of Dr. Mark Saunders, Lynks Group, Shelburne, VT, USA.)

#### 10.3.1.5.2 Diagnostic imaging

Abdominal radiographs may show a loss of detail in the cranial abdomen.[35,55] In some cases, there may also be a suggestion of a mass in the cranial abdomen or transposition of abdominal organs, but all of these findings are rather subjective, and a conclusive diagnosis of pancreatitis is not possible on the basis of abdominal radiographs alone. However, abdominal radiographs are helpful for diagnosing or ruling out obstructive gastrointestinal (GI) foreign bodies, peritonitis, and other causes of vomiting/acute abdomen.

In contrast, **abdominal ultrasonography** is useful for the diagnosis of pancreatitis in both dogs and cats. Over the last 20 years, abdominal ultrasonography has greatly advanced and is still advancing, leading to an improved resolution of the images obtained. This progress has made revisions of ultrasonographic diagnostic criteria necessary. Ultrasonographic changes that suggest the presence of pancreatitis include an enlargement of the pancreas, hypoechogenic areas of the pancreas (suggesting pancreatic necrosis), hyperechogenic areas around the pancreas (suggesting peripancreatic fat necrosis), peri-pancreatic fluid, and hyperechoic areas of the pancreas (suggesting pancreatic fibrosis), but this latter finding is reported with a lower frequency (▶Fig. 10-8). A recent study reported ultrasonographic evidence of focal gastric wall thickening in the area of the pancreas in twelve of 14 dogs with acute pancreatitis, with submucosal thickening in twelve and muscularis thickening in five of these dogs.[57] Whether pancreatic duct size can be considered evidence of pancreatitis is currently still being debated. It should also be considered that, as for imaging of other organs, there may be a delay in the imaging findings in comparison to the actual disease process in the target organ, such that lack of changes upon abdominal ultrasonography may not rule out pancreatitis but may require repeat ultrasonography 24–48 hours later.[58] In one study of 38 dogs suspected of having acute pancreatitis in which abdominal ultrasound was performed at presentation and again 40–52 hours later, twelve (32%) had no ultrasonographic changes at either examination, 14 (37%) only at the second ultrasonographic examination, and only twelve (32%) at both ultrasonographic exams.[58] Conversely, ultrasonographic evidence of pancreatitis does not prove current active disease but may represent the remnant of pancreatic inflammation that is no longer active. It should also be pointed out that recent advances in image resolution make the differentiation of hyperplastic nodules, which are seen in many, especially older, animals, and a mixed echogenicity due to pancreatic inflammation difficult in many patients. Finally, disease severity has an important impact on the diagnostic efficacy of ultrasonography in dogs and cats with pancreatitis. While extensive pancreatic necrosis is relatively easy to identify, mild mixed echogenicity may

be much more difficult to determine. Also, many patients with pancreatitis have ultrasonographic evidence of extrahepatic bile duct obstruction. In summary, while ultrasound provides useful information for the diagnosis of pancreatitis, it has limitations and should not be used in isolation for the diagnosis of pancreatitis.[59]

In recent years, the use of contrast-enhanced ultrasonography (CEUS) has been reported, both in healthy animals as well as in animals with experimental and spontaneous pancreatitis, and its diagnostic efficacy appears to be superior to that of regular ultrasonography. However, CEUS is not currently routinely utilized as a diagnostic modality for evaluating dogs and cats with suspected pancreatitis.

**Contrast-enhanced abdominal CT** is the diagnostic tool of choice for human patients suspected of having pancreatitis.[60] This technology is not only highly sensitive for the diagnosis of human pancreatitis but is also a sensitive tool for the detection of pancreatic necrosis and, thus, a useful prognostic tool. While early studies of abdominal CT for the diagnosis of canine and feline pancreatitis were disappointing, more recent reports have been promising. The normal pancreas has been described as iso- to hypo-attenuating relative to the spleen and liver, while pancreatitis leads to an enlarged hypoattenuating pancreas.[61–64] In one study, contrast-enhanced abdominal CT findings were correlated with time of hospitalization, portal vein thrombosis, and serum cPLI (canine pancreatic lipase immunoreactivity) concentrations.[65] This study also reported contrast-enhanced abdominal CT to be superior to abdominal ultrasound in identifying dogs with more severe forms of acute pancreatitis or those with portal vein thrombosis.[65] However, abdominal contrast-enhanced abdominal CT is not currently routinely used for the diagnosis of pancreatitis in dogs or cats, and further studies to better establish this imaging modality for the diagnosis of pancreatitis are warranted.

Magnetic resonance imaging (MRI) of the abdominal cavity has also been reported to be promising but is not currently routinely employed for the diagnosis of pancreatitis in small animals.[66] One study in ten cats with suspected pancreatitis reported enlargement of the pancreas, T1 hypointensity and T2 hyperintensity of the parenchyma, pancreatic duct dilation, and contrast enhancement.[66]

One study reported on the use of endosonography for the diagnosis of pancreatitis in cats.[67] While this pilot study did not report an improvement of sensitivity over abdominal ultrasonography, the authors noted that subjectively, visualization of the normal pancreas was superior with EUS compared with traditional abdominal US.[67]

#### 10.3.1.5.3 Pancreatitis markers

Additional information can also be found in ▶ Chap. 1.3.4.

**Serum amylase activity** is considered of limited clinical value for the diagnosis of pancreatitis in small animals. Both the sensitivity and the specificity of serum amylase activity have been reported to be approximately 50% in dogs and are even lower in cats.[68]

**Trypsin-like immunoreactivity (TLI)** measures the amount of trypsinogen and trypsin in serum. Serum TLI is considered to be highly specific for exocrine pancreatic function, but trypsinogen and trypsin are very small and are positively charged, leading to rapid renal excretion. In addition, prematurely activated trypsin circulating in the vascular space is scavenged by protease inhibitors, leading to an extremely short half-life and low diagnostic sensitivity for pancreatitis, reported to be approximately 30–60%, making TLI a suboptimal diagnostic marker for pancreatitis in both species.[69,70] However, serum TLI concentration remains the diagnostic test of choice for the diagnosis of EPI (▶ Chap. 1.3.4.1.2).

**Serum lipase activity** has been used for the diagnosis of pancreatitis in humans and other species for many years. Pancreatic acinar cells synthesize and secrete classical pancreatic lipase (pancreatic lipase). When pancreatic acinar cells are damaged, pancreatic lipase is released into the vascular space. However, it is important to note that many other cell types in the body also synthesize and release lipases into the vascular space. Some of these lipases are closely related and belong to the same gene family, while others are not closely related at all.

Lipase in serum can be measured by either catalytic or immunologic assays. Catalytic assays can be based on different substrates, the most common of which are 1,2-diglycerides, 1,2-o-dilauryl-rac-glycero-3-glutaric-acid-(6'methylresorufin) ester (DGGR), or triolein. None of these substrates are specific for the measurement of pancreatic lipase and will also pick-up activity from non-pancreatic lipases in serum. The extent of this cross-reactivity between lipases depends not only on the substrate being used but also on assay conditions, such as the presence of bile acids, colipase, pH, and many other factors. In humans, the effects of other molecules have been well studied for the substrate DGGR and significant interference has been shown to occur due to pancreatic lipase-related protein 2 (PLRP2), hepatic lipase, lipoprotein lipase, various proteases and esterases, and even hemoglobin. In both dogs and cats, the impact of heparin-induced lipases on DGGR-based assays (i.e., hepatic lipase and lipoprotein lipase) have been documented.[71] Also, DGGR-based assays have been shown to be impacted by spiking with human recombinant PLRP2, and

recently, rich expression of PLRP2 has been demonstrated in the gastric mucosa, fat, and renal tubules in dogs. This lack of specificity can lead to false positive results in dogs and cats without pancreatitis. For example, the author has observed dogs without pancreatitis but with chronic liver disease that had an increased serum lipase activity using a DGGR-based lipase activity assay but a normal serum pancreatic lipase concentration. Some laboratories increase the cut-off value for DGGR-based lipase assays to increase specificity, which is associated with a decrease in sensitivity. Several studies have reported "good" correlation between DGGR-based lipase activity assays and pancreatic lipase concentrations measured by an immunoreactivity assay. However, these studies report Cohen's kappa coefficients for agreement in interpretation that are approximately 0.70, which is considered unacceptable for two parameters that measure the same analyte.



**NOTE**

While some dogs and cats with pancreatitis will have increased serum lipase activities, it must be remembered that none of the lipase activity assays currently on the market are specific for the measurement of pancreatic lipase, and false positive results can be expected in various non-pancreatic conditions. Thus, a diagnosis of pancreatitis should not be based on the measurement of serum lipase activity alone.

Also, a recent study reported increased serum lipase activities above 3 times the upper limit of the reference interval in 11% of 1,360 critically ill dogs without any clinical evidence of pancreatitis.[72] Further studies are needed to determine whether these dogs with renal, endocrine, or immune-mediated diseases also had subclinical pancreatitis or whether these increases were due to the primary disease process, leading to the release of non-pancreatic lipases into the vascular space.[72] There are also few studies regarding the use of a triolein-based lipase assay, which is currently the only assay on the market using this substrate.[73,74] One study with 44 dogs with acute pancreatitis and 20 dogs without pancreatitis reported a specificity of 89.5% and a sensitivity of 100%, but the ratio of pancreatitis to non-pancreatitis patients suggested that the patient material used in this study was very selective.[73] A similar study in a small number of cats showed a lower sensitivity of 67%.[75] Also, this assay has been reported to be influenced by icterus, which is commonly observed in both dogs and cats with acute pancreatitis.[76]

In contrast to serum lipase activity, the serum concentration of pancreatic lipase can be specifically measured using immunoassays, **pancreatic lipase immunoreactivity (cPLI and fPLI)**. The analytical specificity has been demonstrated by the findings that serum PLI concentrations are negligible in dogs with EPI (▶Chap. 10.3.2) due to pancreatic acinar atrophy and immunolocalization studies showing that only pancreatic acinar cells express classical pancreatic lipase.[77,78] Also, a study using pancreatic histopathology as a gold standard in 40 clinically healthy dogs reported the specificity of this assay to be 97.5% (using a cPLI >400 µg/L as a cut-off).[79] Because of these findings, increases in serum PLI concentration are specific for pancreatic acinar cell damage.[79] The reported sensitivity ranges widely in dogs, from 21.0% for mild disease to 90.9% for more severe disease. In cats, it ranges from 42.1% for mild disease to 100% for moderate to severe disease. However, these ranges are higher than any other diagnostic test currently available.[3,75,80–88] Of note, when chronic pancreatitis has led to pancreatic fibrosis, serum PLI values can be lower, and the sensitivity is decreased. Several assays for the measurement of serum PLI concentration in dogs and cats are available, and it should be noted that PLI assays are species-specific. Spec cPL and Spec fPL (IDEXX Laboratories, Westbrook, Maine, USA) have been analytically validated and have been used in multiple clinical studies.[89,90] One study of 274 sick cats reported that the false positive rate of a serum fPLI concentration >5.3 µg/L was 10%, while the false negative rate was 24%, confirming a very high specificity (90%) with a moderate sensitivity (76%).[90] In Europe and parts of Asia, cPLI and fPLI assays are also available through Laboklin (Bad Kissingen, Germany). However, external validation showed these assays to fail basic validation parameters.[91] It is unknown whether these assays have since been improved or are fully analytically validated. However, a recent study reported the use of this fPLI assay in 80 cats that had pancreatic biopsies collected, reporting a specificity of 100% and a sensitivity of 57% for mild pancreatitis and 64% for severe pancreatitis.[92] Cats with pancreatic adenocarcinoma also frequently had increased serum fPLI concentrations.[92] A similar study in dogs reported a specificity of 92.5% and sensitivity of 90.9% in dogs with moderate or severe pancreatitis for the Laboklin cPLI assay, but, as expected, also showed increases in dogs with pancreatic adenocarcinoma.[93] It should, however, be noted that pancreatic cancer is rare in both dogs and cats; thus, misdiagnosis is not a major concern (▶Chap. 10.3.3).

Several point-of-care assays are available for the immunologic measurement of pancreatic lipase. The SNAP cPL and SNAP fPL (IDEXX Laboratories, Westbrook, ME) are semiquantitative tests that have been shown to correlate well with the Spec cPL and Spec fPL assays and report results as either "normal" or "abnormal".[82,94] Dogs and




**Fig. 10-9** SNAP cPL: This figure illustrates the assay interpretation of the SNAP cPL test.

**a** Normal: A test spot that is lighter in color than the control spot indicates a serum Spec cPL concentration within the reference interval and suggests that pancreatitis is unlikely.

**b** Abnormal: A test spot that is darker in color than the control spot suggests that serum Spec cPL is above the upper limit of the reference interval, and pancreatitis may be present.

cats with a "normal" result (▶Fig. 10-9a) are unlikely to have pancreatitis, whereas those with an "abnormal" result (▶Fig. 10-9b) might have pancreatitis or a Spec cPL/fPL in the equivocal range. Thus, an abnormal result should always be followed up by the measurement of Spec PL in a reference laboratory to confirm the diagnosis and to arrive at a baseline value that can be used to assess the progression of disease. Another patient-side assay, the VetScan® cPL rapid assay (Zoetis, Parsippany, New Jersey, US), is a lateral-flow device that is read with a proprietary reader. A partial analytical validation study of the VetScan® cPL assay showed that the assay was not linear and showed poor repeatability and reproducibility, with many repeat measurements having results in different diagnostic bins (i.e., normal vs. equivocal vs. pancreatitis).[95] This was confirmed in a second study that was performed under field conditions.[96] Finally, the Vcheck® cPL and Vcheck® fPL (Bionote, Hwaseong, Korea) are available in parts of Asia. Although this species-specific assay has not yet been thoroughly assessed in the primary literature, the Vcheck® cPL for use in dogs failed analytical validation in one study.[96]

Of note, some dogs and cats with conditions that are not considered to be associated with pancreatitis have been reported to show increases in serum lipase activities and/or PLI concentrations.

One study reported increased serum cPLI concentrations in dogs with hyperadrenocorticism, but no effort was undertaken to exclude subclinical pancreatitis.[97,98] Another study reported six dogs with portal hypertension and normal pancreatic histology; two dogs had cPLI concentrations suggestive of pancreatitis and two had DGGR-lipase activities suggestive of pancreatitis.[99] More research is needed to determine whether these increases represent localized subclinical disease, as the author suspects, rather than increases that are due to pancreatitis-unrelated causes.

#### 10.3.1.5.4 Pancreatic cytology

Ultrasound-guided fine-needle aspiration (FNA) of the pancreas is safe in both dogs and cats and is useful in confirming a diagnosis of pancreatitis (▶Chap. 1.7.5.1).[100] The cytologic preparation should show acinar cells confirming the successful aspiration of the pancreas, while the presence of inflammatory cells would prove the presence of pancreatitis (▶Fig. 10-10).[101] However, occasionally, only necrotic debris can be aspirated in patients with acute necrotizing pancreatitis. In addition, especially in chronic pancreatitis, fibrosis may hinder successful aspiration, and inflammatory cells may not readily exfoliate. Finally, pancreatic inflammatory infiltration is often highly localized, and a lack of inflammatory cells upon aspiration is not sufficient to rule out pancreatitis.[6]

#### 10.3.1.5.5 Pancreatic biopsy

Traditionally, histopathological assessment of a pancreatic biopsy has been viewed as the most definitive diagnostic tool for pancreatitis (▶Chap. 1.8.3.4). Pancreatic biopsies can be collected during abdominal exploratory or by laparoscopy. Pancreatitis is suspected based on the gross appearance of the pancreas, and pancreatitis can be confirmed based on histopathological findings. However, as mentioned previously, pancreatic inflammation is often highly localized and may be missed even if several biopsies are collected.[6] Thus, a pancreatic biopsy can be used to confirm pancreatitis (▶Fig. 10-11) but is insufficient to rule it out.

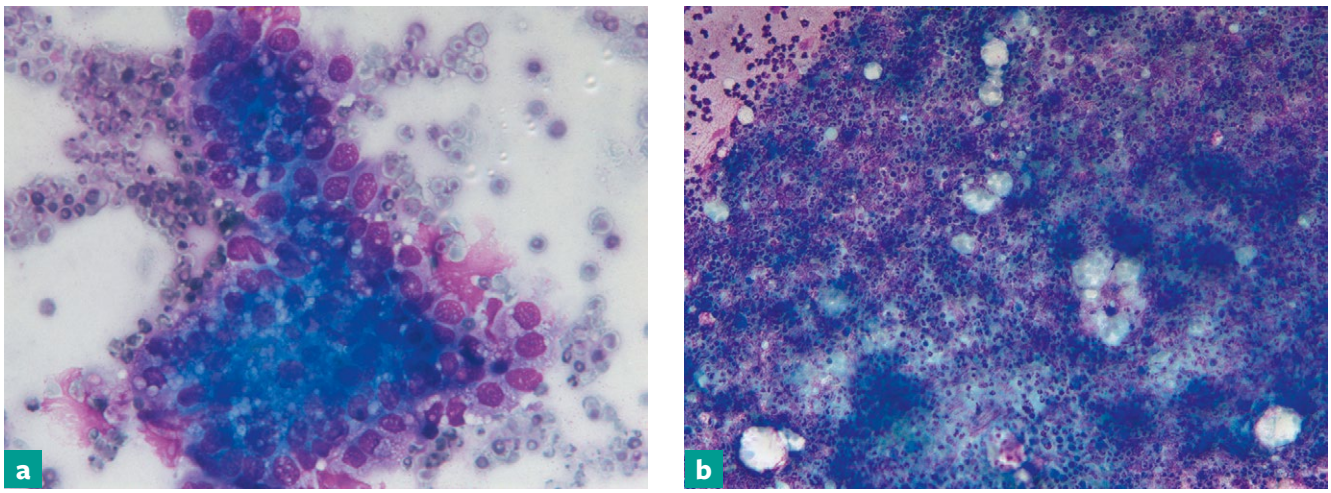


**Fig. 10-10** Acute pancreatitis: This figure shows a cytological preparation from an aspirate from the pancreas of a 7-year-old male castrated domestic shorthair cat with a "pancreatic mass."

**a** There are clusters of acinar cells that are normal in appearance.

**b** The fluid that could be aspirated from the mass showed >95% neutrophils with large amounts of necrotic debris, suggesting acute suppurative pancreatitis.

(Courtesy of Dr. Candice Pei-Hua Chu, Texas A&M University, College Station, TX, USA.)

**NOTE**

While the collection of a pancreatic biopsy in itself is not associated with many complications, many patients with pancreatitis are poor anesthetic risks.

### 10.3.1.6 Management of severe acute pancreatitis

#### 10.3.1.6.1 Introduction

Many mild cases of acute pancreatitis are self-limiting, but severe cases are often associated with significant pancreatic necrosis and systemic complications. Affected dogs and cats require aggressive management and monitoring.

#### 10.3.1.6.2 Treatment of underlying causes

As with any other disease, treatment of the underlying cause of pancreatitis should be the primary goal. However, many, if not most, cases of canine and feline pancreatitis remain idiopathic. In a few cases, the cause of pancreatitis may be obvious (e.g., pancreatitis after abdominal trauma or pancreatic surgery). However, when the cause of the pancreatitis is not obvious, the patient should be very carefully evaluated for any possible risk factors, such as hypertriglyceridemia, hypercalcemia, a history of comorbid conditions, a history of dietary indiscretion, anesthetic history, and drug history (▶ Chap. 10.3.1.2). When a potential risk factor is identified, it should be addressed appropriately.

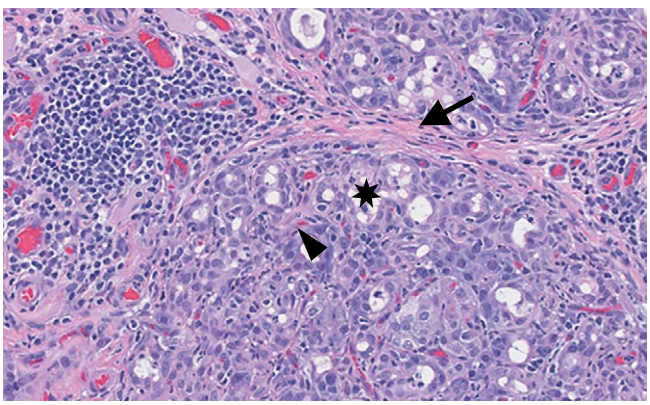


**Fig. 10-11** Moderate chronic active pancreatitis: This figure shows a histopathologic image of a pancreatic biopsy from a cat with moderate chronic active pancreatitis.

The inflammatory infiltrate consists mostly of lymphocytes and plasma cells with few neutrophils. Both inter-lobular (**arrow**) and intra-lobular (**arrowhead**) fibrosis can be appreciated. Also, acinar to ductal metaplasia can be observed (**star**).

If hypercalcemia is present, the underlying cause should be identified and treated accordingly. Severe hypertriglyceridemia in humans is managed with either continuous insulin therapy or plasma apheresis, but neither has been studied in dogs with severe hypertriglyceridemia.[102] Hypertriglycer-

idemia can be secondary or primary, but regardless of the underlying cause should be treated with dietary management (a diet containing <20g fat/1,000 kcal and treats that are low in fat). As in people with hypertriglyceridemia-induced pancreatitis, the goal of therapy is a serum triglyceride concentration <500 mg/dL (5.65 mmol/L).[17] If diet alone is insufficient lipid-lowering drugs, such as fibrates or statins, should be employed.

**CLINICAL PEARLS**

A complete drug history is important as almost any drug may cause pancreatitis as an idiosyncratic reaction. Any drug should be evaluated whether it is still indicated, and if it is, alternative drug choices should be considered.

For example, a dog previously diagnosed with idiopathic epilepsy that is well-controlled with few breakthrough seizures on potassium bromide needs to be switched to an alternative antiepileptic agent.

#### 10.3.1.6.3 Fluid therapy

Fluid therapy is the mainstay of supportive care for dogs and cats with severe forms of acute pancreatitis. Fluid resuscitation has also been recognized as a pillar of management for people with severe acute pancreatitis. However, more recently, caution has been advised that overly aggressive fluid therapy may be associated with an increased risk of acute kidney injury and/or acute respiratory distress syndrome.[103] Thus, fluid, electrolyte, and acid-base imbalances need to be carefully assessed and corrected as early as possible. The type of fluid used for replacement may also be important. Several studies suggested that, at least in humans, the use of lactated Ringers was superior to the use of normal saline.[104–106]

#### 10.3.1.6.4 Identification and management of complications

As already mentioned, pancreatitis can be associated with a variety of local and systemic complications. It is crucial to carefully monitor the patient for the development of any such local or systemic complications. While some complications, such as dehydration and electrolyte abnormalities, may easily be corrected, others, when established, are extremely difficult, if not impossible, to counteract. In human patients, it has been suggested that the presence of failure of any major organ as a complication of pancreatitis for a period of <24 hours does not have any major impact on prognosis. However, most likely, the development of any such organ failure in dogs or cats would have a dramatic negative impact on the overall outcome. Therefore, patients should be carefully monitored, and if any evidence of an impending development of organ failure is identified, aggressive measures should be taken to prevent such complications.

#### 10.3.1.6.5 Nutritional considerations

It used to be common practice to hold dogs and cats with acute pancreatitis NPO (nothing per os), to "rest" the pancreas. However, there is little evidence that such resting of the pancreas has any beneficial effects, and there is mounting evidence that nutritional support is crucial in pancreatitis patients. In humans with pancreatitis, early nutritional support has been shown to have a beneficial effect on outcomes, and enteral feeding is preferable over parenteral nutrition.[107] This has also been demonstrated in a small study in dogs where dogs fed through an esophagostomy tube showed a significantly faster improvement in clinical severity scores than those fed by total parenteral nutrition.[108] Only if vomiting cannot be successfully managed by antiemetic therapy should partial or total parenteral nutrition should be considered. Small amounts of low-fat food should be offered frequently, and the amount can subsequently be gradually increased. Some authors have suggested that recovery diets would be appropriate for dogs and cats with acute pancreatitis unless the patient is lipemic.[109] However, the author of this chapter does not agree with this notion and prefers the use of a low-fat diet (<20g of fat/1,000 kcal).

#### 10.3.1.6.6 Analgesia

Abdominal pain or discomfort is one of the key clinical signs in humans with pancreatitis.[110] While the reported incidence of abdominal pain in dogs and cats is quite low (up to 58% in dogs and up to 25% in cats), this is most likely due to the fact that abdominal pain in dogs and cats can be quite difficult to detect.[35,55] Thus, every canine and feline patient with pancreatitis should be suspected of having abdominal pain and should be managed accordingly. Only if analgesic therapy does not appear to have any clinical impact should it be discontinued.

There are a variety of analgesic options for hospitalized dogs and cats, including meperidine, buprenorphine, butorphanol, fentanyl, morphine, methadone, and lidocaine, just to name a few. The selection of analgesic drugs for outpatients is much more limited. Buprenorphine, gabapentin, and tramadol can be used orally or transmucosally, while patients

with more severe pain can be treated transdermally with a fentanyl patch.[109,111] There have also been reports that maropitant has some analgesic effects.

#### 10.3.1.6.7 Antiemetic therapy

Antiemetic therapy is very important in the treatment of pancreatitis for two reasons. The first is the importance of providing nutritional support by the enteral route, and the second is because vomiting and nausea are debilitating to the patient. A variety of antiemetic drugs are available. Dopamine inhibitors, such as metoclopramide, once the most commonly used antiemetic agents in small animal practice, are considered poor antiemetics and are usually insufficient. In contrast, $HT_3$-antagonists, such as ondansetron (0.1–0.2 mg/kg IV q12h in dogs and 0.1–1.0 mg/kg IV q6–12h in cats) and dolasetron (0.3–0.6 mg/kg IV, SC, or PO q12–24h in both dogs and cats) are very effective. Maropitant is a $NK_1$-antagonist and is highly effective in inhibiting vomiting mediated by both peripheral and central pathways (1 mg/kg SC or slowly IV q24h). Since ondansetron and maropitant work through entirely different mechanisms, the antiemetic effects of combined treatment may be additive, and frequently, dogs and cats with more severe forms of acute pancreatitis are treated with both.

#### 10.3.1.6.8 Appetite stimulants

Dogs and cats with acute pancreatitis are often hyporexic, and while treatment with an antiemetic may also have a positive impact on appetite, many patients remain hyporexic. These patients may benefit from an appetite stimulant. In hospitalized patients, capromorelin (Entyce®; Elanco US Inc, Greenfield, USA) is the most effective treatment option for both dogs and cats (3 mg/kg PO q24h in dogs 1–3 mg/kg PO q24h in cats).[112,113] In rare instances, capromorelin can cause collapse in cats, but most cats will recover quickly. Transdermal mirtazapine is highly effective in cats and may be used as an alternative.

#### 10.3.1.6.9 Anti-inflammatory agents

At the current time, administration of NSAIDs to patients with acute pancreatitis is not considered to be efficacious. All NSAIDs are known to cause GI side effects, and many of them have also been implicated in causing pancreatitis in humans.[36] There are some isolated clinical trials that propose a beneficial effect of NSAIDs in human patients with pancreatitis, but these studies were generally underpowered.[114]

Glucocorticoids were once believed to cause pancreatitis in both humans and veterinary patients.[42,115] However, the scientific basis for this hypothesis is weak, and in fact, in humans, glucocorticoids are generally no longer believed to be a risk factor for pancreatitis.[36] However, it should be considered that patients who receive glucocorticoids generally have diseases that might be considered risk factors for pancreatitis.[36]

There have been some experimental studies suggesting that when used early after induction of pancreatitis, corticosteroids have a beneficial effect.[116] More recently, there was a non-randomized controlled trial in 45 client-owned dogs that suggested that 1 mg/kg prednisolone SC q24h, given from diagnosis to discharge, shortened hospitalization time, shortened the time until serum CRP concentration decreased and improved the 1-month survival rate.[117] These findings suggest that further studies of corticosteroid treatment in dogs and cats with severe acute pancreatitis are warranted but are not sufficient to recommend the routine use of corticosteroids in dogs and cats with severe forms of acute pancreatitis.

#### 10.3.1.6.10 Modulation of inflammatory mediators

Over the last decade, it has become clear that pancreatitis, once established, is characterized by a systemic inflammatory response, and patients that succumb to this disease usually die of systemic complications, such as acute respiratory distress syndrome, acute kidney injury, or multi-organ failure. The formation of neutrophilic extravascular traps (nETs) appears to play an important role in tissue damage caused by the systemic inflammatory response.[118] Therefore, modulation of inflammatory mediators and/or blockage of nET formations may be promising therapeutic targets.[118,119]

The first modulators of inflammatory mediators investigated were platelet-activating factor antagonists (PAFANTs), such as lexipafant. However, despite some initial success, the development of these agents for the treatment of pancreatitis was abandoned.[120] More recently, a leukocyte function-associated factor-1 (LFA-1) antagonist, fuzapladib sodium hydrochloride (brand name Brenda®-Z; Ishihara Sangyo Kaicha, Japan), has been approved for the treatment of canine acute pancreatitis in Japan and has more recently achieved conditional approval in the US (brand name: Panoquell). Fuzapladib mitigates the extravasation of neutrophils from the capillaries and, thus, the formation of nETs and subsequent acute respiratory distress syndrome. In a yet unpublished proof of concept study, fuzapladib dramatically decreased mortality in dogs with experimentally induced pancreatitis. Two other

randomized clinical trials, also yet unpublished, confirmed this beneficial effect in dogs with spontaneous pancreatitis. Publication of these studies in the primary literature and further randomized clinical trials in both dogs and cats will be crucial before fuzapladib can be recommended for routine therapy. However, the initial data are very promising.

#### 10.3.1.6.11 Protease inhibitors

Based on the pathophysiological hypothesis that pancreatitis is ultimately caused by the premature activation of pancreatic digestive enzymes, there have been efforts to treat pancreatitis using protease inhibitors. Aprotinin was one of the first drugs that were evaluated, and the progression of experimentally induced canine pancreatitis could be prevented when dogs were treated with aprotinin.[121] In addition, an initial study with another protease inhibitor, gabexate mesylate, in dogs with experimentally induced pancreatitis showed some promising results.[122] However, studies in human patients with spontaneous pancreatitis did not show any beneficial effect for any of the protease inhibitors investigated. The reason for these seemingly discrepant findings may simply be that the administration of a protease inhibitor in patients with established pancreatitis is simply too late to have any beneficial effect. Having said this, pretreatment of patients that are at risk of developing pancreatitis, for example, patients undergoing a prolonged anesthetic procedure or endoscopic retrograde cholangiopancreatography (ERCP), could be more useful.[123]

#### 10.3.1.6.12 Plasma

Plasma contains a variety of components, including coagulation factors, fibrinolytic factors, protease inhibitors (i.e., $\alpha_1$-protease inhibitor, $\alpha_2$-macroglubulin), and albumin, which may all have a beneficial effect in patients with pancreatitis.[124] However, clinical studies in human patients with pancreatitis failed to show any beneficial effect of using plasma.[125,126] Also, one uncontrolled study in dogs with pancreatitis found that plasma administration was associated with a worse outcome.[127] However, this study was retrospective and it is possible that case selection created a bias leading to this result.[127] Regardless, at this point, there is no evidence that the administration of plasma has any positive impact on outcomes in dogs or cats with severe pancreatitis and should be reserved for patients with a specific indication, such as a bleeding diathesis. Interestingly, in human patients with hypertriglyceridemia-associated pancreatitis, fresh-frozen plasma has been used to quickly and dramatically reduce serum triglyceride concentrations, but this has not yet been explored in canine patients.[128]

#### 10.3.1.6.13 Antibiotics

Many veterinarians routinely treat dogs and cats with acute or chronic pancreatitis with antibiotics; however, there is little scientific evidence to support this. In humans with acute pancreatitis, the routine use of antibiotics is not recommended, even though approximately 33–50% of all human patients with pancreatitis that die of their disease process do so because of infectious complications.[129–132] Of further note, dogs and cats with severe pancreatitis rarely have infectious complications. In contrast, one study reported that cats with pancreatitis frequently have bacterial DNA in the pancreas, but the clinical importance of this finding is unclear.[24] Another exploratory study reported that withholding antibacterial medications in 157 hospitalized cats with pancreatitis was a negative risk factor for a poor outcome, but when correcting the data for multiple comparisons this finding was no longer statistically significant, and the authors concluded that these findings had to be confirmed before being the basis for changes in the management of cats with acute pancreatitis.[133] Thus, the author currently believes that routine antibiotic therapy of dogs and cats with pancreatitis should be avoided. Instead, antibiotics should only be given if an infectious complication is identified or highly suspected as is the case in patients with a urinary tract infection or aspiration pneumonia.

#### 10.3.1.6.14 Dopamine

Dopamine is crucial for splanchnic and pancreatic perfusion, and hypotension and pancreatic hypoperfusion can lead to pancreatitis. One study in cats with experimentally induced pancreatitis has shown that the progression of pancreatitis can be halted if patients are treated with dopamine within 12 hours after the induction of pancreatitis.[134] This is obviously not feasible in spontaneous pancreatitis patients. However, it is possible that patients at risk for pancreatic hypoperfusion (i.e., patients with pancreatitis that have to undergo general anesthesia) might benefit from preemptive dopamine therapy. A low dose (i.e., 2–5 µg/kg/min as a constant rate infusion) could be given, as this dose does not cause peripheral vasoconstriction and thus would not be expected to negatively affect splanchnic perfusion. However, clinical studies would be prudent to support the routine use of dopamine in these patients.

#### 10.3.1.6.15 Antioxidants

There is some evidence suggesting that reactive oxygen species (ROS) play a role in the pathogenesis of pancreatitis.[135] Such ROS can lead to tissue damage and also stimulate an inflammatory response. Thus, it has been hypothesized that antioxidants should have a beneficial effect in patients with pancreatitis. Several uncontrolled studies in humans and one in dogs with acute pancreatitis have suggested such a beneficial effect.[136,137] However, other controlled studies were not able to confirm these findings.[138] Thus, at the current time, there is little evidence to support the use of antioxidants in canine or feline patients with severe acute pancreatitis.

#### 10.3.1.6.16 Other treatment strategies

Hyperbaric oxygen therapy has anecdotally been suggested to ameliorate pancreatitis. However, at this point, there is only minimal evidence in rodent models of pancreatitis and no evidence in dogs and cats with either acute or chronic pancreatitis that such therapy is efficacious. Therefore, given the cost to the owner, hyperbaric oxygen therapy cannot be recommended at this time.[139,140]

Antacids, such as proton pump inhibitors, are frequently used in both dogs and cats that vomit, but there is no evidence for any beneficial effects of such treatment. In fact, in human patients with pancreatitis, acid suppression was associated with intestinal dysbiosis, candida esophagitis, potential risk of pancreatic infection, and mortality.[141,142]

The somatostatin-analog octreotide has anecdotally been used to treat severe acute pancreatitis in dogs, presumably by inhibiting secretory activity, but there are no studies that indicate its efficacy. Furthermore, in a recent study in pigs with experimentally induced pancreatitis, administration of small doses of cholecystokinin (CCK) reduced acinar necrosis and edema.[143] These findings may be explained by the fact that pancreatic secretory activity has been shown to be decreased, rather than increased, early in the course of acute pancreatitis.[144]

#### 10.3.1.6.17 Surgical intervention

A variety of surgical procedures have been suggested for patients with acute and/or chronic pancreatitis, including peritoneal lavage, partial pancreatectomy, and necrosectomy for acute pancreatitis, and partial pancreatectomy and cyst or abscess removal for chronic pancreatitis. There are no studies that have systematically evaluated the effectiveness of pancreatic surgery for either acute or chronic pancreatitis in dogs or cats. The results of such procedures in humans have been disappointing, and current recommendations for surgical intervention for human patients with pancreatitis are rather conservative.[145] There have been isolated reports about surgical interventions in single cases in veterinary patients, but the results are discouraging, and it seems prudent to also be conservative when treating dogs and cats with acute pancreatitis.[21]

Minimally invasive interventions have had an increasing impact on both human and veterinary medicine. For example, in a recent report, a dog with pancreatitis and secondary extrahepatic bile duct obstruction (EHBO) was successfully managed by percutaneous transhepatic cholecystostomy drainage.[146]



**NOTE**

While extrahepatic bile duct obstruction is common in dogs with acute pancreatitis, most of these patients (79% of 42 dogs in one report) survive without surgical intervention (94% of 33 dogs), suggesting that medical management of pancreatitis alone is sufficient in the majority of patients.[147]

### 10.3.1.7 Management of mild chronic pancreatitis

#### 10.3.1.7.1 Introduction

In both dogs and cats, necropsy-based studies indicate that chronic pancreatitis is far more common than acute pancreatitis. However, many cases remain undiagnosed, and far less is known about the optimal management of dogs and cats with chronic pancreatitis than those with acute disease.

#### 10.3.1.7.2 Treatment of the underlying cause

As for acute pancreatitis, determination and management of any underlying causes, if achievable, is important. To that end, serum calcium and triglyceride concentrations should always be evaluated in these patients to identify any risk factors that can potentially be addressed therapeutically. In addition, a careful drug history should be taken, and if possible, medications that are not essential should be discontinued, and others that are essential should be switched to an alternative choice.

#### 10.3.1.7.3 Diagnosis and management of comorbid conditions

It should be noted that many dogs and cats with chronic pancreatitis have comorbid conditions, most notably chronic inflammatory enteropathy (CIE, aka. inflammatory bowel disease [IBD]), chronic hepatitis (in dogs) or cholangitis (in cats), diabetes mellitus, or other endocrine diseases. While this has received limited attention in dogs, comorbid inflammatory disease of multiple abdominal organs is well described in cats and has been referred to as triaditis (i.e., IBD; ▶ Chap. 11.2), pancreatitis (▶ Chap. 10.3.1), and cholangitis (▶ Chap. 9.6.3), although the triaditis name is misleading in humans and refers to an inflammation of the portal triads.[148,149] The true prevalence of triaditis in cats is unknown and the pathophysiology is unclear.[150–153] One proposed pathogenic pathway is that pancreatitis and cholangitis are preceded by intestinal dysbiosis and bacterial translocation, but there is little evidence to support this proposed pathway.[150] Very little is known about the appropriate management of these patients, and management is often limited to the evaluation and treatment of the individual component conditions and careful monitoring.

#### 10.3.1.7.4 Nutritional considerations

In dogs, the use of a low-fat diet (i.e., a diet that contains less than 20 g of fat per 1,000 kcal) is recommended. One recent study showed that feeding a low-fat diet alone led to a dramatic decrease in serum triglyceride concentrations (i.e., consistently less than 500 mg/dL or 5.65 mmol/L) in miniature schnauzers with severe hypertriglyceridemia.[154] Additionally, anecdotal reports suggest that these diets are also efficacious in improving clinical signs as well as decreasing serum cPLI concentrations. In addition, it is important to avoid treats that are high in fat. Vegetables or fruits can often be used as treats. Alternatively, canned low-fat diets can be shaped and either dried or baked to produce a low-fat treat. In cats, the fat content of the diet may be less important. However, it is the author's opinion that diets especially high in fat (e.g., some renal diets and some low-carbohydrate diets) should be avoided.

#### 10.3.1.7.5 Appetite stimulants, antiemetics and antinausea medications

Many dogs and cats with chronic pancreatitis are hyporexic or even anorexic, likely due to nausea. These patients may benefit from an antiemetic medication, such as an $NK_1$-antagonist (i.e., maropitant) or $HT_3$-antagonist (e.g., ondansetron). Also, an appetite stimulant, such as mirtazapine in cats or capromorelin in both dogs and cats, may be useful.

#### 10.3.1.7.6 Analgesia

An analgesic may be indicated in patients that appear to have abdominal pain. For oral application, butorphanol, gabapentin, or tramadol may be appropriate choices. Buprenorphine can be administered transmucosally. Maropitant has also been suggested to have some analgesic effects. In patients with more severe abdominal pain, fentanyl patches would be most appropriate.

#### 10.3.1.7.7 Monitoring

Since the response to any of the management strategies mentioned above may vary between individual patients, monitoring of clinical signs and serum PLI concentration (cPLI in dogs and fPLI in cats) is important. The author measures serum PLI concentrations every 2–3 weeks during the initial management period of each patient with decreasing frequency as changes in management become less frequent.

#### 10.3.1.7.8 Immunosuppressive agents

Autoimmune pancreatitis in humans is characterized by a lymphoplasmacytic infiltration and fibrosis of the pancreas that appears to be mostly centered around the pancreatic duct system, is related to positive staining for IgG4, and responds to corticosteroid therapy.[155] It is interesting to note that most dogs and cats with chronic pancreatitis also have lymphoplasmacytic inflammation of the pancreas. In addition, many dogs and cats with chronic pancreatitis have comorbid inflammatory conditions of other abdominal organs, such as chronic inflammatory enteropathy and/or hepatitis/cholangitis.[148] One report also identified positive IgG4 immunostaining of pancreatic plasma cells, in particular in English cocker spaniels, but also in some other breeds.[156] One report in cats failed to identify IgG4 immunostaining, but further studies are needed to confirm these findings.[157] Also, another subclass of IgG may be more relevant in cats than in humans or dogs with autoimmune pancreatitis. While not all canine and feline patients with pancreatitis may benefit from immunosuppressive therapy, anecdotal reports have shown that some patients do respond quite favorably. Also, a recent case report documented the favorable response of a cat with lymphoplasmacytic pancreatitis to prednisolone therapy.[158] Finally, a dog with chronic pancreatitis, poorly

regulated diabetes mellitus, and atopy was reported to show a swift response to cyclosporine treatment.[159]

The author recommends evaluating and managing patients with chronic pancreatitis for any potential risk factors or comorbid diseases, optimizing their diet, and only treating those patients with glucocorticoids or cyclosporine that do not respond to this management. A baseline serum PLI concentration should be measured before initiating therapy. The author uses immunosuppressive doses of prednisone (up to 2 mg/kg q12h PO in dogs; dose should be decreased to up to 1 mg/kg q12h PO after 5 days and then further decreased every 6 weeks), prednisolone (up to 2 mg/kg q12h PO in cats; dose should be decreased to up to 1 mg/kg q12h PO after 10 days and then further decreased every 6 weeks), or cyclosporine (5 mg/kg PO q12–24h). Patients should be re-evaluated after about 2 weeks, and treatment should only be continued if a beneficial effect can be determined.

#### 10.3.1.7.9 Prognosis

The prognosis for dogs and cats with pancreatitis is largely dependent on the presence of local and systemic complications. Patients without pancreatic necrosis or systemic complications have a good prognosis, while patients with extensive pancreatic necrosis and multi-organ failure have a poor prognosis.[160] In humans with pancreatitis, organ failure in and of itself does not appear to have a major negative effect on outcomes, but the presence of any organ failure for more than 24 hours dramatically worsens the prognosis. In comparison, in dogs and cats, the reversal of even single organ failure is not very successful. There are no estimates on the mortality rate of acute pancreatitis in dogs or cats. In humans with pancreatitis, reports of mortality vary dramatically between 5–40%, depending on the severity of patients included into each study, but also their age, with older patients having a two-fold higher mortality than younger patients in one study.[161] As an example, one study of 1,097 human patients with severe acute pancreatitis in Japan reported an overall mortality rate of 12.4%.[162] Interestingly, the need for dialysis or mechanical ventilation, but not enteral feeding, were risk factors for a negative outcome in human patients with idiopathic pancreatitis (i.e., non-alcohol or cholelithiasis-related pancreatitis).[162] Similarly, in a recent study in dogs with acute pancreatitis, respiratory impairment due to acute lung injury or aspiration pneumonia was associated with death.[163] In another study, hypoantithrombinemia was associated with death.[164] The underlying cause of pancreatitis may also have a dramatic impact on outcome. For example, one study reported that the mortality rate of human patients with acute pancreatitis due to hypercalcemia of malignancy was one in three patients, thus much higher than that of patients with pancreatitis due to other etiologies.[40]

In humans, several severity scoring systems (e.g., Ranson's early prognostic signs, the acute physiology, and chronic health evaluation II [APACHE II] score, or the sequential organ failure assessment [SOFA] score) are used to evaluate patients on admission. This is important because patients may not appear at first to be severely ill clinically but may develop complications and organ failure shortly after admission. Patients that have a high score on admission must be treated more aggressively to prevent organ failure. Several scoring systems and isolated prognostic factors used in humans have been modified for use in dogs or cats, but none have proven consistently reliable in clinical patients so far.[160,165,166] One such scoring system, the canine acute pancreatitis severity (CAPS) scoring system has shown promise in some studies in dogs with severe acute pancreatitis.[164,165] More recently, a scoring system used for dogs with chronic inflammatory enteropathy (CIBDAI) has been modified for use in dogs with pancreatitis (▶Tab. 1-8).

**Modified canine activity index (MCAI)**: This scoring system has been successfully used in two yet unpublished clinical studies, but more studies are needed before this scoring system can be recommended for routine use.

There have also been efforts to use biomarkers for predicting the severity of pancreatitis. One study showed that cPLI and, to a lesser degree, CRP concentrations correlated with clinical severity (personal communication K Keany, 2021). Another study, evaluating dogs with a high mortality of 19%, showed increased serum concentrations of interleukin 6 (IL-6), cPLI, and CRP in dogs with a higher CAPS score.[164] Similarly, a study in 42 cats with pancreatitis showed that serum fPLI concentration, as measured by Spec fPL, correlated significantly with prognosis, while the intensity of ultrasonographic changes did not.[167]

A recent study in humans with acute pancreatitis reported an excellent discriminative power of serum macrophage migration inhibitory factor concentrations for severe disease (area under the curve: 0.95), but this biomarker has not yet been evaluated in veterinary species.[168] Micro RNA-146 expression has also been evaluated in human patients with pancreatitis, but there was significant overlap between groups with different disease severities.[169]

**KEY FACTS**

- Pancreatitis frequently occurs in dogs and cats, and chronic pancreatitis is far more common, yet less frequently diagnosed than an acute disease in either species.
- Pancreatitis varies in severity and can be subclinical, mild, or severe. Severe pancreatitis is associated with both local and systemic complications.
- When stringent criteria are applied, abdominal ultrasound is useful for the diagnosis of pancreatitis.
- Serum PLI concentration (as measured by Spec cPL in dogs and Spec fPL in cats) is both highly specific and sensitive for pancreatitis in small animals.
- Management of acute pancreatitis is mostly supportive and symptomatic, including investigation for a possible cause, fluid therapy, analgesics, antiemetics, appetite stimulants, and providing adequate nutritional support. A novel therapeutic agent, fuzapladib sodium hydrate, has recently been approved for the treatment of acute pancreatitis in dogs in Japan and holds promise as a treatment for pancreatitis in both dogs and cats.
- Management of chronic pancreatitis is aimed at investigating possible causes, diagnosing and managing comorbid diseases (e.g., chronic inflammatory enteropathies, chronic hepatitis/cholangitis, diabetes mellitus), analgesics, antiemetics, appetite stimulants, monitoring, and potentially immunosuppressive therapy.

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
svg.to/9842-10-03-01

## 10.3.2 Exocrine pancreatic insufficiency

Jörg M. Steiner

### 10.3.2.1 Introduction and definition

Exocrine pancreatic insufficiency (EPI), as the name suggests, is a syndrome that is caused by the insufficient synthesis and secretion of pancreatic enzymes.[1,2] The most common cause of EPI is an absolute lack of pancreatic acinar cells that is due to chronic pancreatitis, pancreatic acinar atrophy (▶Fig. 10-12), or, less frequently, pancreatic hypoplasia.

Pancreatic aplasia or hypoplasia can cause clinical signs of EPI and is sometimes suspected when EPI is diagnosed at a very young age, but to date, no case has been documented in the veterinary literature. However, the author is aware of a kitten that was diagnosed with EPI at a very young age and responded well to pancreatic enzyme replacement therapy (PERT). When the kitten was spayed, the pancreas appeared very small but showed a normal histologic appearance, suggesting pancreatic hypoplasia (▶Fig. 10-13 and ▶Fig. 10-14).

Another infrequent cause of EPI is obstruction of the pancreatic duct by a tumor (Hill S, personal communication, 2007). Such an obstruction, if complete, can lead to a lack of digestive enzymes in the small intestinal lumen, despite the normal production of these enzymes by the acinar cells. Long-term, an obstructed pancreatic duct can lead to either pancreatitis, pancreatic atrophy, or both, which then can lead to clinical signs of EPI. The most likely cause of an obstruction of the pancreatic duct is a pancreatic adenocarcinoma or another neoplastic condition (▶Chap. 10.3.3) in nearby abdominal organs or scarring after peritonitis or abdominal surgery. Obstructions of the pancreatic duct have been described in humans but have never been conclusively demonstrated in a dog. In cats, there have been reports of pancreatic flukes (*Eurytrema procyonis;* ▶Chap. 10.3.4.2.1) causing pancreatic atrophy, but these fluke infestations are

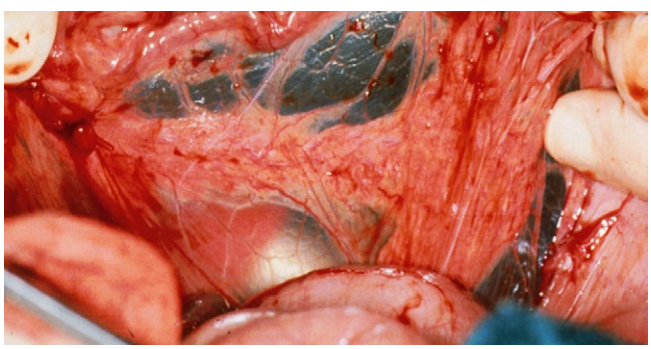


**Fig. 10-12** Pancreatic acinar atrophy

This picture shows a pancreas in a dog with exocrine pancreatic insufficiency with very little remaining pancreatic tissue.

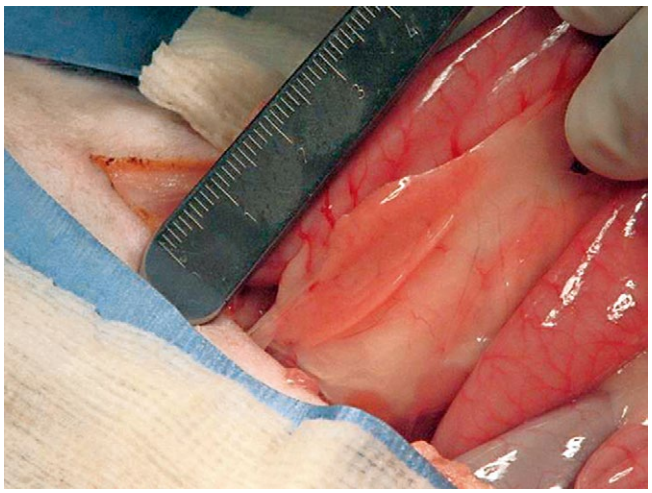


**Fig. 10-13** Suspected pancreatic hypoplasia

This figure shows the pancreas from a cat diagnosed with exocrine pancreatic insufficiency at less than 3 months of age during a routine spay. Note that the pancreas appears extremely small in size, suggesting pancreatic atrophy or pancreatic hypoplasia. (Reprinted from Steiner JM, 2017.[59])

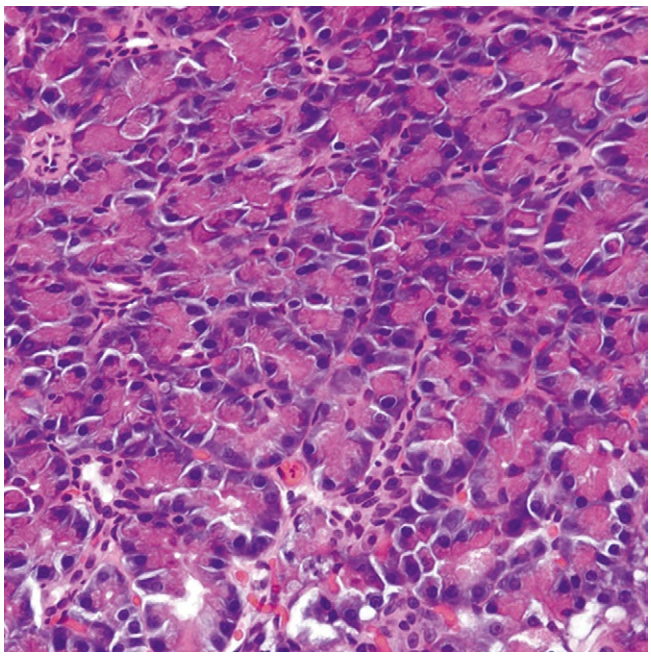


**Fig. 10-14** Suspected pancreatic hypoplasia

This figure shows the histopathological appearance of the pancreas from a cat that had been diagnosed with exocrine pancreatic insufficiency at less than 3 months of age.

Note that the acinar structure appears to be normal, and there is no evidence of either inflammation or fibrosis. Together these findings suggest pancreatic hypoplasia. (Reprinted from Steiner JM, 2017.[59])

rare.[3] Finally, a lack of enteropeptidase in the small intestine could lead to a lack of active digestive enzymes in the small intestines, but such cases have not been reported in either dogs or cats.[4] Both pancreatic duct obstruction and enteropeptidase deficiency do not represent true EPI, but they are related in the sense that they cause identical clinical signs and require identical management to EPI.

### 10.3.2.2 Etiology

The most common cause of EPI in the classical sense is the lack of exocrine pancreatic tissue, is chronic pancreatitis (▶Chap. 10.3.1). As with other organs, chronic inflammation can lead to atrophy and fibrosis, which ultimately can lead to the destruction of enough exocrine pancreatic tissue to cause clinical signs of EPI.

In dogs, pancreatic acinar atrophy (PAA) is almost as common a cause of EPI as is chronic pancreatitis.

**Pancreatic acinar atrophy (PAA)** is almost exclusively seen in German shepherd dogs, rough-coated collies, Pembroke Welsh corgis, Eurasians, and potentially chows.[5–8] Several studies have suggested that PAA in the German shepherd dog and also the Eurasian is inherited as an autosomal recessive trait.[5,9,10] However, a test mating of two affected German shepherd dogs resulted in six puppies, only two of which developed EPI over the course of their lifetime, suggesting that PAA in this breed is not inherited in a simple autosomal recessive fashion.[11] Genome-wide association studies using single nucleotide polymorphisms did not reveal any major loci but pointed towards multiple loci with minor effects, one of which may be the DQB1 allele of the dog *leukocyte antigens* (*DLA*) *class II* gene.[12,13] Mutations of this gene, which play an important role in the regulation of immune function, confer a risk for EPI in both the German shepherd and the Pembroke Welsh corgi.[7,13] This supports the hypothesis that PAA is an immune-mediated disease. Other evidence for an immune-mediated etiology in German shepherds includes the findings that affected dogs are born with a normal pancreas that is infiltrated with a small number of lymphocytes initially, which is followed by atrophy of acinar cells without evidence of inflammatory damage.[6,11]

As stated above, obstruction of the pancreatic duct can also lead to atrophy of the pancreas, but this has only been anecdotally reported in dogs and cats.

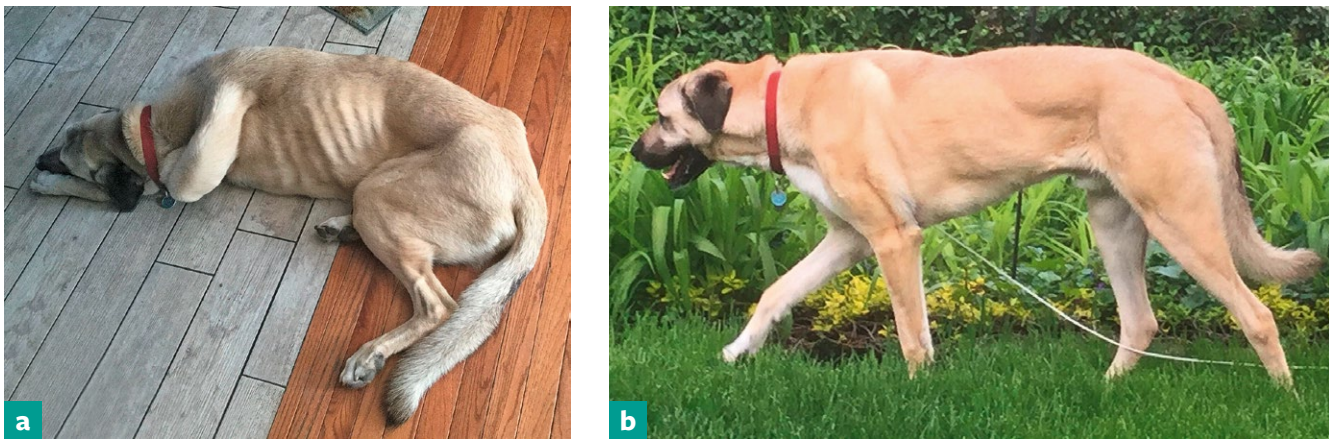


**Fig. 10-15** Exocrine pancreatic insufficiency in a dog

**a** shows the dog before initiation of therapy. The dog has lost a significant amount of weight and has a poor hair coat.

**b** shows the same dog after treatment with pancreatic enzyme replacement therapy

(Courtesy of Roxene and James Moloney, Palos Hills, Illinois, USA.)

### 10.3.2.3 Pathogenesis

Pancreatic secretory products and, most importantly, pancreatic enzymes are crucial for the digestion and absorption of macronutrients. When pancreatic acinar cells are lacking, regardless of the cause, maldigestion occurs. It is important to note that the GI tract is a highly redundant system, and for most pancreatic digestive enzymes, there are other enzymes with the same function that are synthesized and secreted by other organs. For example, pancreatic lipase is crucial for fat digestion, but the stomach also synthesizes and secretes a lipase, gastric lipase, which is responsible for a significant portion of normal fat digestion in dogs.[14] Also, the exocrine pancreas has a huge reserve capacity. In humans, it has been estimated that clinical signs of EPI only ensue when more than 90% of exocrine pancreatic function has been lost.[15]

Maldigestion leads to undigested food components in the intestinal lumen, which can lead to diarrhea, alteration of the small intestinal microbiota, and weight loss.[15–18] Interestingly, though the dysbiosis improves with pancreatic enzyme replacement therapy, it does not normalize.[16] It is important to note that the clinical signs observed may not solely be due to maldigestion. For example, the pancreas secretes large quantities of bicarbonate, which is necessary to buffer gastric acid. A lack of bicarbonate leads to a decrease in duodenal pH, which can have an effect on brush border and pancreatic enzyme activities and also the intestinal microbiota. In addition, the pancreas is believed to synthesize and secrete trophic factors that help maintain a normal GI mucosa, and a lack of these factors may lead to malabsorption in addition to maldigestion. Also, rarely patients have been reported to be presented for neurologic signs. One cat was ultimately diagnosed with D-lactic acidosis, which was hypothesized to be due to intestinal dysbiosis. This cat responded well to pancreatic enzyme replacement therapy (PERT, ▶ Chap. 10.3.2.6.1).[19] In another cat, the neurologic signs were hypothesized to be due to secondary cobalamin deficiency.[20]

In sharp contrast to humans, where intrinsic factor is mainly secreted by the gastric mucosa, the exocrine pancreas is the major source of intrinsic factor in both dogs and cats.[21,22] As a result, the majority of dogs and cats with EPI are cobalamin deficient.[17,18]

### 10.3.2.4 Clinical presentation

EPI can be subclinical.[23] In two large case series of German shepherd dogs, severely decreased serum TLI concentrations were identified in several dogs without any clinical signs.[9,23] Some of these dogs underwent exploratory laparotomy, and their pancreatic mass was found to be severely decreased.[23] This, once again, underscores the overall high degree of redundancy in the process of digestion.

The most consistent clinical sign in dogs and cats with EPI is weight loss (▶ Fig. 10-15).[18,24–26] If the patient is very young, a failure to thrive may be reported instead of weight loss.[27] Loose stools are also commonly observed, but watery diarrhea is rather uncommon.[18,24] Often, affected patients have a poor hair coat, and dogs with EPI are commonly reported to have borborygmus and increased flatulence.[18,24,25] Many dogs and cats with EPI show an increased appetite, and some dogs show coprophagia or even pica.[24] However,

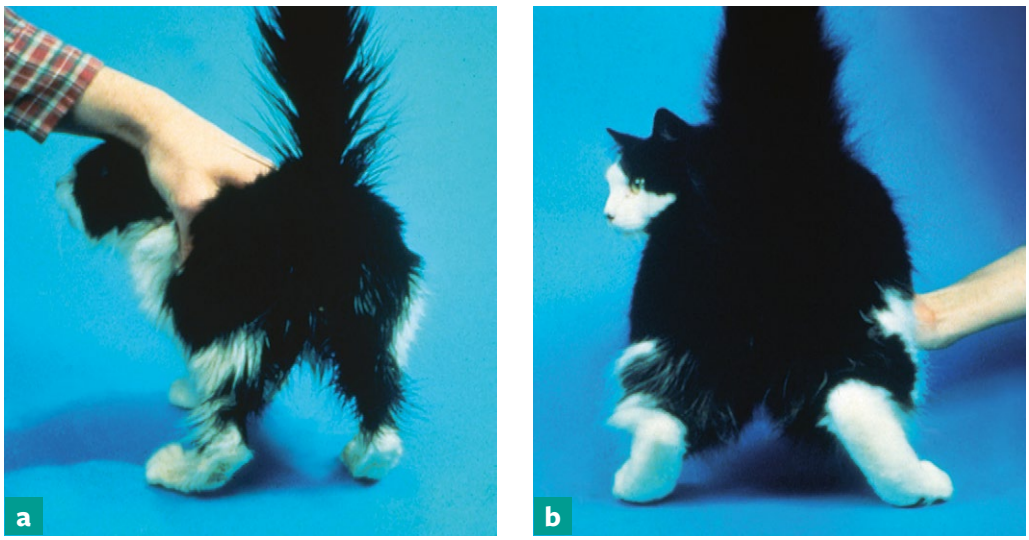



**Fig. 10-16** Exocrine pancreatic insufficiency in a cat

**a** shows the cat before initiation of therapy. The cat has lost a significant amount of weight and has a poor hair coat. In addition, there is greasy soiling of its hair coat in the perineal region.

**b** shows the same cat after treatment with pancreatic enzyme replacement therapy.

(Courtesy of Dr. David A. Williams, University of Illinois, USA.)

some animals have a decreased appetite, which is most likely due to underlying chronic pancreatitis or comorbid disease, such as IBD. In some cats, greasy soiling of the hair coat in the perineal region can be observed (▶Fig. 10-16).[28] Finally, some patients with EPI, mostly those that have EPI as a long-term consequence of chronic pancreatitis, may show clinical signs of comorbid diabetes mellitus.[27]

### 10.3.2.5 Diagnosis

A diagnosis of EPI is made based on the demonstration of a lack of exocrine pancreatic function. Historically, several function tests have been described, including the plasma turbidity test, the para-aminobenzoic acid test, the fecal test for undigested starch and muscle fibers, and the fecal proteolytic activity test, but none of these should be used for the diagnosis of EPI in either dogs or cats.

**CLINICAL PEARLS**

The fecal proteolytic activity test can be used for the diagnosis of EPI in exotic species for which a species-specific trypsin-like immunoreactivity (TLI) test is not available.

**Serum canine and feline trypsin-like immunoreactivity** (**cTLI and fTLI**) are the gold standard tests for the diagnosis of EPI in dogs and cats, respectively.[28,29] The TLI assay is highly species-specific and measures the mass concentration of cationic trypsinogen, cationic trypsin, and some cationic trypsin molecules bound to proteinase inhibitor molecules. Under physiological conditions, only a small amount of the trypsinogen synthesized by pancreatic acinar cells is released into the vascular space. Trypsinogen and trypsin are relatively small molecules and thus get quickly excreted by the kidney. Therefore, only if the pancreas is functioning normally can a small amount of trypsinogen be detected in the serum. In contrast, in patients with EPI, regardless of the cause, the amount of trypsinogen released into the serum, and in turn, serum TLI concentration is severely decreased to undetectable.[28] In general, serum TLI is highly sensitive and specific for the diagnosis of EPI in both dogs and cats.[28,29] However, there are two scenarios where serum TLI can be normal despite the patient having EPI. The first is isolated pancreatic lipase deficiency.[30] It has long been recognized that the rate-limiting enzyme of pancreatic digestion is pancreatic lipase. Thus, patients with an isolated lipase deficiency may have clinical signs of EPI but have a normal serum TLI concentration. Another scenario where serum TLI concentration could be normal in a patient with EPI is a patient with an obstructed

pancreatic duct. Such cases have not yet been described in the literature, but a single dog with this condition has been identified (Hill S, personal communication, 2007).

A **fecal assay for the measurement of pancreatic elastase** in dogs is marketed in Europe. Initial studies showed an acceptable sensitivity and specificity of the assay.[31] However, the estimated positive predictive value was less than 60%.[32] In another study, fecal elastase concentration was shown to be associated with a high number of false positive test results.[33] In this study, six of 26 dogs with a severely decreased fecal pancreatic elastase concentration were shown to have a normal serum cTLI concentrations and thus not have EPI.[33] It is interesting to note that these dogs with a false positive fecal elastase test result for EPI had significantly lower serum CCK concentration than did dogs with a true positive test result.[34] This would suggest that some dogs with chronic small intestinal disease may have fewer neuroendocrine cells in their intestinal mucosa, leading to a decreased stimulation of pancreatic secretion, which may in turn, be associated with false positive fecal pancreatic elastase concentrations. A high rate of false positive test results for fecal elastase concentration has also been observed in several studies in human patients.[35,36] Thus, if fecal pancreatic elastase concentration is to be used to diagnose EPI, any positive result should be verified by measurement of a serum cTLI concentration.

### 10.3.2.6 Therapy

#### 10.3.2.6.1 Pancreatic enzyme replacement therapy (PERT)

Pancreatic enzyme replacement therapy (PERT) is the mainstay of therapy for EPI. Pancreatic enzymes can be replaced by a variety of different options.[37] The online support website https://epi4dogs.com/ provides an extensive list of PERT products that can be utilized in dogs and cats.[38] Dried pancreatic extract from pork pancreas is by far the most common and effective means of PERT. Assuming the product contains at least 70,000 USP units of lipase activity per teaspoon of product, therapy is started with one teaspoon of dried extract per 10 kg body weight each meal. The powder should be mixed with the food immediately before feeding. After the patient has responded completely to such therapy, the dose can be slowly decreased until a minimally effective dose has been reached.

**NOTE**

The content of enzyme activity in the product used may vary from container to container, and thus the minimally effective dose may vary slightly over time.

Pancreatic enzymes are also available as tablets and capsules, but studies in humans and dogs have shown that powder is usually preferable to other formulations.[37,39,40] However, it should be noted that there are many factors that have an impact on the efficacy of PERT. For example, a significant portion of pancreatic lipase is irreversibly inhibited by the low pH in the stomach. Placing pancreatic enzymes in capsules may lead to more pancreatic lipase reaching the intestines, but the capsule may not empty in a timely manner into the small intestine, may open too far distally in the small intestines, or the enzymes may not mix evenly with the chyme, all leading to insufficient efficacy.[41] Many human products utilize microencapsulated enzymes, which have diameters less than 2 mm.[41] However, even such small particles may leave the stomach too late to be effective. Since enzyme capsules and microencapsulated products protect pancreatic lipase, less enzyme is needed with each meal. Two studies have evaluated microencapsulated products in dogs with EPI. While one study was unable to show any significant difference in the efficacy between the microencapsulated and the non-microencapsulated product, the other study did conclude that the microencapsulated product improved response to therapy.[42,43] It should be noted that lipase activity units have been standardized, and 1 USP equals 1 Ph EUR unit.[44] However, analytical lipase activity units differ from pharmacologic units, with 1 international unit of lipase activity (IU) equaling 3 USP of lipase activity.[41] More recently, there have been several attempts to replace pancreatic lipase with microbial lipases that are highly acid-resistant and are thus not affected by gastric inhibition, but these lipases are not yet used routinely for PERT in any species.[45,46]

Side effects of PERT are rare in dogs, but one study reported oral bleeding in three of 25 dogs treated with PERT.[47] When this occurs, a coagulation profile should be evaluated to exclude a vitamin K-responsive coagulopathy, which has been reported in two cats but not in dogs.[48] In the case of a normal coagulation profile, the dose of pancreatic enzymes should be reduced.

Cats often refuse to consume the food mixed with PERT. In such cases, one can attempt to mix the enzymes with some fish oil or tuna first and then mix it into the food. If a patient refuses to consume the pancreatic powder mixed into their food, or in the rare case of a food allergy to the pancreatic

powder, fresh raw pancreas from various species can also be used.[37] Beef, pork, sheep, or game pancreas have all been used. 30–90g (approximately 1–3 ounces) of raw pancreas replace one teaspoon of dried pancreatic extract. The pancreas should be divided into portions for one meal each and frozen. The frozen pancreatic tissue maintains its enzymatic activity for long periods of time. Concerns have been raised about the potential threat of infectious contamination of raw frozen pancreas, but such risk is minimal. Game or ovine pancreas may be infested by *Echinococcus* spp., and infestation with this parasite could potentially cause significant disease or even death. These risks should thus be discussed with the owner before initiating therapy. Pre-incubation of the food with the pancreatic extract does not appear to be necessary to achieve a therapeutic response but may negatively impact owner compliance.

#### 10.3.2.6.2 Individual dietary intervention

Some authors have recommended feeding a low-fat diet to EPI patients. However, it has been shown that fat digestibility does not return to normal even in dogs with experimentally-induced EPI that are treated with PERT, suggesting that fat restriction would further increase the risk of deficiencies of fat-soluble vitamins and essential fatty acids.[49] Several studies have demonstrated that **there is no "optimal" diet** for dogs with EPI, suggesting that, as is the case in humans with EPI, management should be individualized.[50] While one study did not show any benefit of a fat-restricted diet in dogs with EPI, another one was unable to show a beneficial effect of replacing standard triglycerides with medium-chain triglycerides.[17,51] More importantly, one study comparing various diets showed that of the 20 dogs enrolled, eight did best on the diet they had been on before the study, five did best on a high-fat diet, four on a high-fiber diet, and two on a low-residue diet, making the case that while diet can have a significant impact on the management of dogs with EPI, the optimal diet needs to be individualized by trial and error.[52] While similar studies are not available for cats, one should expect that, as in humans and dogs, the diet should be individualized in each patient as well. A reasonable initial dietary approach would be to feed a high-quality maintenance diet and try various specialized diets if treatment success is insufficient on the maintenance diet. In theory, diets with a high non-fermentable fiber content should be avoided as dietary fiber does interfere with fat absorption. It should finally be mentioned that in rare patients, a low-fat diet can be beneficial, but for the reasons mentioned above, this should be considered as a last resort.

#### 10.3.2.6.3 Vitamin supplementation

Most dogs and cats with EPI are cobalamin deficient, and thus every dog and cat with EPI should be evaluated for possible cobalamin deficiency.[17,18,53] If cobalamin deficiency is identified, cobalamin supplementation should be added to the management of the patient. Cobalamin is a water-soluble vitamin that can be administered parenterally or orally for supplementation.[54] The exact dose requirements for dogs and cats are unknown, but over-supplementation with cobalamin is not associated with known side effects. Thus, relatively high doses of cobalamin are chosen. It should also be noted that there is now a commercial PERT product (Panzquin®, Nutramax Laboratories Veterinary Sciences, Lancaster, SC) that contains cobalamin, obliviating the need for additional cobalamin supplementation. For parenteral supplementation, a dose of 250 µg in cats and 250–1,500 µg in dogs is given subcutaneously once a week for 6 weeks, followed by another dose a month after that. A serum cobalamin concentration should be re-assessed a month after the last dose. For oral supplementation, 250 µg of cyanocobalamin in cats and 500–1,000 µg in dogs is given daily for 120 days with re-evaluation of serum cobalamin concentration 3–4 weeks after the last dose. Some EPI patients that have been appropriately supplemented with cobalamin will have a normal or even supranormal serum cobalamin concentration at the time of re-evaluation and the cobalamin supplementation can be discontinued. However, other animals will require life-long cobalamin supplementation. It is crucial to note that cobalamin deficiency was the only independent risk factor for a poor outcome in a large retrospective study of dogs with EPI, with survival in cobalamin deficient dogs being only 3.7 years compared with 7.4 years in dogs that were not cobalamin deficient.[17] Serum concentrations of most fat-soluble vitamins have also been shown to be decreased in dogs with EPI and can also be assumed to be decreased in cats.[51,55] However, vitamin supplementation of fat-soluble vitamins has not been investigated in these patients and over-supplementation with these types of vitamins may cause side effects. Vitamin E supplementation (400–500 IU PO q24h for 1 month) has been suggested by some, but a beneficial effect has not been demonstrated.

#### 10.3.2.6.4 Therapy adaption for non-responders

Many patients with EPI will respond well to enzyme replacement therapy and cobalamin supplementation (if hypocobalaminemic). However, a small group of patients does not respond adequately to such standard therapy. The type, formulation, and dose of the enzyme supplement should be

reviewed and if there is any suspicion that PERT may be insufficient, the protocol should be adjusted accordingly. Also, patients should be evaluated for comorbid conditions, such as IBD, diabetes mellitus, or intestinal dysbiosis. Diabetes mellitus can be observed in EPI patients with underlying chronic pancreatitis as the resulting atrophy does not spare the pancreatic islet cells. Therapy of concomitant diabetes mellitus is essential in such patients.

If there is no evidence of any comorbid disease, the diet can be switched as individual responses to various diets can differ.[52] Also, secondary intestinal dysbiosis usually corrects itself in patients with EPI that are being treated with PERT.[56] However, in a subset of patients, it does not, requiring additional measures. Tylosin at a dose of 25 mg/kg q12h for 6 weeks has traditionally been used in such patients.[56] A probiotic or fecal microbiota transplantation represents alternative approaches to modify the intestinal microbiome.

If patients still do not respond to PERT, a proton pump inhibitor may be useful in increasing treatment success. Omeprazole (0.7–1.0 mg/kg q12h) leads to improvement of fecal quality in some dogs and cats with EPI. When using PERT, a large portion of the pancreatic lipase is destroyed by the low pH in the stomach. By increasing the pH in the stomach, this portion may be decreased and the therapeutic response may be improved. However, it should be noted that while an increase in gastric pH will decrease the amount of pancreatic lipase being destroyed during its passage through the stomach, it also will increase the amount of gastric lipase that is destroyed and therefore, may not lead to a significant change in lipid digestibility. However, human EPI patients treated with PERT and omeprazole showed a superior response over patients treated with $H_2$ antagonists.[57]

If none of these measures lead to control of the clinical signs, a decrease in the dietary fat may be effective. However, as mentioned above, feeding a low-fat diet may be associated with complications and should only be viewed as a last resort.

#### 10.3.2.7 Prognosis

EPI is usually a life-long condition as pancreatic acinar cells can generally not regenerate. Having said this, there are anecdotal reports of isolated cases of resolving EPI.

Most dogs and cats with EPI can be successfully managed and will have a normal quality of life and a normal life expectancy (▶Fig. 10-15b and ▶Fig. 10-16b). Factors reported to be associated with a poor outcome in dogs with EPI were cobalamin deficiency or failure to respond to PERT within the first 2–3 months of therapy.[58] In cats, an fTLI <4.0 µg/L or cobalamin supplementation was reported to improve response to therapy.[18]

**KEY FACTS**

- Exocrine pancreatic insufficiency (EPI) is the second most common exocrine pancreatic disease in both dogs and cats but is more common in dogs than in cats.
- Weight loss is the most consistent clinical sign in both dogs and cats with EPI, followed by loose voluminous stools (often with steatorrhea).
- Measurement of serum trypsin-like immunoreactivity by a species-specific immunoassay is the diagnostic test of choice for EPI in both dogs and cats.
- Management of EPI in dogs and cats involves pancreatic enzyme replacement therapy and parenteral or oral cobalamin supplementation if serum cobalamin concentration is decreased.
- Most dogs and cats with EPI respond well to therapy and have a good quality of life and a normal life expectancy.

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
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### 10.3.3 Exocrine pancreatic neoplasia

Katja Steiger

True neoplasms of the exocrine pancreas are rare in dogs and cats. In contrast, hyperplastic conditions (i.e., nodular hyperplasia) are common, especially in older animals.[1] Primary neoplastic diseases of the exocrine pancreas are either benign (pancreatic adenomas) or malignant (pancreatic carcinoma, ▶Fig. 10-17), and they are further subclassified as ductal or acinar, depending on the morphological growth pattern and the presumed cell line of origin.[2]

Pancreatic adenomas are usually singular and can be differentiated from pancreatic nodular hyperplasia (which often occurs multifocally) by the presence of a capsule and compression of the adjacent parenchyma.

In contrast to humans, where pancreatic adenocarcinoma is the fourth most common cause of cancer death,[3] malignant epithelial neoplasia is rather rare in dogs and cats.[4] In humans, pancreatic ductal adenocarcinoma is the most prevalent malignant pancreatic neoplasm arising from the interlobular ducts with a distinct molecular background (i.e., hotspot mutation of the *KRAS* gene). In domestic ani-




**Fig. 10-17** Gross image of pancreatic carcinoma (**PaCa**) in a 4-year-old cat, invasively growing into the duodenum (**D**) and stomach (**S**) (bar 1 cm).

(Courtesy Prof. Dr. Walter Hermanns, Institute of Veterinary Pathology, Ludwig-Maximilians University Munich, Germany.)

mals, acinar cell neoplasms of the pancreas (▶Fig. 10-18) are more frequently described[5,6] compared with ductal or tubular types, and *KRAS* mutations have not been detected in canine and feline acinar cell carcinomas.[7] Undifferentiated (anaplastic) carcinomas with no evidence of squamous or glandular differentiation have also been recorded in dogs and cats,[2] and a few cases of pancreatic sarcoma, as well as involvement of the pancreas in cases of lymphoma, have been reported.[8–10] However, it is questionable whether these tumors should be considered primary neoplastic lesions of the exocrine pancreas, metastatic lesions of extrapancreatic tumors, or localized lesions of a multicentric neoplasm. A recent study reported a high prevalence of cystic pancreatic tumors in cats, indicating that these types of tumors should be considered as a differential diagnosis in cats with cystic intra-abdominal masses, although these tumors have not yet been described in the World Health Organization (WHO) classification of tumors of domestic animals.[5]

### 10.3.3.1 Etiology and pathogenesis

As in humans, the etiology of neoplastic conditions of the exocrine pancreas in dogs and cats is unknown, although in human patients, smoking, alcohol consumption, obesity, as well as some germ-line mutations (i.e., hereditary forms of pancreatic cancer) are known risk factors for the develop-

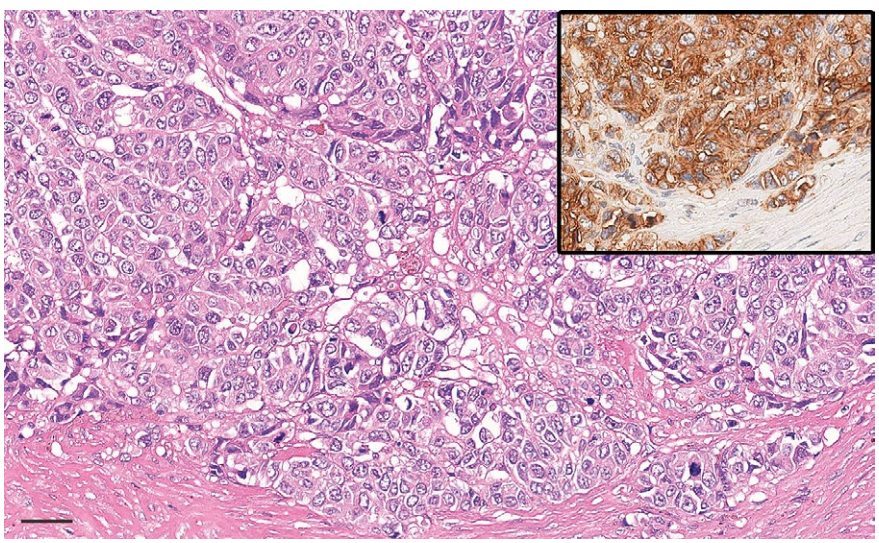


**Fig. 10-18** Histopathological image of an acinar cell carcinoma in an 8-year-old Labrador retriever showing strong amylase expression (**inset**) within the tumor cells. (bar = 30 µm)

ment of neoplasms of the exocrine pancreas.[11] While malignant neoplasms of the exocrine pancreas seem to occur more frequently in older dogs and cats, they can also be observed in patients <10 years of age.[4,12] One study of feline exocrine pancreatic carcinomas discovered an increased prevalence of diabetes mellitus in affected cats, which raises the question of whether diabetes mellitus might be a predisposing factor, as has been shown in humans.[13]

An increased risk of developing pancreatic carcinoma has been reported in Airedale terriers, boxers, Labrador retrievers, and cocker spaniels.[4] However, such breed disposition has not been confirmed by more recent studies.[6]

#### 10.3.3.2 Clinical presentation and diagnosis

The clinical presentation of dogs and cats with exocrine pancreatic neoplasia is nonspecific. Neoplastic lesions can lead to the transposition of organs in the cranial abdomen. However, these changes may be subclinical, and the diagnosis of pancreatic cancer is sometimes made as an incidental finding during necropsy examination. In a case series of 58 cats, the clinical signs most commonly reported were anorexia (46%), weight loss (37%), lethargy (28%), vomiting (23%), icterus (14%), constipation (9%), and diarrhea (3%).[10] The clinical signs reported in other cases included a palpable abdominal mass, hematochezia, decreased grooming, vocalization, polyuria, fever, dehydration, a distended cranial abdomen, and voluminous, pale, soft stools.[9] Polyuria may be a clinical sign of concurrent diabetes mellitus. Obstructive jaundice has also been described in cats with pancreatic carcinoma.[14] Also, in cats, several cases of paraneoplastic alopecia related to pancreatic neoplasms have been reported.[13,15–17] The alopecia is characterized by generalized alopecia of the ventrum, limbs, and face in most cases, with diffuse zones of alopecia in the remaining cats.[17,18]

A study on 23 dogs described lethargy (61%), anorexia (35%), vomiting (35%), and abdominal pain (4%) as the most common clinical signs.[19] Small numbers of dogs with multifocal necrotizing steatitis have also been described that were ultimately diagnosed with pancreatic carcinoma.[20] Finally, clinical signs related to metastatic lesions have also been reported in some cases of pancreatic carcinoma and may present as lameness, bone pain, or dyspnea.

In a small number of human patients, the neoplastic growth can obstruct the pancreatic duct, causing secondary atrophy of the remaining exocrine pancreas, leading to EPI.[21] Even though such cases have not yet been reported in the cat and have only been anecdotally reported in a single dog, this possibility should be considered. In addition to a transposition of abdominal organs, adenocarcinomas can also be associated with tumor necrosis when the tumor outgrows its vascular supply. Tumor necrosis, in turn, might cause a local inflammatory response, which can lead to the development of clinical signs of pancreatitis.[20] Finally, exocrine pancreatic tumors can also spread to neighboring or distant organs.[19,22]

Neutrophilia, anemia, hypokalemia, bilirubinemia, azotemia, hyperglycemia, and elevations of hepatic enzyme activities have all been reported in affected patients, but the results of routine blood tests may be unremarkable.[9,13] Increases in serum hepatic enzyme activities and/or serum bilirubin concentration are identified most commonly.[6,23] Hyperglycemia, when present, is related to the comorbid destruction of pancreatic beta cells.

Canine or feline serum pancreatic lipase immunoreactivity (cPLI/fPLI) is often increased in animals with acute pancreatitis and those with pancreatic neoplasia. This underlines the relevance of histopathology in the diagnosis of exocrine pancreatic disease.[24,25] Some anecdotal reports have suggested that serum lipase activities may be extremely high in dogs with pancreatic carcinoma, but this has not been substantiated by recent studies, showing increased serum enzyme activities in dogs with pancreatic neoplasia compared with those with a normal pancreas, but not different from dogs with acute pancreatitis.[6,25]

Radiographic findings are also nonspecific in most cases and include a decreased contrast in the cranial abdomen, suggesting peritoneal effusion into this area, transposition of the spleen caudally, and shadowing in the pyloric region. [9] However, in some cases, abdominal radiographs can suggest the presence of a mass in the cranial abdomen.[23,26,27] Ultrasonographic examination of the abdomen is very helpful, and in most cases, a soft tissue mass can be identified in the region of the pancreas, although in many cases, the continuation of the mass with pancreatic tissue cannot be conclusively identified.[23] In cats, cystic pancreatic tumors should be considered a differential diagnosis of intra-abdominal cystic masses.[5]

Similarly, neoplastic lesions of the neighboring organs may be falsely presumed to be of pancreatic origin. Also, patients with severe pancreatitis may show an ultrasonographic mass effect in the area of the pancreas that must not be confused with pancreatic carcinoma.[26] If peritoneal effusion is identified on abdominal ultrasound, a sample should be aspirated and evaluated cytologically. However, it is important to consider that this technique has a lower success rate than tissue aspiration, partly due to the difficulty in differentiating neoplastic epithelial cells from reactive mesothelial cells in cavity fluid. On the other hand, fine-needle aspirates (FNA) of solid tumors have a high diagnostic accuracy when confirming an acinar carcinoma, whereas ductal adenocarcinomas may not yield sufficient cells for a cytological diagnosis.[23,28]

Additionally, the presence of secondary pancreatitis and peri-pancreatic steatitis may obscure an underlying neoplasm.[29] If a definitive diagnosis is not successfully achieved after cytological evaluation of an FNA, an ultrasound-guided biopsy may be required. Histopathology is the gold standard for the diagnosis of pancreatic neoplasia, and several recent studies suggest that the pancreas of dogs and cats can be safely biopsied.[6,30,31]

Pinard et al.[19] recommended staging of pancreatic cancer in dogs with respect to the most recent Union for International Cancer Control TNM staging system.[32]

#### 10.3.3.3 Treatment and prognosis

Pancreatic adenomas are benign and theoretically do not need to be treated unless they cause clinical signs secondary to impinging on surrounding organs. However, since the final diagnosis of pancreatic carcinoma is often made by way of a surgical biopsy, a partial pancreatectomy should be considered even in cases of a suspected pancreatic adenoma. The prognosis in these cases is excellent.

Patients with pancreatic carcinoma often present at a late stage of the disease. Therefore, the prognosis is usually grave. Metastatic disease at the time of diagnosis has been reported to occur in 78% of dogs and 81% of cats with pancreatic carcinoma.[12,13,19] The most common sites of metastatic disease are the liver, abdominal and thoracic lymph nodes, mesentery, intestines, and lungs, but various other metastatic sites have also been reported.[6,13,19] Median survival times have been reported to be 97 days in cats[13] or one day to 19 weeks in dogs.[6,19,25] In those few cases where gross metastatic lesions are not identified at the time of diagnosis, surgical resection of the tumor may be attempted, but owners should be forewarned that clean surgical margins are only rarely achieved. Total pancreatectomy and pancreaticoduodenectomy, though theoretically possible, have not been described in dogs or cats with spontaneous disease. However, one report has detailed the management of dogs after experimental total pancreatectomy.[33] One dog with total pancreaticoduodenectomy was euthanized after 6 days due to complications associated with the surgical procedure.[19] Also, extrapolation from human patients suggests high morbidity and mortality for this procedure. The complicated postsurgical lifelong management of EPI (▶Chap. 10.3.2) and diabetes mellitus make total pancreatectomy less than desirable.[34] A study showed a 165-day survival time for cats with pancreatic carcinoma undergoing surgery compared with 30 days for cats that did not.[13] In human patients, the use of pancreatic surgery for the treatment of pancreatic adenocarcinoma is highly controversial; however, both the safety and efficacy of pancreatic cancer surgery have improved considerably in the past decade, enabling perioperative mortality of around 3% and 5-year survival approaching 30–40% after resection and chemotherapy. Surgical resection and adjuvant multi-agent chemotherapy (gemcitabine plus capecitabine or modified FOLFIRINOX; FOLFIRINOX is a combination chemotherapeutic protocol used for humans with advanced PDAC using folinic acid, fluorouracil, irinotecan hydrochloride, and oxaliplatin) is the standard of care in human patients with resectable pancreatic cancer.[35,36] However, until recently, chemotherapy or radiation therapy has shown little success in veterinary patients with pancreatic carcinomas.[37,38] No specific chemotherapy protocols have been established for pancreatic carcinomas in veterinary medicine due to the rarity and generally poor prognosis of this tumor. Cats receiving chemotherapy with either single gemcitabine, single carboplatin, a combination therapy of those two, or mitoxantrone showed prolonged survival times (165 days). However, a single case report of a cat with pancreatic carcinoma recently reported the successful management with surgical resection and toceranib phosphate with a reported progression-free interval of 1,148 days compared with an overall mean survival of 97 days reported for cats with pancreatic carcinoma.[13,37] It remains to be studied whether these promising results can be confirmed through further studies. Also, the use of nonsteroidal inflammatory drugs was been noted to be coincident with a worse outcome in one study in cats.[13]

**KEY FACTS**

- In contrast to humans, primary malignant cancer (i.e., pancreatic carcinoma) is rare in both dogs and cats.
- The clinical presentation of dogs and cats with pancreatic carcinoma is similar to those with pancreatitis, but pancreatitis is far more common than exocrine pancreatic neoplasia.
- Pancreatic carcinomas are frequently diagnosed late in the course of the disease and prognosis is usually guarded to poor.
- Surgical excision, potentially followed by chemotherapy, is the treatment of choice in dogs and cats with pancreatic carcinoma, but total pancreatectomy should be avoided.

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
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## 10.3.4 Rare diseases of the exocrine pancreas

Jörg M. Steiner

### 10.3.4.1 Pancreatic and peripancreatic fluid collections

Pancreatic and peripancreatic fluid collections are composed of fluid alone or may contain solid components when associated with pancreatic or peripancreatic necrosis.[1] In humans, the terminology for these fluid collections has been clarified.[1] Since inconsistent definitions are being used in the veterinary literature, it seems prudent to adopt the classification system agreed upon for humans.[1,2]

#### 10.3.4.1.1 Acute peripancreatic fluid collection

This kind of fluid collection usually develops during the early stages of edematous pancreatitis and does not contain any solid components or a solid wall structure.[1] Most of these acute peripancreatic fluid collections have been reported to be sterile in humans and are likely to also be sterile in dogs and cats. Ultrasonographically, these fluid collections appear as homogenously hypoechogenic structures without a clear wall. Most of these acute peripancreatic fluid collections will resolve spontaneously and do not require any intervention.

#### 10.3.4.1.2 Pancreatic pseudocyst

A pancreatic pseudocyst is a collection of sterile pancreatic juice that contains no solid material and is enclosed by a wall of fibrous or granulation tissue.[1] In humans, pancreatic pseudocysts are believed to represent a disruption of the pancreatic duct system that may represent a complication of pancreatitis but can also occur secondary to pancreatic trauma or pancreatic neoplasia.[1] Several cases of pancreatic pseudocysts in dogs and cats have been described.[3–8] The clinical signs are usually nonspecific and mimic those of pancreatitis.[2] Vomiting and anorexia are the most consistent clinical signs in both dogs and cats with a pancreatic pseudocyst. In one dog and one cat each, the pancreatic pseudocyst led to extrahepatic bile duct obstruction, in turn leading to icterus as an additional clinical sign.[8,9] In some cases, a mass can be palpated in the cranial abdomen. On abdominal ultrasound, a cystic structure in close proximity to the pancreas can be identified (▶ Fig. 10-19). In most cases described so far, the cystic structure was associated with the left lobe of the pancreas.[2,3] Abdominal computed tomography (CT) can also be utilized to further differentiate pancreatic mass lesions, but abdominal ultrasound is likely diagnostic in most patients.[2]

Aspiration of a pseudocyst is relatively safe and should be attempted for both diagnostic and therapeutic purposes.[3] The drained fluid from a pancreatic pseudocyst should be of low cellularity. If measured, amylase and lipase activity or PLI concentrations of the aspirated fluid are usually very high and, at least in humans, are useful to differentiate a pseudocyst from a cystic neoplastic lesion, but those are rare in both dogs or cats.

Pancreatic pseudocysts can be treated medically or surgically. Surgical correction can involve extirpation of the pseudocyst, external drainage, or internal drainage. Internal drainage is the preferred method in humans, and surgical extirpation is only recommended in cases where the pseudocyst is small. Medical management of pancreatic pseudocysts involves ultrasound-guided percutaneous aspiration and close monitoring of the size of the pseudocyst. This approach was successful in several cases described in the literature.[3] In one dog, ultrasound-guided ethanol ablation, a procedure also reported in some human patients with pancreatic pseudocysts, was attempted after the recurrence of a pancreatic pseudocyst.[5] Unfortunately, the dog developed severe complications leading to shock immediately post-procedurally and was euthanized.[5] Drainage may be considered in cases where the clinical signs persist or when the size of the pseudocyst does not decrease significantly over time. Both percutaneous and surgical drainage have been described. Surgical drainage can involve external or internal (i.e., into the stomach or the duodenum) drainage, but case numbers are too small to determine the optimal approach.[2] In one dog, surgical drainage and omentalization were successfully used to treat a pancreatic pseudocyst.[6] Also, a pancreatic pseudocyst in a cat was successfully treated by laparoscopic drainage with omentalization.[7] Further exploration of omentalization would seem especially interesting as the reported prognosis for the surgical treatment of pancreatic fluid collections in veterinary patients is poor.[3,10] In humans, state-of-the-art drainage of pancreatic fluid collections involves echoendoscopically-guided stenting using a lumen-apposing metal stent, but this has not been described in dogs or cats and echoendoscopy is rarely used in veterinary medicine in general.[11,12]

#### 10.3.4.1.3 Acute necrotic pancreatic fluid collection

Acute necrotic fluid collections arise during acute necrotizing pancreatitis when necrotic debris undergoes liquefaction and can be located entirely within the pancreatic parenchyma or in the immediate peripancreatic space. Most acute necrotic fluid collections are sterile, but they can also be infected. Ultrasonographically, these fluid collections appear as hypoechoic

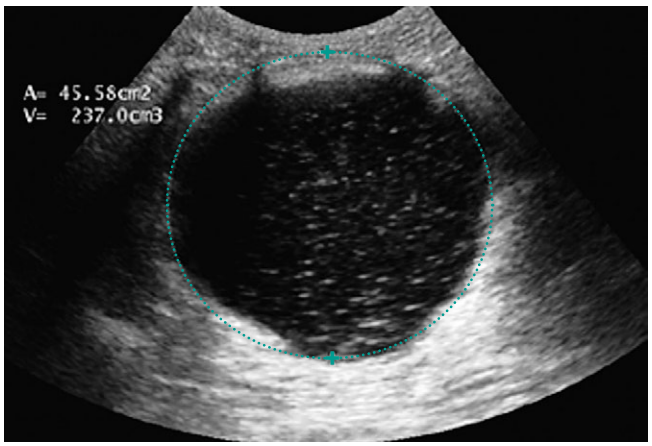



**Fig. 10-19** Pancreatic pseudocyst

This image shows the ultrasonographic image of a pancreatic pseudocyst in a dog. The pseudocyst is characterized by a large almost completely anechoic structure that is associated with the pancreas. In this patient, the volume of the pseudocyst was estimated to be 237 mL. (Courtesy of Dr. Kathy Spaulding, Texas A&M University, USA.)

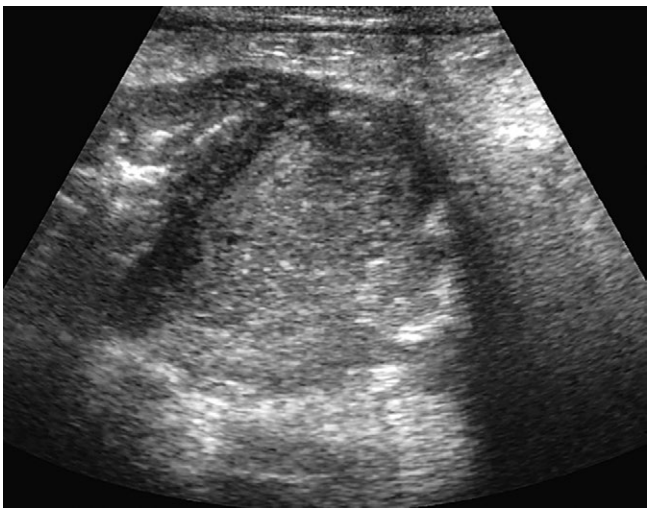


**Fig. 10-20** Walled-off pancreatic necrosis

This image shows the ultrasonographic image of walled-off pancreatic necrosis in a dog. The walled-off necrosis is characterized by a large hypoechoic structure. In most cases, pancreatic walled-off necrosis is more echoic than a pseudocyst; however, in some cases, it cannot be differentiated ultrasonographically. Walled-off pancreatic necrosis is sterile in most dogs and cats. (Courtesy of Dr. Kathy Spaulding, Texas A&M University, USA.)

structures of mixed echogenicity without a solid wall. Aspiration and cytological examination, as well as microbiological evaluation of the material, should be undertaken to determine whether the fluid collection is sterile or not. Sterile acute fluid collections have not been described in dogs or cats but are usually considered a part of pancreatic necrosis in patients with severe pancreatitis.

Acute necrotic fluid collections do not require surgical intervention unless they are infected, in which case the patient should be treated systemically with antimicrobials based on sensitivity testing when available. In humans, intervention is only indicated if there is no improvement, persistent biliary duct obstruction, or the patient cannot tolerate oral intake.[13] However, even minimally invasive procedures, mainly echoendoscopically placed lumen-opposing metal stents, which are currently not routinely available for small animals, are associated with a worse outcome when compared with delaying the procedure until the lesion has progressed to a walled-off necrosis (which by definition requires a minimum period of 4 weeks after the initial diagnosis of pancreatitis).[13] Surgical debridement has not been extensively studied in small animals, but in one report all five dogs that underwent debridement and drainage for an acute necrotic fluid collection died or were euthanized during the postoperative period.[14] Thus, the author believes that surgery should also be delayed in dogs and cats if at all clinically feasible.

#### 10.3.4.1.4 Walled-off pancreatic necrosis

Walled-off pancreatic necrosis represents necrotic tissue that has been encapsulated. Most cases of "pancreatic abscesses" described in the veterinary literature should probably be considered to represent cases of a walled-off pancreatic necrosis. Similarly to an acute necrotic fluid collection, a walled-off necrosis is also sterile in most human patients, but can occasionally be infected, which also appears to be rarely the case in dogs and cats.[9,10,15–17] It should, however, be noted that while one study reported a positive culture in only two of 13 fluid samples, the same study reported positive culture results for peritoneal fluid in seven of twelve dogs. The clinical signs are nonspecific but may include vomiting, abdominal pain, anorexia, lethargy, diarrhea, and dehydration.[2,17] In some patients, a mass in the cranial abdomen can be identified upon abdominal palpation.[10,17] Common clinicopathological findings are neutrophilia with a left shift, elevation of serum lipase activity or PLI concentration, elevations of hepatic enzyme activities, and hyperbilirubinemia.[10,15] One cat was presented for continued weight loss and vomiting after having been treated for diabetes mellitus and was determined to have uncontrolled diabetes mellitus.[18] Abdominal ultrasound shows a hypoechoic structure that can be of variable size and may be irregular (▶ Fig. 10-20).

As is the case for drainage of pancreatic pseudocysts, drainage of a walled-off necrosis can be accomplished by internal or external drainage, and omentalization may be beneficial.[19] Surgical drainage and aggressive antimicrobial therapy are the treatment of choice in human patients with an infected walled-off necrosis. Surgical drainage may also be considered in dogs and cats with a walled-off pancreatic necrosis.[10] However, one cat with an infected walled-off necrosis was successfully treated by ultrasound-guided drainage and antibiotic therapy alone.[18] It should also be noted that in one report only 56% of nine dogs survived the immediate postsurgical period, and in another report, only 29% of 36 dogs were discharged from the hospital.[15,17] Also, the dogs that survived to discharge had a mean hospitalization time of 12.4 days, highlighting the importance of preparing the owner for a guarded prognosis and a prolonged recovery period.[17] Thus, given the mixed results and the risks, difficulties, and expenses associated with anesthesia, surgery, and postoperative care, one should carefully consider the indications for surgical intervention, such as evidence of an enlarging mass and/or sepsis in a patient that is not responding well to medical therapy. Also, based on the lack of identifiable infectious organisms in most cases reported in the literature, the need for antimicrobial therapy in small animals is questionable unless an organism can be identified upon bacterial culture.

### 10.3.4.2 Pancreatic parasites

Pancreatic parasites are very rare in both dogs and cats. Some parasites can be found in the pancreas, but those infections usually result in a more systemic illness. For example, many dogs infested with *Heterobilharzia americana* will have trematodes in the pancreatic parenchyma, which can lead to pancreatic inflammation and clinical signs of pancreatitis.[20] However, most, if not all, of these dogs have more widespread infestation and a wide variety of clinical signs.[20] Similarly, cats with *Toxoplasma gondii* have frequent involvement of the pancreas, but a primary pancreatic infection has only been reported in a single cat.[21] However, there are two parasites that rarely occur in cats, which have been reported to mostly cause pancreatic pathology:

#### 10.3.4.2.1 *Eurytrema procyonis*

*Eurytrema procyonis*, a pancreatic fluke of the cat, can be found in the pancreatic ductular system of foxes, raccoons, and cats.[22] The infestation can be subclinical but can also lead to pancreatic inflammation or thickening of the pancreatic ductular system, pancreatic fibrosis, and in rare cases, exocrine pancreatic insufficiency (EPI).[23,24] The diagnosis can be made by the detection of characteristic eggs in fresh feces.[24] Fenbendazole (30 mg/kg PO q24h for 6 consecutive days) has been recommended for therapy.[25]

#### 10.3.4.2.2 Amphimerus pseudofelineus

*A. pseudofelineus* is a liver fluke that can also infest the pancreas and lead to pancreatitis.[26] In addition to cats, humans and dogs can also be infested.[27] While this parasite is considered to be quite rare, a high prevalence has been reported for an indigenous group, Chachi, in Ecuador, and one study reported a prevalence for this parasite of 71.4% in cats and 38.7% in dogs in Chachi communities.[27] Diagnosis can be made on fecal examination by formalin-ethyl acetate sedimentation.[28] In one report, treatment with praziquantel (40 mg/kg PO q24h for 3 consecutive days) was successful in the management of infection with *A. pseudofelineus*, but comorbid symptomatic therapy for pancreatitis also may be needed.[28] The dose of praziquantel recommended for the treatment of this parasite is very high but is similar to the dose recommended for schistosomiasis in people and dogs.

### 10.3.4.3 Pancreatic bladder

A pancreatic bladder, sometimes also referred to as a pancreatic pseudobladder, is an abnormal extension of the pancreatic duct.[29] Pancreatic bladders can be congenital or acquired. Only a few cats and no dogs with pancreatic bladders have been described in the literature.[29] These cats were presented with clinical signs compatible with biliary duct obstruction. Appropriate management has not been studied, but surgical removal may be indicated in cases presenting with clinical signs.

### 10.3.4.4 Pancreatolithiasis

Pancreatolithiasis has been previously reported in humans and cattle and has been experimentally induced in dogs but has only been reported in three cats to date.[29–32] Clinical signs observed included lethargy, vomiting, diarrhea, anorexia, hematuria, and weight loss, and one of the cats was found recumbent.[29,30,32] On abdominal ultrasound, the presence of two distinct gallbladders was suspected in two of the cats, but abdominal exploratory in one of these cats found that the structure observed represented a pancreatic pseudobladder secondary to obstruction of the duct system.[29,30,32] One cat was euthanized, while in the other two, the stones were surgically removed. One of these cats did well, while the other one

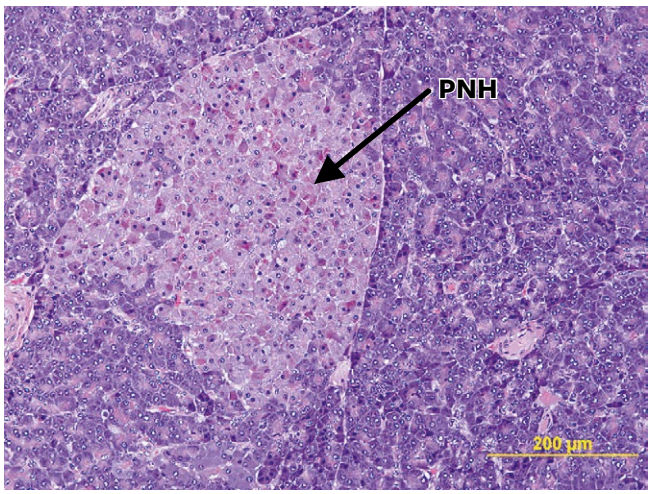



**Fig. 10-21** Pancreatic nodular hyperplasia
This figure shows the histopathological appearance of pancreatic nodular hyperplasia (**PNH**) in a dog. This finding of a proliferation of well-differentiated pancreatic epithelial cells is very common in dogs and cats. In dogs, the presence of pancreatic hyperplastic nodules has been associated with age. (H&E, 20x)
(Courtesy of Dr. Shelly Newman, University of Tennessee, USA)

deteriorated 1-week post-surgery and was euthanized.[29,30,32] In all three cats, the calcium carbonate pancreatoliths had caused an obstruction of the pancreatic duct, followed by chronic pancreatitis, and EPI.[29,30,32]

#### 10.3.4.5 Pancreatic nodular hyperplasia

Pancreatic nodular hyperplasia (▶Fig. 10-21) occurs quite frequently in older dogs and cats.[33,34] In one study, 81 of 101 dogs (80.2%) evaluated at necropsy showed nodular hyperplasia in at least one section.[34] The frequency of nodular hyperplasia was correlated with age but not with pancreatic inflammation, fibrosis, and/or atrophy.[34] Disseminated small nodules can be found throughout the exocrine portion of the pancreas. These lesions may be visible during abdominal ultrasound, but differentiation from pancreatitis or pancreatic adenocarcinoma may be difficult.[33] During necropsy, pancreatic nodular hyperplasia can be differentiated from pancreatic adenomas by the absence of a capsule in cases of nodular hyperplasia.[35] Nodular hyperplasia does not lead to functional changes and does not cause any clinical signs. It is, therefore, most frequently diagnosed incidentally. Pancreatic nodular hyperplasia does not require any therapy.

**KEY FACTS**

- Pancreatic and peripancreatic fluid collections in dogs and cats are rare complications of pancreatitis, which may or may not contain any necrotic material, may or may not be walled off, and are most commonly sterile but can rarely be infected.
- Pancreatic and peripancreatic fluid collections require intervention only if they continue to grow, fail to regress over time, or contain infected material.
- Several systemic parasitic diseases can involve the pancreas, including schistosomiasis in dogs and toxoplasmosis in cats.
- In cats, infestations of the pancreas with a liver fluke, *Amphimerus pseudofelineus,* and the pancreatic fluke, *Eurytrema procyonis,* have been described.

**References**
The complete list of references for this chapter can be downloaded from vetline.de:
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# 11 Diseases that affect more than one organ of the gastrointestinal tract

## 11.1 Adverse reactions to food – allergy versus intolerance

Albert E. Jergens, Elizabeth R. Drake

### 11.1.1 Introduction

Adverse food reactions (AFR) are recognized as potential causes of various gastrointestinal (GI) and dermatological signs in dogs and cats. The true prevalence of these disorders is largely unknown. Accurate recognition of food-related GI and cutaneous reactions is required to avoid misdiagnosis and improper treatment of other primary gastrointestinal diseases, such as inflammatory bowel disease (IBD), antibiotic-responsive enteropathy (dogs), and alimentary lymphoma (AL; cats). This chapter provides a practical overview of the etiopathogenesis, clinical signs, diagnosis, management, and prognosis of AFR in companion animals.

### 11.1.2 Terminology

Adverse food reactions can be divided into two categories based on their etiology: immunological and non-immunological reactions (▶Fig. 11-1).[1] **Food allergy** implies an immunological response to a food or food additive. In contrast, **food intolerance** denotes a non-immunological reaction to a food or food additive. Food idiosyncrasy, food toxicity, food poisoning, anaphylactoid, pharmacological, and metabolic food reactions are all forms of food intolerance, which can be encountered clinically (▶Tab. 11-1). In a practical sense, food allergy and food intolerance may be associated with similar inciting food ingredients, clinical signs, diagnostic findings, and treatments and may not be easily distinguishable.

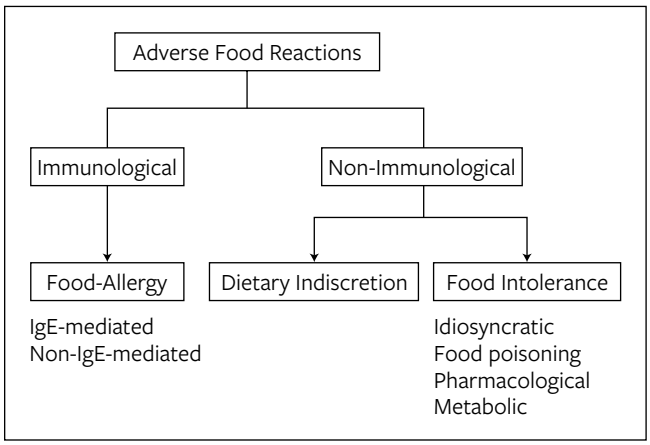



**Fig. 11-1** Adverse food reactions
This figure shows the different types of adverse food reactions seen in veterinary patients.

**Tab. 11-1** Types of adverse food reactions[1]

| Type of intolerance | Response | Examples |
|---|---|---|
| Food idiosyncrasy | Abnormal host response to a food substance or additive | Reaction to certain food additives |
| Food intoxication/poisoning | Host response to organisms contained in food or the presence of food toxins | Aflatoxicosis and botulism |
| Anaphylactoid food reaction | Mimics real anaphylaxis but is not mediated by an immunological release of chemical mediators | Radiopaque contrast media, nonsteroidal anti-inflammatory drugs (e.g., acetylsalicylic acid) |
| Metabolic food reaction | Affects metabolism of the host after food intake | Lactose intolerance (disaccharidase deficiency) |
| Pharmacological food reaction | Drug-like effect of a food substance on the host | Chocolate toxicosis, histamine found in fish |

### 11.1.3 Etiopathogenesis of food allergy

Both the intestinal mucosal barrier and the phenomenon of oral tolerance work synergistically to minimize the risk of food hypersensitivity reactions. The mucosal barrier consists of interrelated immunological and non-immunological components, which

1. block the penetration of ingested antigens (via an intact intestinal epithelial barrier, normal peristalsis, and a mucus glycocalyx coat);
2. promote the degradation of ingested antigens (via gastric acid, pancreatic enzymes, and brush border enzymes);
3. facilitate antigen exclusion from the mucosa (via antigen-specific secretory IgA [sIgA] in the gut lumen).

Oral tolerance is defined as the specific local and systemic immunological unresponsiveness to an orally administered antigen.[2] This immune suppressor function is derived by generating antigen-specific regulatory T lymphocytes (cellular immunity) and sIgA (humoral immunity), which is secreted onto the mucosal surface. Impairment of these mucosal defense mechanisms predisposes patients to adverse immunologic responses and food allergies.

The immunological mechanisms responsible for food allergy in companion animals are not fully known. In dogs, allergen-specific IgE-mediated responses can be measured during sensitization and after oral challenge, suggesting that IgE may play a role in the pathogenesis of the disease.[2,3] In dogs with AFR, it was shown that duodenal gene expression of $Th_1$-, $Th_2$- and $T_{reg}$-related cytokines was similar to healthy dogs and did not change with dietary provocation, suggesting that the intestinal mucosa is not the primary site of T-cell activation leading to cutaneous food hypersensitivity.[4] Moreover, the predominant $CD8^+$ T-cell phenotype and gene expression in skin lesions of client-owned dogs with AFR persisted following the use of novel protein home-cooked diets for at least 8 weeks while clinical signs resolved.[5] In cats, both eosinophilia and clinical signs (dermatitis, vomiting) were reduced following a 12-week intervention with a limited allergen diet.[6] Endoscopy of the stomach and duodenum showed mild to moderate eosinophilic infiltrates in the gastric and duodenal mucosa of some cats.

### 11.1.4 Adverse food reactions

The specific dietary allergens a patient can develop an adverse reaction to have not been fully documented. In humans with food allergy, food allergens are almost exclusively glycoproteins of a molecular mass range of 10–70 kDa.[7] There is no data defining the exact molecular mass of food allergens in dogs or cats. Factors such as stability and immunogenicity of the protein are likely to play an essential role in defining the allergenicity of different dietary components. For example, allergens maintain their stability to a varying degree when treated with heat, acid, or proteases. Furthermore, allergenicity can be influenced by food processing, where protein denaturation destroys some epitopes (antigenic determinates) or exposes new ones, with a decrease or increase in allergenicity, respectively.[7]

Due to the large number of dietary ingredients in commercial pet foods, it may be difficult to identify specific food allergens. A recent meta-analysis evaluating 297 dogs having at least one offending food allergen reported that beef, dairy products, chicken, and wheat were the most common allergens causing cutaneous AFR (CAFR).[8,9] These data are useful for estimating the prevalence of different allergens causing CAFR and should be first used for allergen provocation. In cats, the most important allergens causing CAFR are beef, fish, and chicken.

Whether animals most commonly develop single or multiple food hypersensitivities has not been established. According to Walton et al., multiple hypersensitivities are uncommon in dogs and cats.[10] In contrast, Harvey and Patterson showed that 35–48% of dogs with food hypersensitivity were allergic to more than one food component.[11,12] Similarly, Guilford et al. showed that 50% of cats with chronic gastrointestinal signs had food hypersensitivities toward multiple food allergens.[13] Cross-reactivity among food allergens has not been extensively investigated but appears to be unlikely.

#### 11.1.4.1 Clinical presentation

Canine or feline dietary AFR may manifest clinically as dermatological and/or GI signs. Evidence-based data indicates that the prevalence of CAFR is low for dogs presenting to veterinarians for any diagnosis (1–2%) or among those with skin diseases (median 6%; range: 0–24%).[14] For cats presenting to a university hospital, the reported prevalence of CAFR is very low (0.2%).[15] Vomiting and diarrhea are the most common non-cutaneous signs reported in more than 20% of dogs and cats with AFR.[16] Other clinical signs, including anaphylaxis, conjunctivitis, and increased frequency of



**Fig. 11-2** Adverse food reaction

This figure shows periocular alopecia, hyperpigmentation, and excoriations secondary to intense pruritus resulting from an adverse cutaneous reaction to beef protein.



**Fig. 11-3** Adverse food reaction

This figure shows erythema, alopecia, and excoriations on the ear lobe secondary to intense pruritus resulting from an adverse cutaneous reaction to beef protein.

defecation, were reported less commonly in dogs. In cats, uncommon non-cutaneous signs of AFR include conjunctivitis, salivation, flatulence, and respiratory signs.

There is no age, gender, or breed predisposition for CAFR in dogs. Several different breeds (German shepherd dogs, Labrador retrievers, golden retrievers, and West Highland white terriers) appear overrepresented for the development of AFR.[17] The reported age of onset may vary, but approximately 40% of dogs develop cutaneous manifestations of AFR by one year of age. Dermatological manifestations typically occur as generalized nonseasonal moderate to severe pruritus, or the patient may present with otitis externa as the only clinical sign. Other cutaneous manifestations, including recurrent bacterial (presumed staphylococcal) and yeast skin infections, otitis externa, and atopic dermatitis, may occur in the same canine patient (▶ Fig. 11-2, ▶ Fig. 11-3, ▶ Fig. 11-4). Regarding non-cutaneous signs, a high number of dogs (70–88%) with AFR exhibit vomiting and/or diarrhea.[17] In most cases, the diarrhea is of large bowel origin and is accompanied by an increased frequency of defecation, tenesmus, or both. In some studies, clinical improvement of GI signs was observed following a change in diet, but re-challenge with the original diet was not performed in all instances.

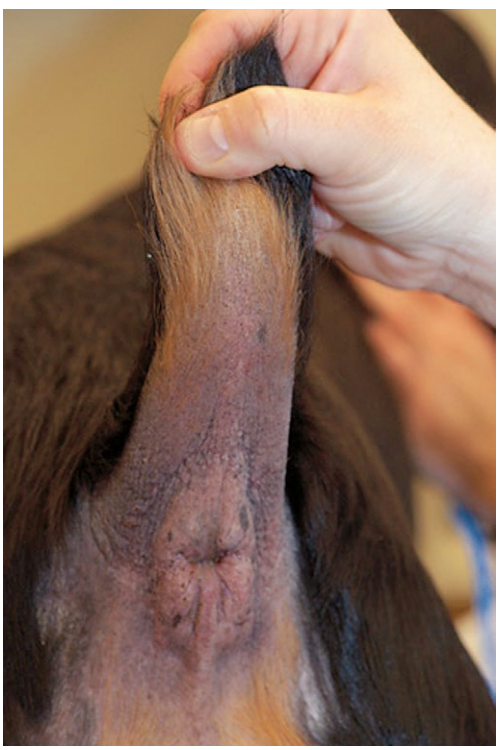


**Fig. 11-4** Adverse food reaction

This figure shows perianal alopecia, erythema, lichenification, and hyperpigmentation secondary to intense pruritus resulting from an adverse cutaneous reaction to chicken protein.

The evidence-based literature shows a wide age range for the development of CAFR in cats (4 months to 15 years; median 3.9 years).[15,17] Age and gender predispositions have not been reported. Siamese, Burmese, and Persian cats appear overrepresented and may be at an increased risk for CAFR. Nearly all cats with CAFR exhibit manifestations of pruritus involving the face, head/neck, ears, and ventral abdomen. The predominant cutaneous lesions include symmetrical self-induced alopecia, head (face) and neck self-traumatic dermatitis, and military dermatitis. Gastrointestinal signs, such as vomiting and/or diarrhea, are the most frequently reported non-cutaneous signs in affected cats.

### 11.1.4.2 Other disorders

Food-related immunological responses may contribute to the pathogenesis of several different enteropathies in the dog and cat (▶Tab. 11-2). In contrast to AFR, these conditions are only associated with the GI tract in affected dogs and cats.

### 11.1.4.3 Diagnosis

An elimination dietary trial is considered the gold standard for the diagnosis of canine and feline AFR. Other diagnostic tests, including serum testing for food-specific IgE, intradermal testing with food antigens, lymphocyte proliferation tests, and gastroscopy/colonoscopy following an oral challenge (endoscopic examination of mucosal appearance post-stimulation) with different food antigens are not recommended for making a clinical diagnosis of AFR in dogs and cats.[1] Patch testing with food antigens may be used as an aid in choosing the ingredients for an elimination diet in selected dogs but should not be used for diagnosis of AFR.

### 11.1.4.4 Treatment

#### 11.1.4.4.1 Concept of a dietary trial

The first step of a dietary trial is to discontinue the previous diet (offending food or ingredients) and feed an elimination diet followed by a challenge with the patient's original diet (▶Fig. 11-5). If clinical signs recur on the old diet and resolve on the elimination diet, a clinical diagnosis of an AFR is made. Overall, elimination diet trials are successful in 90% of dogs and cats with CAFR.[21] Provocation testing can help identify the offending food or ingredient but may be impractical in some clinical settings. It may be more challenging to conduct diet trials in cats due to their fastidious dietary habits. A recommendation for an appropriate home-cooked or commercial elimination diet can then be made based on the results of the challenge studies.

#### 11.1.4.4.2 Defining an elimination diet

The ideal elimination diet should

1. include a hydrolyzed protein or a single novel, highly digestible protein source;
2. avoid protein excess;
3. avoid additives and vasoactive amines;
4. be nutritionally adequate for the animal's life stage and condition.

A variety of different elimination diets may be fed, including a home-cooked elimination diet, a commercial selected protein diet, and a commercial hydrolyzed diet.[1]

**Tab. 11-2** Role of food-related immunological responses in chronic enteropathies

| Disorder | Role of food allergens | Treatment(s) |
|---|---|---|
| Idiopathic inflammatory bowel disease[18] | Dietary antigens may contribute to GI inflammation; microbiota dysbiosis seen with IBD contributes to gut inflammation | Sequential therapy: begin with an elimination diet ± immunosuppressive drugs to control GI signs |
| Gluten-sensitive enteropathy[19] | Inherited enteropathy of Irish setters; aberrant mucosal immune response to gliadin | Gluten-free diet |
| Protein-losing enteropathy of SCWT[20] | Inherited enteropathy of SCWT; severe AFR leads to enteritis and PLE | Elimination diet ± immunosuppressive drugs |

**GI** = gastrointestinal; **IBD** = inflammatory bowel disease; **PLE** = protein-losing enteropathy; **SCWT** = soft-coated wheaten terrier; **AFR** = adverse food reaction

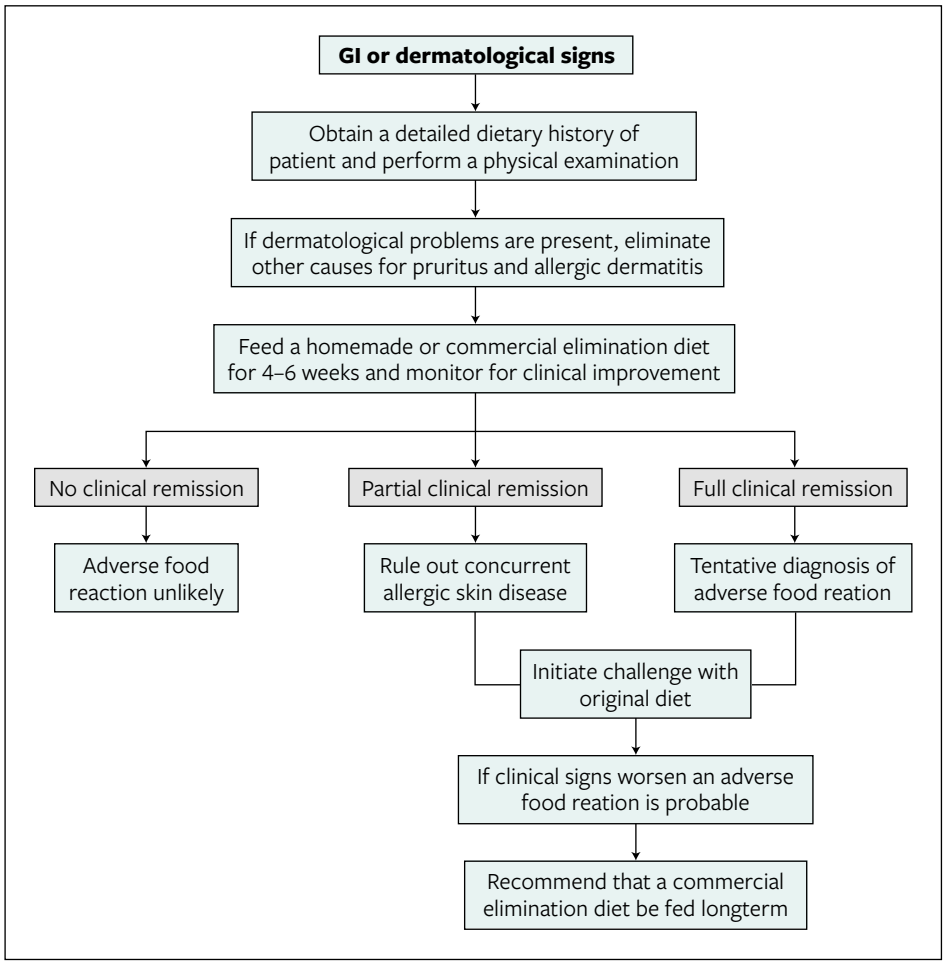



**Fig. 11-5** Practical approach to elimination trials for the diagnosis of adverse food reactions (modified from Gaschen et al. 2011[22])

**GI** = gastrointestinal

A home-cooked elimination diet should consist of a single protein source and single carbohydrate source, with both ingredients not present in previously fed diets.

Suggested food components in dogs include fish, rabbit, venison, rice, potatoes, and tofu.

Cats, being obligate carnivores, do well on all-meat diets.

Home-cooked diets are often advocated as the initial test food for dogs and cats with suspected AFR. While it is generally best to gradually introduce the new diet over 3–4 days, many patients, especially dogs, will immediately eat the new diet. Caution is advised when feeding homemade diets for longer than 3 weeks, as they may be nutritionally unbalanced.[23] Ideally, consultation with a veterinary nutritionist is recommended for optimal formulation if long-term use is anticipated.

Most commercial selected protein diets are indicated for the long-term management of dogs and cats with AFR. These products are attractive because they are convenient, balanced, and nutritionally complete for either dogs or cats. However, different studies have shown that proteins not listed on the label were also included in the prescription formulation.[24] Importantly, the clinical significance of extra-label proteins in AFR was not evaluated through properly conducted feeding provocation trials. In animals failing to respond to a single elimination diet, a second diet may be indicated to confirm a diagnosis.

Protein hydrolysate diets contain proteins that have been hydrolyzed into smaller peptides and amino acids, which reduces the potential allergenicity of the diet. These diets are useful in reducing clinical signs of CAFR but also in

reducing GI signs in dogs with chronic (small intestinal) enteropathy.[25] The clinical superiority of one elimination diet versus another in the treatment of AFR has not been established.

#### 11.1.4.4.3 Duration of a dietary trial

The optimal duration of a dietary trial has been subject to considerable debate. Generally speaking, approximately 50% of dogs with CAFR will show a marked reduction in their clinical signs after 3 weeks of diet change, with more than 85% of dogs showing a positive response to diet trials from 5 weeks onward.[21] In another study looking at cumulative percentages of clinical remission, it took approximately 4, 6, and 8 weeks of an elimination diet for 50, 80, and 90% reduction of clinical signs in cats with CAFR.[21] Some dogs with chronic GI signs will respond to shorter elimination periods (2–4 weeks), as evidenced in several small clinical trials.[25,26] Cats with food sensitivity may respond to an elimination dietary trial in as short as 3–7 days.[13]

#### 11.1.4.4.4 Interpreting dietary trials

A clinical diagnosis of an AFR can be made if the level of pruritus and/or the severity of GI signs markedly decrease subsequent to an elimination dietary trial. However, a challenge with the original diet is necessary to confirm the diagnosis but may not be possible in all instances with adequate client compliance. Elimination trials may be difficult to interpret because of concurrent allergic skin disease. Thus, flea-allergy dermatitis and atopic dermatitis should be ruled out through appropriate diagnostic testing in partial responders.

#### 11.1.4.5 Prognosis

The prognosis for AFR is generally good once the disorder is correctly identified and treated with an appropriate dietary elimination trial. In the author's experience, the offending food component is rarely identified since provocation testing may not be permitted by many pet owners. Clients should be counseled that long-term (indefinite) feeding of a home-cooked elimination diet, commercial selected protein diet, or hydrolyzed diet is usually required to maintain clinical remission. There is some evidence that dogs with diet-responsive chronic enteropathy maintain long-term remission when fed an elimination diet for at least 12 weeks.[27]

**KEY FACTS**

- Adverse food reactions (AFR) may be immunologically (i.e., food allergy) or non-immunologically (i.e., food intolerance) mediated.
- Dermatological signs (pruritic dermatitis) of AFR predominate in both dogs and cats.
- A dietary elimination trial is the most important diagnostic tool in dogs and cats with suspected AFR.
- The prognosis for AFR is generally good once the disorder is correctly identified and treated with an elimination dietary trial.

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
svg.to/9842-11-01

## 11.2 Chronic inflammatory enteropathies

Edward Hall and Karin Allenspach

### 11.2.1 Introduction and definitions

The collective term **chronic inflammatory enteropathy** (CIE) is used in canine and feline gastroenterology to describe patients affected by persistent or recurrent gastrointestinal (GI) signs where there is histopathological evidence of inflammation. Infectious causes of chronic intestinal inflammation are excluded, and CIEs are considered idiopathic.[1] The inflammation may affect the stomach, small intestine (SI), large intestine (LI), or a combination of those sites. A severe CIE may present as protein-losing enteropathy (PLE) with hypoalbuminemia (▶Chap. 7.3.8).

By consensus, an enteropathy is deemed chronic if it persists, either continuously or intermittently, for a minimum of 3 weeks. A broad umbrella term, **chronic enteropathy** (CE), encompasses not only inflammatory intestinal conditions but also neoplastic diseases such as alimentary lymphoma (AL; ▶Chap. 11.3). However, confusingly, regions of lymphoplasmacytic inflammation may be seen adjacent to sections of lymphoma, leading to the hypothesis that chronic inflammation may transform a CIE into AL.

For many decades, CIEs have been called **inflammatory bowel disease** (IBD) indiscriminately.[2,3] However, the use of the term "IBD" in small animal gastroenterology is problematic:

- Firstly, it is not a single condition, and several infections and other diseases may be associated with chronic intestinal inflammation (▶Tab. 11-3).
- Secondly, various histopathological types of intestinal inflammation have been described, with **lymphoplasmacytic enteritis** (LPE) and **eosinophilic enteritis** (EE) being the most common. Others, such as **neutrophilic enteritis** of cats and **granulomatous enteritis,** may have an underlying infectious etiology.
- Thirdly, CIEs are now more usefully defined by their response to empirical treatments as food-responsive enteropathies (FREs) and **steroid**- or **immunosuppressant-responsive enteropathies** (SREs or IREs, respectively), a classification that does not necessarily correspond to the histopathological appearance.

Indeed, the term IBD has been borrowed from human gastroenterology, where it mostly refers to two specific conditions: Crohn's disease (CD) and ulcerative colitis (UC). Canine and feline CIEs bear little resemblance histologically or clinically to either form of human IBD, although they may share a common etiology (▶Chap. 11.2.2).

Poorly defined conditions, sometimes called **minimal change enteropathies**, have no overt inflammation histopathologically, but molecular techniques show changes in inflammatory molecules. Absence of or mild inflammation is characteristic of FREs. The descriptive diagnosis **antibiotic-responsive diarrhea** (ARD), formerly (but incorrectly) called **small intestinal bacterial overgrowth** (SIBO), is considered to be an idiopathic version of **small intestinal dysbiosis** (SID, ▶Chap. 7.3.4). Biopsies in ARD show minimal changes by light microscopy, but changes in brush border enzyme activity and the induction of inflammatory cytokines have been described.

Assuming intestinal inflammation can be confirmed by biopsy (▶Chap. 11.2.5), to qualify as an idiopathic CIE, no underlying cause for the inflammation should be present. Thus, the clinician must rule out known causes through systematic investigation before reaching a diagnosis, which is – by definition – of unknown cause.

**Tab. 11-3** Causes of chronic small intestinal inflammation

| Category | Specific conditions |
|---|---|
| Chronic infection (▶Chap. 7.3.1) | *Cryptosporidium*<br>*Giardia*<br>*Histoplasma*<br>*Toxoplasma*<br>*Prototheca*<br>*Pythium* and other zygomycetes |
| Enteropathic bacteria (▶Chap. 7.3.1.2) | *Campylobacter* spp.<br>*Clostridium* spp.<br>*Salmonella* spp.<br>Pathogenic *E. coli* |
| Granulomatous (histiocytic ulcerative) colitis (▶Chap. 8.3.1.2) | Adherent and invasive *E. coli* |
| Food intolerance/allergy (▶Chap. 11.1) | - |
| Associated with other primary gastrointestinal diseases | Lymphoma<br>Lymphangiectasia<br>Lipogranulomatous lymphangitis |
| Idiopathic | Lymphoplasmacytic enteritis<br>Eosinophilic enteritis<br>Mixed inflammation |

## 11.2.2 Etiopathogenesis

Over the last 15 years, studies have shown that the pathogenesis of canine CIE is complex and involves an overly reactive cell-mediated response due to the loss of immune tolerance to antigens found in the food and the complex commensal microbiome in genetically susceptible hosts.

### 11.2.2.1 Intestinal microbiota

Dogs with CIE exhibit dysbiosis of the intestinal microbiome (▶Chap. 7.3.4), which is thought to be both a sequela and a potential perpetuating factor of the inflammation.[4–8] A decrease in microbial diversity, along with an increased abundance of members belonging to the *Enterobacteriaceae* family (and specifically *E. coli*), a significantly higher number of clones belonging to *Proteobacteria* spp., and a significantly lower abundance of *Clostridia* spp. were found to be the most consistent changes of the microbiome in dogs with CIE. In general, these changes can be characterized as an increase in pro-inflammatory bacterial phyla, along with a decreased abundance of anti-inflammatory phyla and decreased diversity, all of which were also associated with IBD in humans.[9]

There is evidence that some of these microbiome changes could be breed-associated. In the duodenum of German shepherd dogs (GSD) with CIE, bacterial clones within the order

*Lactobacillales*, traditionally labeled "beneficial" bacteria, were found significantly more frequently than in the duodenum of healthy dogs, as well as in other breeds of dogs presenting with CIE.[10] Furthermore, recent studies have investigated the functional significance of this dysbiosis, asking what metabolites are produced by the dysbiotic microbiome and what systemic effects this may have.[4,11] It appears that the fecal metabolome in CIE cases displays over-represented bacterial secretion systems and transcription factors and under-represented amino acid metabolism.[12] The serum metabolites 3-hydroxybutyrate, hexuronic acid, ribose, and gluconic acid lactone were significantly more abundant in dogs with CIE than healthy controls. These data suggest the presence of oxidative stress in the intestinal epithelium and functional alteration of the GI microbiota in dogs with CIE, which can persist even in the face of a clinical response to medical therapy.[11] Another recent study also showed that the lipid metabolism in dogs with CIE is disturbed, again indicating increased oxidative stress and membrane damage in the intestinal epithelium.[13] Encouragingly, in FRE dogs, these changes were minimized after treatment, suggesting that dogs with FRE revert to a more normal metabolism after successful treatment. Just as with the antibiotic treatment of ARD, colonic commensals are the main groups of bacteria diminished in the microbiome of dogs with CIE. This results in a severely decreased production of secondary bile acids. The metabolic consequences of this can be grave because secondary bile acids are essential as hormonal messengers in intestinal homeostasis, liver metabolism, and immunity.

#### 11.2.2.2 Genetic predisposition

Mutations in mucosal pattern recognition receptors (PRRs), such as *NOD2* (nucleotide-binding oligomerization domain-containing protein 2) and *TLR4* (Toll-like receptor 4), amongst others, are considered predisposing factors for IBD in people.[14] In dogs, breed associations also suggest CIEs may have a genetic component and may be a polygenic disease, with many genetic mutations contributing to the increased risk of developing intestinal inflammation. In the GSD, several studies have investigated the genetic basis of the disease. In a candidate gene analysis, single nucleotide polymorphisms (SNPs) in canine *TLR2*, *TLR4*, and *TLR5* were associated with CIE in GSDs.[15] The polymorphisms identified in the *TLR5* and *TLR4* genes have been further evaluated in a case-control study with over 50 cases and GSD breed controls. The G22A SNP in *TLR5* was significantly associated with CIE in GSDs. The *TLR5* risk-associated genotype results were also mirrored in non-GSD breeds: the heterozygote genotype for all four SNPs occurred significantly more frequently in a population of 96 dogs of different breeds with CIE compared with the non-GSD control population.[16] Further evaluation of the functional significance of the canine *TLR5* SNPs showed a significant increase in the activity of NF-κB (nuclear factor kappa-light-chain-enhancer of activated B-cells) when cells transfected with the risk-associated *TLR5* haplotype were stimulated with bacterial flagellin compared with cells expressing the risk-protective *TLR5* haplotype.[17] Furthermore, whole blood from dogs carrying the risk-associated *TLR5* haplotype produced significantly more TNF after stimulation with flagellin than blood from carriers of the risk-protective haplotype. Thus, the direct functional impact of the canine CIE risk-associated *TLR5* haplotype is a hyper-responsiveness to flagellin.[17] A follow-up genome-wide association study involving 98 cases and 98 controls revealed an additional 16 genes to be associated with CIE in GSDs, many of which were associated with classical $Th_2$-type cytokine responses (e.g., IL-13, IL-4, and IL-5).[18] This finding could have important implications for investigating novel treatment options as affected GSDs, especially in Europe, often express a severe CIE clinical phenotype that is difficult to control with conventional treatment options.[10,19]

#### 11.2.2.3 Intestinal mucosal immune system

The concept of impaired immunoregulation in canine CIE is supported by observations of increased numbers of immunoglobulin-producing plasma cells and cytokine-producing T-cell subsets. Inflammation is thought to result from inappropriate cytokine production by a range of T-cell subsets. In dogs, there is a mixed $Th_1$- and $Th_2$-profile demonstrated in several case series.[20] Most studies have shown an increased IL-12 and IL-23 production in the mucosa of dogs with CIE,[21,22] although the results are not as marked as in humans with IBD. However, NF-κB activation was confirmed in two studies in dogs with CIE, pointing to an important role of cytokines in the pathogenesis of the disease.[23,24]

Macrophages and T-cells infiltrating the lamina propria may produce large amounts of IL-1β[25,26] in response to an overactive immune activation to commensal bacteria (▶Fig. 11-6). Overexpression of IL-1β in FRE dogs before treatment is reduced after successful dietary management. Thus, IL-1β overexpression in the mucosa of dogs with CIE could represent a good target for novel treatment options.

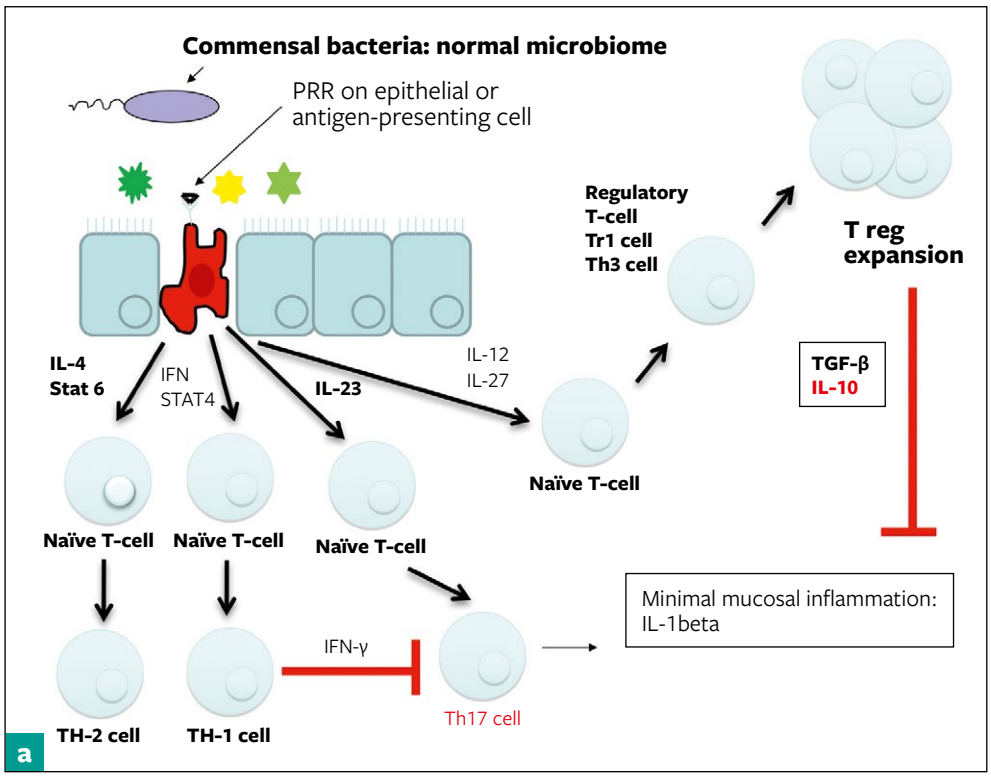
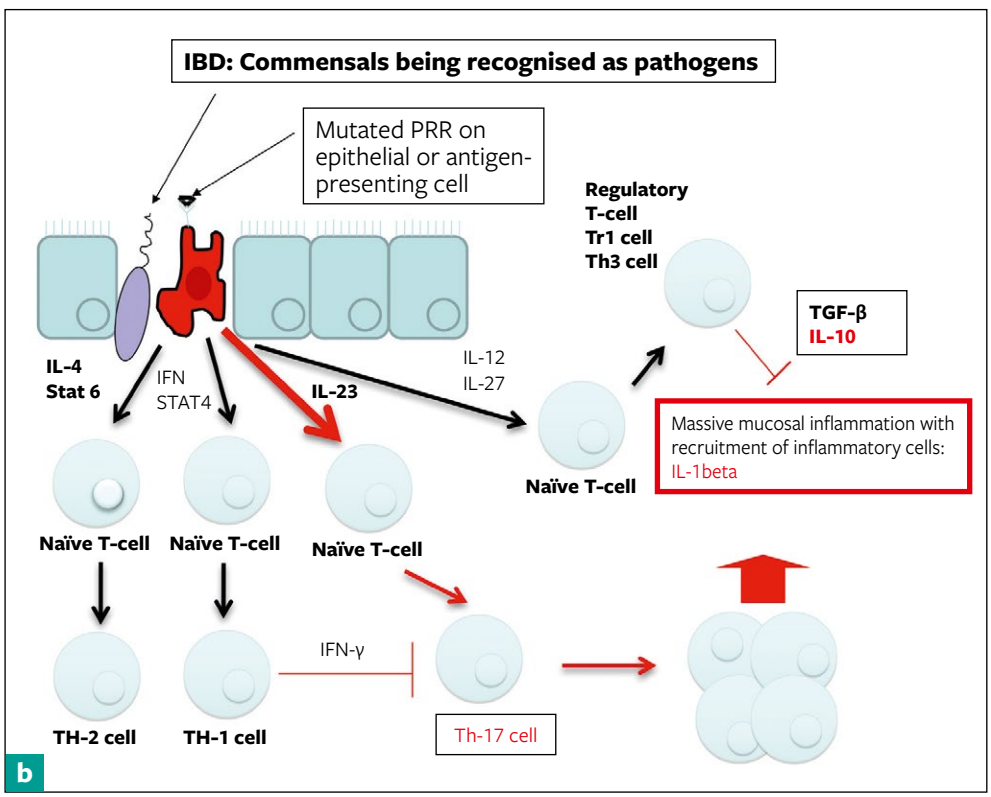



**Fig. 11-6** A current hypothesis for the pathogenesis of canine chronic inflammatory enteropathy (CIE)

**a** In the normal intestinal mucosa, pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs), interact with pathogen-associated molecular patterns (PAMPs) from commensals in the intestinal lumen. These send signals to naïve T-cells to differentiate primarily into T regulatory ($T_{reg}$) cells. $T_{regs}$ produce anti-inflammatory cytokines, such as TGF-β and IL-10. With canine CIE, intestinal dysbiosis drives the messaging toward a pro-inflammatory pathway of $T_h$ cell differentiation, resulting in the production of pro-inflammatory cytokines, mainly IL-1β.




**b** Mutations in *TLR5* can result in hyper-responsiveness to flagellin. Intestinal dysbiosis in canine CIE is characterized by an increase in *Enterobacteriaceae* (which express flagellin), further increasing pro-inflammatory responses of the mucosa. Moreover, the inflammatory cytokines will lead to architectural changes in epithelial cells, such as increased leakage through tight junctions, resulting in increased permeability. This, in turn, will result in more bacteria breaching the mucosal barrier, therefore leading to a vicious circle of inflammation.

### 11.2.3 Classification

Idiopathic CIEs are no longer considered a single disease entity, and some, such as granulomatous colitis, are now known to have a cause. Variations of the histopathological appearance exist, although the significance of the differences is not clear because the clinical signs and treatments are generally the same. The histological diagnosis typically reports the predominant inflammatory cell type present and forms the basis for this traditional classification. However, close inspection of the biopsies usually shows a mixture of inflammatory cells. This historical classification may be spurious, with "lymphoplasmacytic inflammation and an eosinophil component" more often being reported. Architectural changes, such as complete or partial villus atrophy, villus fusion, and crypt abscessation, indicate inflammation, whatever the cell type present. The severity of that inflammation (mild, moderate, or severe) helps characterize CIEs further (▶Chap. 1.8.1).

However, other classifications exist. The simplest relates to the region of the GI tract affected (i.e., gastritis, enteritis, colitis, or combinations thereof, e.g., gastroenteritis, enterocolitis, or gastroenterocolitis). Breed-specific forms of CIE are named when the condition appears particularly prevalent in the breed, although whether they are truly unique is not clear. More useful is a clinical classification based on the response to empirical treatment, i.e., whether the clinical signs are food-responsive (FRE), antibiotic-responsive (ARD), or steroid- or immunosuppressant-responsive (SRE, IRE).

#### 11.2.3.1 Lymphoplasmacytic inflammation

##### 11.2.3.1.1 Idiopathic lymphoplasmacytic enteritis

The most common form of idiopathic intestinal inflammation reported in dogs and cats is idiopathic lymphoplasmacytic enteritis (LPE), characterized by infiltration of the SI mucosa by lymphocytes and plasma cells (▶Fig. 11-7). However, other causes of lymphoplasmacytic infiltration of the SI must be excluded before a diagnosis of idiopathic LPE can be confirmed (▶Tab. 11-3). However, even within idiopathic LPE, variations exist in its pattern within the lamina propria (e.g., intraepithelial, villous, upper crypt, or lower crypt), the ratio of lymphocytes to plasma cells, and the severity.

There may also be variations in the regional distribution of the inflammation, with gastritis sometimes occurring with LPE. Lymphoplasmacytic colitis (LPC) was, historically, often reported as an isolated problem. The presence of hypocobalaminemia in many apparent cases of colitis would suggest it is a more diffuse disease. With endoscopy to obtain concurrent duodenal, ileal, and LI biopsies, it has been shown that isolated idiopathic LPC only occurs occasionally, and enterocolitis is more likely.

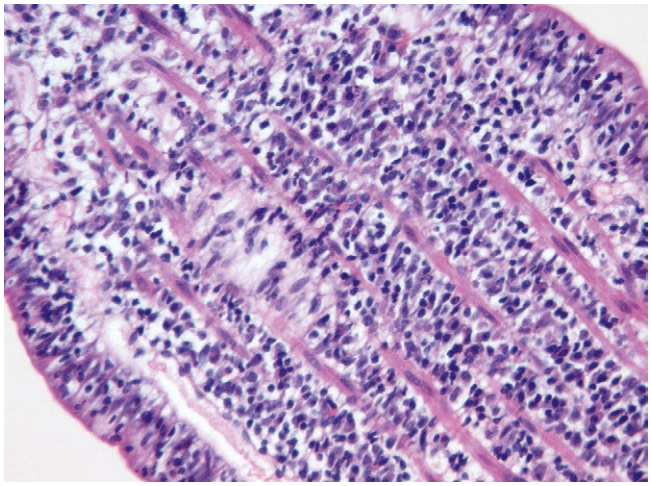


**Fig. 11-7** Lymphoplasmacytic enteritis
Histological appearance of a duodenal biopsy specimen from a dog showing increased numbers of lymphocytes in the lamina propria and epithelium.

In cats, isolated colitis is most commonly associated with *Tritrichomonas blagburni* infection (▶Chap. 8.3.3).

##### 11.2.3.1.2 Breed-related enteropathies

Several dog breeds appear susceptible to LPE (▶Fig. 11-8), but whether these represent specific conditions, genetic predispositions, or coincidence is currently unclear.[27] Siamese cats are also considered to be predisposed to LPE.

**Lymphoproliferative enteropathy of the basenji**

This condition appears to be an inherited form of LPE of such severity that it has been termed lymphoproliferative enteropathy. It has been linked to an immunoproliferative small intestinal disease (IPSID) in humans, as both conditions are associated with intense intestinal inflammation. However, an associated gammopathy (alpha heavy-chain disease) and predisposition to lymphoma do not occur in basenjis. Signs of chronic, intractable diarrhea and emaciation are most common and usually progressive. PLE often develops with consequent hypoalbuminemia, with spontaneous intestinal perforation in severe cases. Treatment is generally unsuccessful and dogs die within months.[28]



**Fig. 11-8** Dogs with chronic inflammatory enteropathy

**a** A 3-year-old German shepherd dog with a mixed cell inflammatory enteropathy appearing underweight and stunted compared with an age-matched control.

**b** A 4-year-old Rottweiler with severe lymphoplasmacytic enteritis and a consequent protein-losing enteropathy showing abdominal distension due to ascites.

### Protein-losing enteropathy in soft-coated wheaten terriers

A reportedly unique clinical syndrome with a poor prognosis is seen in soft-coated wheaten terriers (SCWTs). Affected dogs may present with signs of PLE, a protein-losing nephropathy (PLN), or both. A mutation in the expression of the glomerular protein nephrin has been identified as the cause of the PLN. However, it is not directly associated with the PLE and may be a coincidental breed predisposition to LPE. Affected SCWTs often express perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) when they have a PLE.[29]

### German shepherd dog enteropathy

This breed appears predisposed to a range of CIEs (ARD, LPE, and EE) and exocrine pancreatic insufficiency (EPI, ▶Chap. 10.3.2). A genetic predisposition related to the mucosal immune system may be responsible (▶Chap. 11.2.2).

### Shar-pei enteropathy

Chronic LPE, associated with marked hypocobalaminemia, is recognized in this breed, but the exact cause and optimal treatment are currently unknown.[30]

### 11.2.3.2 Eosinophilic enteritis

This histopathological form of CIE is the second most frequently diagnosed after LPE. It may also involve the stomach, colon, or both in eosinophilic gastroenteritis (EGE) and/or colitis. Dogs and cats of any breed and age can suffer eosinophilic enteritis (EE), although it is most common in younger adult animals. Boxers, GSDs, and Doberman pinschers may be predisposed. Severe EE has been associated with a PLE and, rarely, with spontaneous gastrointestinal perforation. An unusual form in cats, *feline gastrointestinal eosinophilic sclerosing fibroplasia* (FGESF), is reported.

Endoscopically, EE cannot be distinguished from LPE. However, anecdotally, spontaneous mucosal hemorrhage seems more common in EE, and occult bleeding or hematemesis, melena, or hematochezia are perhaps more common. Variable mucosal architectural disturbances are present in conjunction with a mixed infiltrate of inflammatory cells with eosinophils predominating. However, as with LPE, diagnostic criteria vary between pathologists. It can be challenging to identify eosinophils with hematoxylin and eosin stains, and they are better visualized using special stains such as Sirius Red. However, neither stain identifies degranulated eosinophils, which are more likely to be significant in active disease. A monoclonal antibody against eosinophil peroxidase can detect both intact and degranulated eosinophils, and

increased numbers are seen in dogs with LPE, EE, and mixed inflammation (▶Fig. 11-9).[31] As with other forms of IBD, a diagnosis of EE should only be made once other causes of eosinophilic infiltration, such as parasitic and allergic diseases, have been eliminated.

#### 11.2.3.2.1 Feline gastrointestinal eosinophilic sclerosing fibroplasia

The disease is most often observed in middle-aged cats, with male cats, especially ragdolls, over-represented.[32] Cats affected with feline gastrointestinal eosinophilic sclerosing fibroplasia (FGESF) generally have a long history of vomiting, diarrhea, or both. Palpable lesions are typically firm but non-painful and most commonly situated near the pylorus or ileocecocolic junction. Masses feel "gritty" on fine-needle aspiration due to the presence of mature collagen bundles. Bacteria can be detected within masses, but a consistent infective agent has not been identified. A major differential diagnosis is a feline infectious peritonitis (FIP)-induced granuloma in the ileal region, with coronavirus infection confirmed by immunohistochemistry.

### 11.2.3.3 Neutrophilic enteritis

Most cases of neutrophilic enteritis are probably not idiopathic CIEs. Increased numbers of neutrophils in intestinal biopsies raise a suspicion of an inflammatory response to bacteria, and treatment with antibiotics may be indicated before considering immunosuppressant therapy. The molecular technique of fluorescence in situ hybridization (FISH) is a very sensitive method for identifying bacteria in tissue that are not visible with Gram's stain. In a series of cats with neutrophilic enteritis, FISH showed a close association between neutrophils and *Campylobacter coli* organisms in the mucosa.[33] FISH can also identify *Salmonella* infection within tissues.

### 11.2.3.4 Granulomatous enteritis

Granulomatous inflammation of the SI, similar to CD in humans, is considered rare, although older reports of a condition called "regional enteritis" bear a strong resemblance.[34,35] Histiocytic ulcerative (granulomatous) colitis (HUC/GC), seen predominantly in boxers and French bulldogs, is related to adherent and invasive *E.coli* infection.[36] Successful treatment with enrofloxacin has been reported, and immunosuppressant treatment worsens the condition; it is no longer considered an idiopathic CIE (▶Chap. 8.3.1.2).

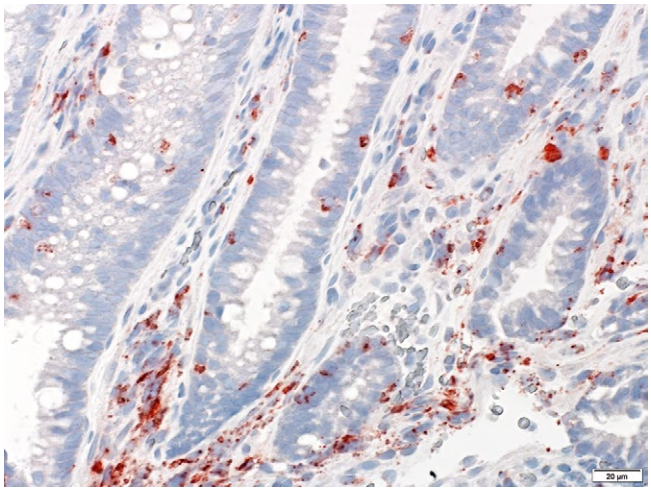



**Fig. 11-9** Staining of eosinophils in a chronic inflammatory enteropathy

Eosinophils assessed by eosinophil peroxidase (Epx) immunohistochemistry in an endoscopic biopsy from the duodenum of a dog with a mixed inflammatory response. The presence of a few intact eosinophils and eosinophil granules in the extracellular matrix, indicating degranulation, is noted (red-brown color). Scale bar = 20 µm.

(Courtesy of Dr. Savita Rao, University of Minnesota, USA.)

### 11.2.3.5 Lymphangiectasia

Idiopathic **lymphangiectasia** is a CE with characteristic lacteal dilation and disruption, causing loss of lipoproteins and may manifest as a PLE (▶Chap. 7.3.8). Whether this condition is primarily inflammatory is controversial: lymphangitis of mesenteric lymphatics and lipogranuloma development are noted in some cases having surgical biopsies, but it is unknown whether this is the cause or a consequence. Clinical improvement is sometimes seen with anti-inflammatory doses of prednisolone, but some cases resolve with an ultra low-fat diet or even spontaneously.[37]

### 11.2.3.6 Antibiotic-responsive diarrhea

A syndrome of idiopathic ARD is typically seen in young GSDs and other large-breed dogs. Polymorphism in mucosal toll-like receptors may underpin the condition, but histopathology cannot confirm the diagnosis as there are no overt inflammatory changes. Clinical signs are chronic continual or intermittent diarrhea, stunting and poor body condition, and either increased appetite and even coprophagia or hyporexia. Once exocrine pancreatic insufficiency (EPI; ▶Chap. 10.3.2) in young GSDs has been ruled out, and fenbendazole and diet trials have failed, it is reasonable to trial antibacterials such as tylosin or metronidazole (or oxytetra-

cycline where available), before steroid therapy which may worsen clinical signs. Use of an antibiotic trial in dogs that do not fit the category of a young GSD or large breed dog is discouraged.[38]

### 11.2.4 Clinical presentation

Idiopathic CIEs are generally considered the most common cause of chronic GI signs in dogs and cats, but the true prevalence is poorly documented. The condition may be over-diagnosed due to the ease of getting endoscopic duodenal biopsies, the difficulties in interpreting histopathological specimens (particularly if collected endoscopically), and the failure to rule out adequately other causes of mucosal inflammation. However, in a retrospective study by Volkmann et al. (2017)[39] of 136 dogs with chronic diarrhea, 90%, were diagnosed with a primary enteropathy. Of these 123 dogs, 71% had an inflammatory enteropathy, of which 66% were diet-responsive, 23% idiopathic, and 11% antibiotic-responsive.

#### 11.2.4.1 Signalment

No sex predisposition has been reported in dogs or cats, but CIEs are more common in middle-aged animals of both species. Apart from ARD, they are very uncommon in animals less than 12 months of age when anatomical, infectious, and dietary causes of diarrhea are much more prevalent. Few features distinguish the different forms of CIE, although dogs and cats with FREs tend to be younger and have milder clinical signs, and anecdotally, EE is more likely to cause GI bleeding.

Although idiopathic CIEs can potentially occur in any dog or cat breed, certain breed predispositions are recognized (▶Chap. 11.2.3.1.2).



A syndrome of "triaditis" has been reported in cats, characterized by concurrent LPE, lymphocytic cholangitis, and chronic pancreatitis.[40]

#### 11.2.4.2 Clinical signs

Clinical signs in individual patients are variable and may include some or all of the signs listed in ▶Tab. 11-4. It should be noted that clinical signs may wax and wane, and external triggers such as sudden diet change, "stress" (e.g., kenneling), or changes in the estrous cycle are sometimes associated with clinical relapses.

Signs are caused by GI inflammation and the consequent dysbiosis, with potentially increased SI secretion and/or malabsorption. However, clinical signs are variable between patients, reflecting the severity of the inflammation, the region of the GI tract affected, and, perhaps, the temperament of the patient.

**Tab. 11-4** Clinical signs associated with chronic inflammatory enteropathies

| Sign | Characteristic |
|---|---|
| Abdominal discomfort/pain | Restlessness that may lead to hyporexia |
| Altered appetite | Polyphagia |
| | Hyporexia/anorexia |
| | Eating grass |
| Dyspnea | Pleural effusion |
| | Pulmonary thromboembolism |
| Excessive borborygmus and flatus | Belching |
| | Flatus |
| Fluid accumulation due to hypoalbuminemia | Ascites |
| | Edema |
| | Pleural effusion |
| Large intestinal-type diarrhea | Hematochezia |
| | Mucoid stool |
| | Increased frequency and tenesmus |
| Small intestinal-type diarrhea | Large volume |
| | Watery |
| | Melena |
| Vomiting | Bile and/or food |
| | Hair (cats) |
| | Grass (dogs) |
| | Hematemesis |
| Weight loss | Sarcopenia |
| | Loss of body fat |

The nature of the signs can be correlated approximately with the region of the GI tract that is affected:

- Vomiting and hematemesis are more common if gastric or upper SI inflammation is present, and in cats, vomiting is often the predominant sign.
- Signs of colitis include mucoid diarrhea, fecal tenesmus, increased frequency of defecation, and hematochezia.

Vomiting, diarrhea, and weight loss are the most common clinical signs. Hematemesis and melena are seen less commonly and are usually associated with more severe disease and, anecdotally, more often with EE compared with LPE. Signs of colitis may result from colonic inflammation or may result from prolonged SI diarrhea or the presence of agents that stimulate colonic secretion (e.g., bacteria, bacterial toxins, deconjugated bile acids, or hydroxylated fatty acids).

Weight loss may result from decreased appetite, malabsorption, GI loss of protein, or a combination of these. Appetite can be variable: polyphagia may be present in the face of significant weight loss, indicating malabsorption, whilst anorexia is more likely with severe inflammation or if persistent vomiting causes esophagitis. CIEs may be associated with significant GI protein loss and a PLE (▶Chap. 7.3.8). Milder inflammation may not affect appetite at all unless there is postprandial pain. Thromboembolism and remote organ failure is a feature seen in some patients with PLE. This may cause other signs, such as abdominal pain with portal vein thrombosis and dyspnea with pulmonary thromboembolism. Other extraintestinal clinical signs are not commonly recognized in dogs and cats with CIE, with type III, non-erosive, enteropathic polyarthritis being the most commonly reported complication in dogs.[41]

To fully evaluate patients with CIEs, monitor the response to treatment, and compare clinical trials, the classification of clinical signs with a disease activity index is helpful. The Canine Inflammatory Bowel Disease Activity Index (CIBDAI) scores a variety of clinical signs.[42] The Canine Chronic Enteropathy Clinical Activity Index (CCECAI) and the Feline Chronic Enteropathy Activity Index (FCEAI) include some laboratory parameters (▶Chap. 1.1).[43,44]

#### 11.2.4.3 Physical examination

Findings range from no physical abnormalities through abdominal discomfort to more severe signs of melena and hematochezia, and emaciation, with ascites, edema, pleural effusion, or a combination in PLEs. Thickened bowel loops may be palpated in cats. However, ultrasonographic measurements often reveal no actual thickening in dogs with CIEs; the perception of increased thickness may be false, caused by increased tone in the muscle layers.[45] Truly thickened bowel loops are more likely caused by AL (▶Chap. 11.3), other neoplasms (▶Chap. 7.3.9), or fungal infections (▶Chap. 7.3.1.5) such as pythiosis.[46]

### 11.2.5 Diagnosis

Although the clinical signs and physical examination findings may be suggestive of a CIE, intestinal biopsy is ultimately necessary for a definitive diagnosis. The term idiopathic CIE is restricted to cases in which intestinal inflammation is found without an obvious underlying cause and, therefore, other etiologies must be excluded. Consequently, before intestinal biopsies are collected, laboratory evaluation and diagnostic imaging examinations must be performed. Such investigations are not intended to provide a definitive diagnosis of a CIE but to help eliminate the possibility of extraintestinal disease (e.g., pancreatitis, hypoadrenocorticism, renal failure, and hepatic failure), anatomical intestinal disease (e.g., tumor, intussusception, or chronic foreign body), or infectious causes of intestinal inflammation. Furthermore, by determining whether a focal or diffuse intestinal disease is present, the most appropriate method of intestinal biopsy can be chosen.

#### 11.2.5.1 Laboratory tests

##### 11.2.5.1.1 Minimum database

There are no pathognomonic changes in a minimum database of hematology and serum biochemistry in CIEs (▶Chap. 1.3.2), but they help rule out non-GI causes of clinical signs. Significant GI bleeding or the presence of a PLE will be identified.

##### 11.2.5.1.2 Fecal examination

Fecal examination by flotation techniques should eliminate known helminth parasitic causes of mucosal inflammation. However, given that *Giardia* spp. may not always be detected, empirical treatment with fenbendazole is recommended. Fecal polymerase chain reaction (PCR) is the best method of diagnosing *Tritrichomonas blagburni* infection in cats (▶Chap. 8.3.3). Culture for bacterial pathogens is more problematic, as known pathogens can be found in the stool of healthy animals, and their presence in patients with CIE does not necessarily prove a causal relationship (▶Chap. 7.3.1.2).

#### 11.2.5.1.3 Adjunctive tests

##### Serum folate and cobalamin concentrations

Measurement of serum folate and cobalamin concentrations in dogs and cats is important as folate and cobalamin deficiencies are often associated with CIEs. Although not pathognomonic, deficiencies require therapeutic correction. In particular, cobalamin deficiency may in itself have systemic metabolic consequences and cause intestinal dysfunction. Anecdotal evidence suggests that the response to treatment of CIE may be suboptimal unless cobalamin deficiency is addressed.

##### Vitamin D status

Hypovitaminosis D can occur in CIEs and is a negative prognostic indicator. Whether it is merely a marker for ill health and whether supplementation is needed is unclear.[47–49]

##### Serum markers of inflammation

Serum acute phase proteins (APP), such as C-reactive protein, may be increased in dogs with CIE. However, given that APPs are non-specific markers of inflammation, these tests alone are not diagnostic, although they provide a crude, non-invasive means of assessing disease severity and monitoring response to treatment.

##### Fecal biomarkers

**Occult blood** This test identifies GI bleeding that is not grossly visible as melena or hematochezia, particularly when iron deficiency anemia is detected.

**Fecal alpha$_1$-proteinase inhibitor** Measurement of the fecal loss of alpha$_1$-proteinase inhibitor ($\alpha_1$PI) may be a sensitive test for PLE before hypoproteinemia develops.

**Fecal calprotectin** Measuring calprotectin in fecal samples appears to be of value in detecting GI inflammation and monitoring the response to treatment.[50]

#### 11.2.5.1.4 Diagnostic imaging

Radiographic and ultrasonographic studies should be performed to document whether focal or diffuse disease is present, document any anatomical GI disease, and show any involvement of other abdominal organs. Used in conjunction with specific clinical signs, and laboratory testing, the information from imaging studies enables an appropriate choice of a biopsy method (i.e., upper and/or lower GI endoscopy or exploratory laparotomy) that will most likely lead to a definitive diagnosis.

#### 11.2.5.1.5 Empirical treatment trials

In patients without any criteria of immediate concern (▶ box "Criteria of concern"), it is recommended that empirical treatments are tried before biopsy, as any finding of inflammation still obligates the clinician to then try empirical treatments. This is because intestinal inflammation is a final common pathway: different causes of inflammation cannot be distinguished by light microscopy, and not all of them need immunosuppressant treatment.

Therefore, assuming the patient is stable and eating, it is recommended to give a 3-day treatment with fenbendazole (50 mg/kg q24h PO) to eliminate any occult parasitic infection, especially *Giardia* spp., then followed, if necessary, by an exclusion diet trial. Most clinicians find that a hydrolyzed diet is more likely to be successful compared with a single novel protein source. Most patients respond within 2–3 weeks of introducing the diet, allowing a diagnosis of an FRE to be made and obviating the need for any biopsy.

Patients that fail fenbendazole and diet trials have previously then had an antibacterial trial. However, antibiotic stewardship to reduce bacterial resistance is now so important that a trial is usually reserved for young, large breed dogs, especially GSDs, likely to have idiopathic ARD.

**NOTE**
The indiscriminate use of metronidazole in chronic diarrhea is discouraged.

In dogs of other breeds and ages and in cats, a steroid trial is now recommended before trialing antibacterials.[38]

**Criteria of concern indicating further diagnostic investigation is required**

- Anorexia
- Persistent, frequent vomiting
- Severe weight loss
- Hypoalbuminemia <15 g/L
- Hypocobalaminemia
- Unexpected physical examination and/or imaging findings

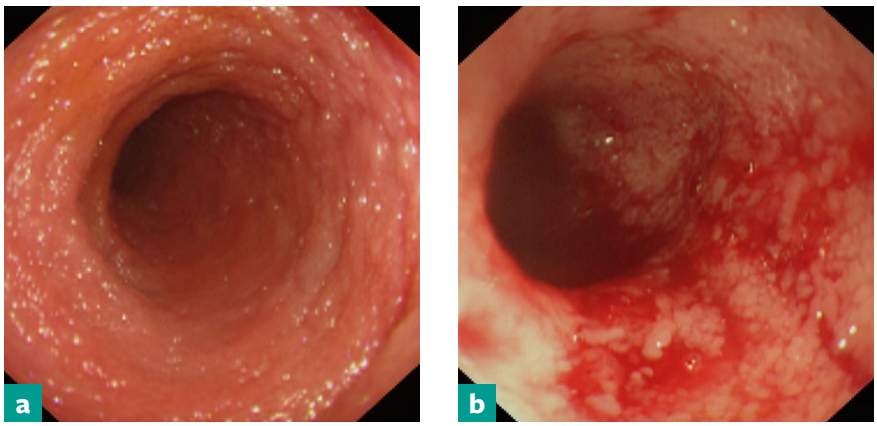



**Fig. 11-10** Endoscopic appearance of the intestine of patients with chronic inflammatory enteropathies

**a** Lymphoplasmacytic enteritis in a dog, showing duodenal erosions and ulcers

**b** Eosinophilic enteritis in a dog showing spontaneous duodenal bleeding

#### 11.2.5.1.6 Intestinal biopsy

The simplest and least invasive method of sample collection is endoscopic biopsy. However, numerous limitations exist, including small sample sizes, superficial and often fragmented samples, difficulty processing small samples, and the fact that tissue can only be collected from the stomach, proximal SI, distal ileum, and colon. Studies have shown that ileal biopsies in dogs are more likely to be diagnostic than duodenal biopsy,[51] and AL is more likely in the ileum of cats than in the upper GI tract.[52] However, an ileal biopsy is not always achievable by endoscopy. The endoscopic appearance of the intestinal mucosa may give some clues as to the presence of intestinal inflammation, and a scoring system has been published. Increased granularity, irregularity, and friability with the presence of erosions, ulceration, and spontaneous hemorrhage are all potential markers of intestinal inflammation (▶Fig. 11-10). However, interpretation of the gross appearance of the mucosa is somewhat subjective, and obvious changes are not invariably present despite histopathological evidence of inflammation. Furthermore, similar changes may be seen in other intestinal conditions, especially intestinal neoplasia.

In some cases, exploratory celiotomy and full-thickness biopsy are necessary. However, this is more invasive, and wound healing may be impaired by hypoproteinemia or if corticosteroids need to be given urgently. It may be more suitable for cats, given the tendency for concurrent hepatic and pancreatic involvement requiring biopsy of these organs and the small size of endoscopic biopsies sometimes achieved in this species (▶Chap. 1.5).

Intestinal biopsy is essential to prove intestinal inflammation and thus confirm a diagnosis of CIE; the disease may not be inflammatory due to functional rather than morphological abnormalities. However, pragmatically, neither may need a biopsy if a positive response to a diet trial is obtained beforehand.

Unfortunately, the histopathological assessment of intestinal biopsies, although considered the gold standard, has marked limitations.[53–55] Interpretation of intestinal histopathology remains problematic, particularly for endoscopic biopsies as sampling and interpretive problems can occur; misdiagnosis is always a concern. One problem is a poor agreement between pathologists: this may be due to the size and sometimes poor quality of endoscopic biopsies, potential patchiness of any inflammation with failure to biopsy the affected region, the subjective nature of interpretation of the degree of inflammation, or the presence of edema (due to hypoproteinemia) leading to difficulties in assessing cell density. The WSAVA GI Standardization Group tried to resolve these inconsistencies (▶Tab. 11-5). It recognized that lymphocytes and plasma cells are always present in the intestinal mucosa, and simply using increases in cellularity as a marker of inflammation is too subjective. Thus, a standard grading scheme that assessed architectural abnormalities in conjunction with changes in cellularity was developed.[56] This scheme has subsequently been refined (▶Tab. 11-5), but discordance between pathologists remains.[57]

Another difficulty is that the distinction of severe LPE from lymphoma can be difficult, particularly with endoscopic biopsies, as histological confirmation of lymphoma is made most readily when lymphocytic infiltration of muscle layers

**Tab. 11-5** Histopathological standards for the diagnosis of intestinal inflammation

| WSAVA Gastrointestinal Standardization Group[74] | Jergens et al. 2014[57] |
|---|---|
| **Morphological features** | |
| Villus stunting | Villus atrophy |
| Epithelial injury | Epithelial injury |
| Crypt distension | Crypt changes |
| Lacteal dilation | - |
| Mucosal fibrosis | - |
| **Inflammation** | |
| Intraepithelial lymphocytes | Intraepithelial lymphocytes |
| Lamina propria lymphocytes and plasma cells<br>Lamina propria eosinophils<br>Lamina propria neutrophils | Lamina propria infiltrates |
| Other | - |

is seen on full-thickness surgical biopsy specimens. Immunohistochemistry, PCR for antigen receptor rearrangement (PARR) analysis for clonality, and histology-guided mass spectrometry may be needed to make the distinction.[58]

Ultimately, the primary clinician should interpret histopathology results cautiously and relate them to the clinical presentation. Results should be questioned if the histopathological diagnosis does not fit the clinical picture or if the response to apparently appropriate therapy is poor. In some cases, repeat biopsy and biopsy of other sites (e.g., by exploratory laparotomy) may be required.

### 11.2.6 Treatment

Regardless of the histological type of CIE diagnosed, treatment has traditionally relied on immunosuppressant therapy, usually combined with dietary modification, antibacterials, and supportive treatments. However, considering the large proportion of cases that respond to a hydrolyzed diet trial, a staged approach to therapy is now recommended whenever possible. Immunosuppressant medication is only used if there is a failure to respond to diet or in severely ill patients with criteria of concern (▶ box "Criteria of concern"), and immediate intervention with immunosuppressant medication may be essential but given concurrently with diet and other therapies. Attempts to taper immunosuppressants down to the minimum effective dose should follow once the patient is in remission whilst maintaining dietary control. Changes in disease activity indices may provide objective evidence of treatment success.

#### 11.2.6.1 Diet

The diets recommended for patients with CIE are either hydrolyzed diets or an easily digestible exclusion diet based on a single-source protein that is novel to the patient. Their efficacy may reflect that they are highly digestible even to an inflamed SI. However, hydrolyzed diets contain peptides too small to activate sensitized mast cells. Both they and single-source protein diets decrease intestinal antigenic diversity and load and potentially decrease mucosal inflammation either directly or indirectly by altering the intestinal microbiome.

Well-cooked rice is the preferred carbohydrate source because of its high digestibility, but potato, corn (maize) starch, and tapioca are alternative options. It is probably appropriate that they are gluten-free, although the prevalence of gluten sensitivity in small animals is unclear. If severe malabsorption is evident, fat restriction may reduce clinical signs. However, fat restriction is rarely necessary and may make it more difficult to resolve any weight loss. Modification of the n3:n6-fatty acid ratio may also modulate the inflammatory response and be of some benefit in the treatment and maintenance of remission.

#### 11.2.6.2 Dietary supplements

##### 11.2.6.2.1 Prebiotics

Prebiotics are dietary substrates selectively used by a limited number of beneficial bacterial species, resulting in alterations in the luminal microbiome and may have benefits in CIEs. Non-digestible carbohydrates, such as lactulose, inulin, fructooligosaccharides (FOS), and mannan oligosaccharides (MOS), are the prebiotics most frequently used in commercial diets.

##### 11.2.6.2.2 Probiotics

Probiotics can directly antagonize pathogenic bacteria, but they also modulate the microbiome and mucosal immune responses. At present, the most appropriate organism(s) to use as probiotics is(are) uncertain but are likely to vary between dogs and cats and even between individuals.

#### 11.2.6.2.3 B vitamin supplementation

**Folic acid** Folate malabsorption may accompany severe and prolonged CIEs. The clinical consequences of hypofolatemia are not understood, but oral supplementation is easily achieved with the administration of 0.5–1 mg of folic acid per day.

**Cobalamin** Malabsorption of cobalamin (vitamin $B_{12}$) is common in patients with CIEs and can have significant clinical consequences.[59] Cobalamin deficiency causes methylmalonic acidemia, which may, in part, cause the ill-thrift and poor appetite seen in many patients. Also, experimental cobalamin deficiency causes intestinal mucosal pathology, and it seems logical that the correction of a deficiency is necessary before an optimal response to therapy can be achieved. The total dose required to achieve normocobalaminemia is variable, as serum concentrations do not accurately reflect cellular depletion. However, there are no known adverse consequences of hypercobalaminemia, and potential overdose is of little concern. Weekly subcutaneous injections of between 250 µg (cats and small dogs) up to 1 mg (large breed dogs) of cyanocobalamin for 6 weeks are recommended. Intramuscular hydroxocobalamin may be retained longer than synthetic cyanocobalamin. However, daily oral administration of vitamin $B_{12}$ for 12 weeks was as effective in dogs and cats.[60,61] Serum cobalamin concentration should be rechecked after 4–6 weeks and ideally should be supranormal.

### 11.2.6.3 Fecal microbiota transplantation

Fecal microbiota transplantation (FMT) is the administration of a "live" fecal infusion from a healthy donor to a patient with disease to help improve health. It may alter the intestinal microbiome leading to reduced intestinal inflammation. In humans, FMT has been used successfully to treat resistant *Clostridium difficile* infection, and in puppies with parvovirus enteritis, its use has aided recovery.[62] There are ongoing studies of FMT use in CIEs, but there are many uncertainties (e.g., how to screen the donor, what dose to use, and the route of administration). There is a risk of transmitting antibiotic-resistant pathogens; therefore, the use of FMT to treat CIEs is presently not recommended.

### 11.2.6.4 Immunosuppressant drugs

Assuming a diet trial is unsuccessful, the most important therapy for idiopathic CIE is immunosuppression, although it should be considered a last resort. Signs of iatrogenic hyperadrenocorticism are common with immunosuppressive doses of prednisolone. Most signs resolve as the dose is tapered, although muscle atrophy may be permanent; however, the patient's quality of life is often adversely affected during treatment. Thus, if a relapse consistently occurs when the dose is reduced, alternative drugs can be added to provide a "steroid-sparing" effect (▶Chap. 11.2.6.4.3 and ▶Chap. 11.2.6.4.4). Alternatively, novel steroids with fewer side-effects can be used.

#### 11.2.6.4.1 Prednisolone (prednisone)

In dogs and cats, glucocorticoids are used most frequently, and prednisolone (or prednisone in the USA) is the drug of choice. Side-effects are common, but an increased appetite is of benefit in hyporexic patients. Dexamethasone should probably be avoided because it has been shown to have a deleterious effect on the expression of enterocyte brush border enzymes in other species.

The standard initial dose of prednisolone is 1–2 mg/kg PO per day is given for 2–4 weeks. Higher initial doses (up to 4 mg/kg/day) are sometimes recommended, particularly in cats, but there is no evidence of greater efficacy, and side-effects can be severe. A dose rate of 40 mg/m$^2$ may be more appropriate in large and giant breed dogs. Once-daily administration reportedly produces less hypothalamic-pituitary-adrenal suppression than a split dose. In severe cases, when oral absorption may be inadequate, initial parenteral administration may be beneficial.

Once remission is achieved, the dose is tapered slowly over the subsequent weeks to months. The rate of tapering is somewhat empirical and often designed to fit in with convenient revisit opportunities; a 25–50% reduction every 2–4 weeks until signs recur is typically recommended. In most cases, therapy can be reduced to a low maintenance dose given q24–48h, as only in a minority of cases can it be completely withdrawn.

In some cases, an initial response to steroids is followed by a relapse and a lack of further response even when doses are increased. Some of these cases probably represent either an incorrect initial diagnosis or, possibly, transformation to AL. However, resistance to steroids may develop because of the induction of the *multiple drug resistance* (*MDR1*) gene and expression of P-glycoprotein.[19,63]

#### 11.2.6.4.2 Budesonide

An enteric-coated formulation of budesonide, a locally active steroid, has been used successfully in maintaining remission in human IBD with minimal hypothalamic-pituitary-adrenal

suppression, as 90% of the drug is metabolized during its first-pass through the liver after absorption. However, induction of ALP and development of a steroid hepatopathy have been seen in dogs, hypothalamic-pituitary-adrenal suppression has been demonstrated, and no benefit compared with prednisolone has been shown.[64] The optimal dose of this drug has not yet been determined.[65] Anecdotally, doses should not exceed 3 mg/day in dogs and 1 mg/day in cats, and 1 mg/m$^2$/day has been recommended.

#### 11.2.6.4.3 Cytotoxic agents

A range of cytotoxic agents can be used as "steroid-sparing" agents to treat CIEs. Azathioprine in dogs and chlorambucil in dogs and cats are the usual choices, and mycophenolate mofetil has shown some benefit. Cyclophosphamide has few advantages over azathioprine and is rarely used. Methotrexate is effective in treating human CD but is not widely used in companion animals. In dogs, it can cause diarrhea but is better tolerated in cats.

**Azathioprine** at 2 mg/kg/day PO can be used in dogs, combined with prednisolone or prednisone, when the initial response to steroid therapy is poor, or side-effects are marked, and a steroid-sparing drug is required. However, its activity may show a delayed onset (up to 6 weeks), and given its myelosuppressive potential, regular monitoring of the hemogram is necessary. Idiosyncratic bone marrow toxicity has been linked to the activity of the thiopurine methyltransferase (TPMT), the major enzyme involved in the degradation of 6-mercaptopurine, the active metabolite of azathioprine.[66] Azathioprine is not generally recommended for cats, partly because cats have very low activities of TPMT and partly because the coated tablets cannot be split and need reformulation to a suitable size.

**In cats, chlorambucil** (2–6 mg/m$^2$/day until remission, then tapering) is a better choice of a cytotoxic immunosuppressive agent, and there is one report of its use in canine CIE.[67]

#### 11.2.6.4.4 Cyclosporine

The risks associated with using cytotoxic agents make the use of cyclosporine to treat CIEs attractive. One study reports the successful treatment of 11/14 dogs with steroid-resistant CIE.[68] Cost and potential side-effects (diarrhea, inappetence, gingival hyperplasia) probably make it a second choice after glucocorticoids as it is safer than cytotoxic agents. The recommended dose (5 mg/kg q12–24h PO) is similar to the licensed dose for treating atopic dermatitis, but the dose may need to be increased in poorly responsive and severe cases. However, actual tissue concentrations in the GI tract probably do not correlate with serum concentrations as the molecule undergoes enterohepatic recycling.

### 11.2.6.5 Antibacterial therapy

The use of antimicrobials in patients with non-food responsive CIE has been justified, in part, by the potential to treat any undiagnosed enteropathogens or secondary small intestinal bacterial dysbiosis and in part by the perceived importance of bacteria in the pathogenesis of CIE. Metronidazole is the preferred antibacterial. However, the benefit of adding metronidazole to prednisolone therapy has not been shown.[44]

### 11.2.6.6 5-Aminosalicylic acid derivatives

Human UC is often treated with 5-aminosalicylic acid (5-ASA) products.[69] Idiopathic colitis can also be treated with 5-ASA derivatives administered in a pro-drug formulation that is only active in the colon, as long as the colitis is neither secondary to SI disease nor part of more diffuse inflammation. The safety and efficacy of the pro-drug balsalazide (4-aminobenzoyl-β-alanine-mesalazine) have not been evaluated in small animals and cannot be recommended.

#### 11.2.6.6.1 Mesalazine

Native 5-ASA is available as a slow-release enteric formulation for human UC. The safety of such oral formulations in dogs and cats is unclear and cannot be recommended. Suppositories and foams containing mesalazine, given per rectum, are available.

#### 11.2.6.6.2 Sulfasalazine

This is the most commonly used preparation. It is a pro-drug with a diazo-bond binding sulfapyridine to 5-ASA being cleaved by colonic bacteria to release free 5-ASA, which acts locally in high concentrations in the colon as an anti-inflammatory agent. Hepatoxicity can occur, but its major side-effect is keratoconjunctivitis sicca (KCS), and Schirmer tear tests should be performed regularly. KCS is believed to be a complication of the sulfa-moiety, although it has been seen with olsalazine, which contains no sulfonamide.

#### 11.2.6.6.3 Olsalazine

This pro-drug comprises two 5-ASA molecules joined by a diazo bond. Again, free 5-ASA is released by colonic bacteria. This drug was developed to reduce the frequency of KCS, although occasional KCS is still reported. The dose is one-half the dose of sulfasalazine as it contains twice the amount of 5-ASA.

### 11.2.6.7 Adjunctive treatments

#### 11.2.6.7.1 Fluid therapy

Intravenous fluid therapy should be given if the patient is dehydrated, but most CIE patients have a chronic disease and reach a compensatory state, and do not need fluid support. If PLE and hypoproteinemia exist, plasma transfusion (or other colloidal support) may be indicated during the peri-operative period associated with intestinal biopsy to support the cardiovascular system during general anesthesia. Giving plasma at other times to try to increase serum albumin concentrations is an expensive waste.

#### 11.2.6.7.2 Diuretics

In PLE, ascites and other fluid accumulations may be reduced by giving diuretics: spironolactone at 1–2 mg/kg PO q12h may be more effective than furosemide.

#### 11.2.6.7.3 Antithrombotics

Thromboembolism is a feature of some dogs with PLE, and the use of either prophylactic low-dose aspirin (0.5 mg/kg PO q12h) or clopidogrel (2–4 mg/kg/day PO) may be indicated in PLE.[70]

### 11.2.6.8 Surgery

In human CD, granulomas can cause intestinal obstruction and fistulation, and surgical resection may be necessary. Surgery is not indicated in canine and feline CIEs, except perhaps in FGESF patients treated aggressively with a combination of cytoreduction, ranging from debulking and biopsy to complete surgical resection, immunosuppressant therapy, and antimicrobial agents.

### 11.2.6.9 Novel therapies

New drugs are being developed and used increasingly for human IBD patients to target the underlying pathogenetic mechanisms. Novel immunosuppressants, monoclonal antibody therapy, cytokines, and transcription factors are being trialed in human IBD patients and may be suitable for small animals in the future. Drugs that target TNF-α (e.g., thalidomide and pentoxifylline) may be useful for treatment because of the importance of this cytokine in disease pathogenesis. However, anti-TNF-α monoclonal antibody therapy, as used in human IBD, will only be suitable for canine and feline CIEs when a species-specific monoclonal antibody is available.

Stem cell therapy has been proposed for treating CIEs. Allogeneic adipose-derived mesenchymal stem cell therapy appears to be safe and potentially effective for dogs and cats suffering from chronic enteropathy, but preliminary results require significant follow-up studies.[71,72]

## 11.2.7 Prognosis

Except for those patients with a FRE, the prognosis for cats and dogs with idiopathic CIE is generally guarded. Immunosuppressants can have significant side-effects, and resistance may develop, with transformation to AL a theoretical risk. Several markers of a poor prognosis have been identified: high clinical activity index score, including anorexia, high endoscopic score, hypoalbuminemia, hypocobalaminemia, and increased blood urea and serum pancreatic lipase concentrations.[19,43,73]

**KEY FACTS**

- Chronic inflammatory enteropathies (CIEs) are a common cause of chronic vomiting and/or diarrhea in dogs and cats.
- The etiology of CIEs is hypothesized to be a breakdown in mucosal tolerance to the normal enteric flora with a likely genetic predisposition to immune dysregulation.
- Clinical signs of CIEs reflect the type of inflammation, the anatomical site, severity, and chronicity.
- Idiopathic CIEs are diagnosed based on histological evidence of inflammation in the absence of an underlying cause.
- An exclusion diet trial is indicated before immunosuppressant treatment.

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
svg.to/9842-11-02

## 11.3 Gastrointestinal lymphoma

Sina Marsilio

### 11.3.1 Introduction

Lymphomas are characterized by a clonal expansion of one (or few) lymphocytic clones, which are mostly of either T-cell or B-cell origin. Gastrointestinal lymphomas in both cats and dogs can be classified by morphologic evaluation (small vs. large cell, distribution within the mucosa, e.g., epitheliotropism), immunophenotyping (B-cell, T-cell, NK cell), anatomical location, and biological behavior (low grade vs. high grade). Although all are derived from lymphocytes, clinical presentation, treatment, and prognosis are fundamentally different between different forms of lymphomas, especially in cats. While the majority of alimentary lymphomas in cats are low-grade small-cell lymphomas, alimentary lymphomas in dogs are usually high-grade large cell lymphomas with involvement of other abdominal organs or part of a multicentric disease process. However, small-cell alimentary lymphomas are now more commonly recognized as a separate disease entity in dogs.

### 11.3.2 Feline gastrointestinal lymphoma

#### 11.3.2.1 Epidemiology and etiopathogenesis

The incidence of feline alimentary lymphoma has rapidly increased over the past decades.[1] Although the etiopathogenesis of feline gastrointestinal lymphoma is largely unknown, several hypotheses have previously been investigated. The association between feline leukemia virus (FeLV) and lymphoma in cats is well established.[2,3] Before the advent of a vaccine most cases of feline lymphoma were associated with FeLV infection.[2,3] With the start of mass testing and vaccination programs in the 1980s and 1990s, the prevalence of FeLV antigenemic cats and FeLV-associated lymphomas has significantly decreased.[1,4] However, the association between FeLV and lymphomas of the gastrointestinal tract has always been (and still is) less clear than that of lymphoma of other anatomical locations, such as the mediastinum. Studies using immunohistochemistry or PCR found virus or provirus antigens in 0–80% of cases.[5–7] Discrepancies may represent population differences as well as variations of test sensitivities. Nevertheless, today, cats with leukemia or mediastinal lymphoma tend to be young and FeLV positive, while those with GI lymphoma are typically older and FeLV negative.[6,8–13] Even in the "post-FeLV era," lymphomas remain the most common feline neoplasms,[1,9,10,14–16] with the alimentary tract being affected in 42–52% of cases.[9,10,14,17–19] Besides FeLV, other proposed etiopathogeneses include feline immunodeficiency virus (FIV) infections[20–22], *Felis catus* Gammaherpesvirus 1 infection[23], and gastric infection with *Helicobacter heilmannii*[24] and other mucosa-invasive bacteria.[25] Lastly, it has been suggested that chronic inflammation increases the risk of developing alimentary small-cell lymphoma, as cats with small-cell lymphoma often have concurrent inflammatory changes in other intestinal locations.[16,26,27]

#### 11.3.2.2 Classification

About 75% of gastrointestinal lymphomas in feline patients are low-grade small-cell lymphomas.[26] They consist of small lymphocytes representing a mature, well-differentiated population of cells with generally low mitotic rates.[26] Lesions are usually diffuse and mostly confined to the mucosa but occasionally progress into transmural infiltrates.[26] Clinical progression is usually slow, with clinical signs often present over weeks to months. Therefore, these lymphomas are referred to as low-grade small-cell lymphomas. Over 90% of small-cell lymphomas are of T-cell origin, and they usually arise in the jejunum, duodenum, and ileum (in descending order of occurrence).[26]

High-grade intermediate and large-cell lymphomas may be of B- or T-cell origin.[26] They may occur within the mucosa or transmurally and are commonly located in the ileum/ileocolic junction, jejunum, stomach, and duodenum (in descending order of occurrence). The majority of B-cell lymphomas are large-cell lymphomas, occurring as transmural lesions in the stomach, distal jejunum, or ileocolic junction. Lesions are often localized and eccentric but can also occur as diffuse infiltrates. High-grade large-cell lymphomas are usually readily diagnosed based on morphologic features alone (i.e., H&E-stained biopsy specimens or cytology), while the lineage (B- or T-cell origin) has to be determined by immunohistochemistry.

A third, less common form of lymphoma in cats is large granular lymphocyte (LGL) lymphoma. This form is of cytotoxic T-cell or natural killer (NK) cell origin, and the neoplastic cells often have intracytoplasmic eosinophilic granules.[28–30] The vast majority of LGL lymphomas arise in the gastrointestinal tract, causing segmental or centrifugal thickening or multiple masses within the small intestine; however, extra-gastrointestinal involvement is common. LGL lymphomas are often readily diagnosed upon cytological examination of samples acquired by fine-needle aspiration.

#### 11.3.2.3 Clinical presentation

Various studies found gastrointestinal lymphomas to arise in middle-aged to older cats with a median age of about 13 years and an age range from 4–20 years.[26,31–35] However, the vast majority of cats are older than 6 years of age. Many cats have a history of chronic enteropathy or were previously diagnosed with inflammatory bowel disease (IBD, ▶Chap. 11.2). In addition, cats often have inflammatory lesions in other parts of the gastrointestinal tract.[16,26,32,36] Therefore, it has been postulated that IBD might be a risk factor. However, this has yet to be proven in long-term longitudinal studies.

Clinical signs of gastrointestinal lymphoma in cats are similar for all types of lymphomas and also virtually indistinguishable from other chronic enteropathies. The most common clinical signs are weight loss (>80% of cats), vomiting, diarrhea, and/or anorexia or, less commonly, polyphagia.[16,29,30,33,37] In the author's and others' experience[38], weight loss is often overlooked due to its very gradual progression over weeks to months. Cats often develop significant sarcopenia, especially noticeable around the spine. Abdominal fat pads are often preserved even in otherwise significantly underweight cats with marked weight loss. Besides sarcopenia[39] and a generally low body condition score, a physical examination may reveal segmental or diffusely thickened intestinal loops and abdominal discomfort/pain often located in the cranial abdomen, possibly related to concurrent pancreatitis and/or cholangiohepatitis (▶Chap. 10.3.1 and ▶Chap. 9.6.3).[33,40,41] Large-cell lymphomas and LGL lymphomas tend to show a more aggressive clinical behavior with a more acute onset of clinical signs and rapid clinical progression. In addition, abdominal masses, intussusception, obstruction, or even perforation are more commonly associated with large-cell and LGL lymphomas.[26,30,42,43]

#### 11.3.2.4 Diagnosis

A definitive diagnosis of gastrointestinal lymphoma usually requires more invasive and expensive testing. Therefore, it is important to rule out other diseases that can cause similar clinical signs of GI disease. A complete blood count (CBC), chemistry profile, serum total T4 concentration, FeLV-antigen and FIV-antibody test, and urinalysis should be performed as baseline tests. If diarrhea is present, fecal flotation and testing for *Giardia* spp., *Cryptosporidium* spp., *Campylobacter* spp., and *Tritrichomonas blagburni* should be performed. Dependent on the geographic regions, fungal diseases, such as histoplasmosis, should be excluded before further diagnostics and immunosuppressive therapy are pursued.

Cobalamin (vitamin $B_{12}$) is a water-soluble vitamin present in dietary proteins. In the small intestinal tract, it is bound to intrinsic factor which, in cats, stems mostly from pancreatic secretion.[44,45] Cobalamin is absorbed in the distal small intestinal tract, especially the ileum, through binding of intrinsic factor to its respective receptors.[45] Thus, hypocobalaminemia serves as a surrogate marker for generalized severe malabsorption in the distal small intestinal tract and has previously been associated with disease severity in cats with chronic enteropathy.[46–48] Hypocobalaminemia is present in up to 78% of cats with gastrointestinal lymphoma, and thus, the measurement of serum cobalamin concentration should be part of the work-up for cats with chronic gastrointestinal signs.[31,47,49] However, the absence of hypocobalaminemia does not exclude the presence of small intestinal disease.[50]

Other common laboratory abnormalities include a decreased or increased serum folate concentration associated with malabsorption or small intestinal dysbiosis, respectively, and increased serum fPLI concentration, indicative of concurrent pancreatitis.[46,49]

Abdominal radiographs are usually unrevealing; thus, from a diagnostic and cost-benefit standpoint, abdominal ultrasonography is the most sensible mode of imaging for these patients. Common abnormal findings are diffuse, segmental, or focal intestinal wall thickening, loss of layering, hypoechogenicity, hypomotility, and mesenteric lymphadenopathy (▶Fig. 11-11).[29,30,33,51–53] However, the absence of ultrasonographic findings does not exclude the presence of gastrointestinal lymphoma, especially if diffuse.

The clonal but small and well-differentiated population of lymphocytes in small-cell lymphoma is generally indistinguishable from the polyclonal lymphocyte population seen in inflammatory lesions, such as IBD, without further information about the tissue architecture. Therefore, cytology is generally not helpful in diagnosing small-cell lymphomas, and endoscopic or surgical biopsy with a histopathologic assessment of hematoxylin and eosin stain (H&E)-stained slides is required. However, many large-cell and LGL lymphomas can be diagnosed based on cytology alone or combined with immunocytochemistry, flow cytometry, or PARR.[19,29,30] If large-cell lymphoma is suspected, fine-needle aspirates of liver and spleen may aid in the diagnosis, as other abdominal organs are frequently affected in cats with alimentary large-cell lymphoma.

Histopathological examination of tissue specimens remains the gold standard for the diagnosis of alimentary lymphoma (▶Fig. 11-12a and b). Given the vastly different treatment regimens and prognoses for the different types of lymphoma in cats, it is of paramount importance to determine the type of lymphoma. However, ambiguous cases frequently exist,

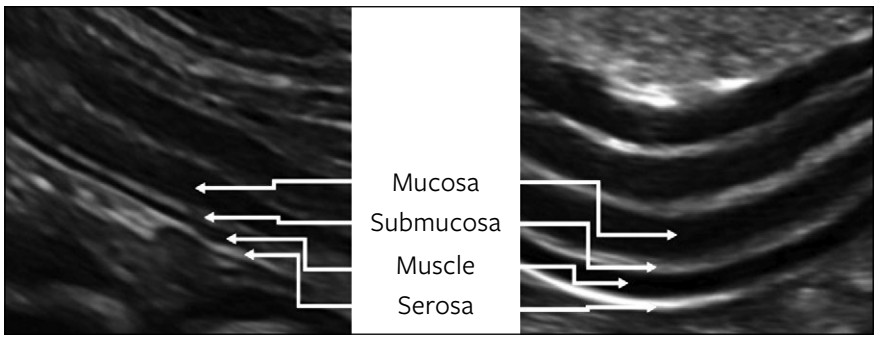



**Fig. 11-11** Small-cell intestinal lymphoma (SCL)

Sagittal ultrasound images of a cat with normal small intestine (**left**) and a cat with intestinal small cell lymphoma (**right**). The mucosal, submucosal, muscularis, and serosal layers are indicated with **arrows** in the far field. Compared with normal intestines, the muscularis propria is thickened in the cat affected with SCL.

(Courtesy of Drs. LaPorte, McLarty, and Wanamaker, UC Davis, School of Veterinary Medicine, USA.)

especially for the differentiation of inflammatory lesions from small-cell lymphoma. Ancillary tests include immunohistochemistry and PCR for antigen receptor rearrangement (PARR).[9,28,36,54,55] Immunohistochemistry is the first step for further differentiation between IBD and SCL in ambiguous cases. Specific immunohistochemical stains include CD3 for T-cells and CD20, CD79a, or PAX-5 for B-cells (and potentially other cells). Immunohistochemical staining helps determine whether all lymphocytes are of a single lineage or whether the infiltrate consists of a mixture of T-cells, B-cells, and plasma cells, the former supporting a diagnosis of lymphoma, the latter a diagnosis of inflammation, i.e., IBD (▶Fig. 11-12b). While immunohistochemistry can determine the cell lineage, it cannot determine whether these cells are polyclonal or (mono-)clonal. Clonality can be assessed in many ways, including flow cytometry, southern blot analysis, and PCR. PARR is the most commonly used method, as it can be performed on formalin-fixed, paraffin-embedded tissue samples.[36]

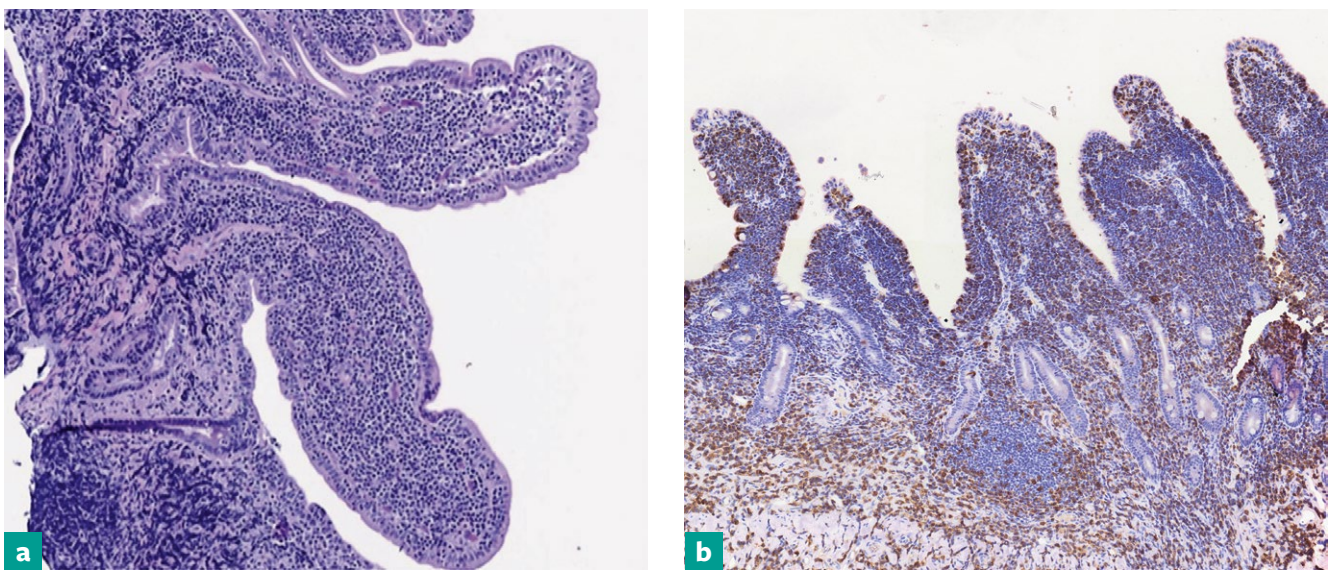



**Fig. 11-12** Low-grade T-cell lymphoma in a cat. Endoscopically-obtained small intestinal biopsy

**a** Hematoxylin and eosin stain shows dense infiltrates with a monomorphic population of small mature lymphocytes in the lamina propria and the epithelium.

**b** Immunohistochemistry using antibodies against the CD3 T-cell receptor confirms that most lymphocytes seen on H&E stain positive for CD3 (brown) and thus are of T-cell lineage.

Virtually any substance can be the target of a cellular immune response, and immune responses are mediated by the antigen receptor. Therefore, antigen receptors have an extremely high diversity.[56] Clonality assays permit visual assessment of the diversity of the antigen receptors. The presence of diverse receptors suggests the existence of inflammatory lesions (i.e., polyclonal), while uniform receptors indicate neoplastic lesions (i.e., clonal). The cell lineage cannot be determined by PARR, as in up to 10% of cases, T-cells can rearrange B-cell receptor genes and *vice versa* in a process of cross-lineage rearrangement.[57] Clonality does not always mean malignancy. Benign clonal expansions have been described in various diseases in humans[58,59] and dogs,[60] and it is even a well-documented phenomenon in elderly otherwise healthy people.[61] Similarly, recent studies evaluating clonality assays in humans and cats found specificities as low as 54.3% in humans[62] and 33.3% in cats.[63,64] Therefore, IHC and PARR should always be interpreted together and in the context of all available data, ideally by the same laboratory.

#### 11.3.2.5 Treatment and prognosis

As a general rule, small-cell lymphomas have a more favorable prognosis with higher response rates and longer median survival times than large-cell and LGL lymphomas. However, many studies on the treatment regimens and outcomes in cats with lymphoma either did not differentiate between grades and cell sizes or between anatomical locations (intestinal vs. extraintestinal lymphoma) and thus the published outcomes are somewhat confounded.

There are different protocols described for the treatment of small-cell lymphoma in cats with chlorambucil and prednisolone. However, in the author's and others' experience, many cats with small-cell lymphoma initially respond to treatment with steroids as well. Chlorambucil can be administered continuously at a dose of 2 mg PO q48–72h (usually at home) or as a pulse-dose protocol at 20 mg/m$^2$ PO every 2 weeks.[31,33–35] The pulse-dose regimen can be particularly helpful in fractious cats, as clients can bring the cat to the veterinary clinic to administer chlorambucil every 2–3 weeks, if necessary. Prednisolone is given initially at a dose of 1–2 mg/kg PO q24h and then gradually reduced to 0.5–1 mg/kg q24–48h.[31,33–35]

Treatment with chlorambucil and corticosteroids is mostly well-tolerated, and if they occur, adverse effects are generally mild. Myelosuppression and gastrointestinal toxicity are the most common side effects of chlorambucil. An uncommon but potentially more serious side effect of chlorambucil is hepatotoxicity, with about 10% of cases reported to experience a moderate to severe increase in serum liver enzyme activities.[35] A CBC and chemistry profile should be performed initially every 2–3 weeks, for alternate-day dosing, or before each chlorambucil administration, for the pulse-dose regimen. Once remission is achieved and no persistent myelosuppression has been observed over a few months, monitoring intervals can be extended to approximately every 6 weeks. If myelosuppression is documented, treatment should be delayed by 1–2 weeks. All alkylating drugs may cause irreversible bone marrow suppression; thus, downward trends of cell counts over time should be noted. Periodic drops of neutrophils or platelets that recover by treatment-delay require 25% dose reductions (for pulse-dosing) or increases of the dosing interval (e.g., from every 2- to 3-day dosing), but not necessarily permanent discontinuation of chlorambucil. However, non- or slowly recovering cytopenias require treatment discontinuation or protocol alterations. Some authors recommend discontinuation of treatment after 1 year if the cat is in remission at that time, while others continue treatment with chlorambucil and corticosteroids indefinitely. The median survival time of cats with SCL is reported to be between 1.5 and 3 years.[31,33–35]

Intermediate and large-cell lymphomas are commonly treated with multiagent cytotoxic chemotherapy protocols, such as L-CHOP (L-asparaginase, vincristine, cyclophosphamide, doxorubicin, and prednisolone), with or without resection of affected intestinal segments if lesions are discrete (▶ Tab. 11-6).[42,43,65] Alternatively, lomustine (CCNU) 40 mg/m$^2$ every 4–6 weeks with or without debulking surgery, concurrent steroid treatment, and/or initial treatment with L-asparaginase has been used for cats with intermediate to large-cell gastrointestinal lymphoma.[66] High-grade lymphomas treated with multiagent cytotoxic chemotherapy protocols have a response rate between 24% and 60% and median survival times between 1.5 and 3 months. However, in a subset of cases, long-term survival can be achieved by chemotherapy alone or combined with enterectomy in cases with discrete lesions. Response to therapy and achieving remission are the most consistent positive prognostic indicators while immunophenotype does not appear to be associated with the outcome in feline intestinal high-grade, large-cell lymphoma.[43]

Large granular lymphocyte (LGL) lymphomas are generally highly aggressive tumors with a guarded to grave prognosis.[29,30] Few studies assessed treatment protocols and survival times for cats with LGL lymphomas, including enterectomy, CHOP-based chemotherapy, lomustine, corticosteroids, and a combination of treatments. The median survival times ranged between 3 weeks and 3 months.[29,30] Generally, LGL lymphoma appears to be uniformly fatal, with very few cats reported to survive for more than 6 months. The presence of clinical signs and circulating neoplastic cells are considered negative prognostic indicators for LGL lymphomas.[28–30]

**Tab. 11-6** Comparison of response and outcome data in cats with high-grade, large cell, or large granular lymphocyte lymphoma

| Authors | Cohort | n | n (GI)[a] | Treatment | CR % | PR % | PFI (days; range) | MST (days; range) | MST CR (days) | MST PR (days) | Negative prognostic factors |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Limmer et al. 2016[65] | Intermediate to high-grade lymphoma | 26 | 10 | CHOP (12w) (+ rescue) | 46 | 27 | – | 78 (9–2230) | 454 | 82 | |
| Collette et al. 2016[43] | Intermediate to high-grade lymphoma | 119 | 75 | CHOP (25w) (+ rescue) | 38 | 24 | 56 (2–2019) | 97 (2–2019) | 318 | 85 | Cats with alimentary lymphoma were less likely to show CR |
| Gouldin et al. 2017[42] | Discrete intermediate to high-grade GI lymphoma | 20 | 20 | Surgical resection and adjuvant CHOP | – | – | 357[d] (0–1585) | 417 (12–2962) | – | – | Clinical stage |
| Rau et al. 2017[66] | Intermediate to high-grade GI lymphoma | 32 | 32 | Lomustine | 22 | 28 | 132 (31–1450) | 108 (4–1488) | 330 (84–1488)[e] | | Hyporexia, anemia, lomustine dose <40 mg/m$^2$ |
| Finotello et al. 2018[30] | Large granular lymphocyte lymphoma | 109 | 100 | mixed, see below | 0 | – | 5[f] | 21 | – | – | Substage b, circulating neoplastic cells, lack of chemotherapy administration, lack of treatment response |
| | | 11 | – | Enterectomy[g] | – | – | – | 42 | – | – | |
| | | 20 | – | CHOP | – | – | – | 60 | – | – | |
| | | 5 | – | Lomustine | – | – | – | 90 | – | – | |
| | | 42 | – | Steroids | – | – | – | 15 | – | – | |
| | | 30 | – | no treatment | – | – | – | 5 | – | – | |
| Elliot et al. 2018[78] | Relapsed high-grade lymphoma | 19 | 10 | DMAC | 0 | 26 | 14 (4–39) | 17 (4–67) | – | – | |

**CR** = complete remission; **MST** = median survival time; **PFI** = median progression free interval; **PR** = partial remission; **n** = number; **a** = number of cats with gastrointestinal and/or abdominal lymphoma; **12w** = 12-week maintenance free protocol; **25w** = modified 25-week University of Wisconsin-Madison (UW-25) chemotherapy protocol; **b** = cell lineage was determined in 44 out of 119 cats; **c** = PFI; **d** = disease free interval; **e** = median survival time for CR and PR; **f** = time to progression; **g** = some cats received adjuvant chemotherapy; **CHOP** = vincristine, cyclophosphamide, doxorubicin, and prednisolone; **DMAC** = dexamethasone, melphalan, actinomycin D, cytosine arabinoside

### 11.3.3 Canine gastrointestinal lymphoma

Gastrointestinal lymphoma in dogs can occur as part of multicentric lymphoma[67] or occur primarily in the gastrointestinal tract.[68] While, primary intestinal lymphoma accounts for approximately 5–20% of all canine lymphomas there are few systematic studies on this most common extranodal form of canine lymphoma. Primary gastrointestinal lymphoma in dogs is most commonly of T-cell origin and generally has a poor outcome.[67,69–71] Due to the lack of scientific data, not much is known about the epidemiology of primary gastrointestinal lymphoma in dogs.

#### 11.3.3.1 Classification

Similar to feline gastrointestinal lymphoma, alimentary lymphoma in dogs can be classified into small-cell, low-grade and intermediate- to large-cell, high-grade lymphoma, with the

latter being the most common form. While large-cell lymphomas can occur as localized intestinal masses, diffuse lesions affecting the small intestine, stomach, and large intestine (in decreasing order of frequency) are more common.[68,72] In contrast to cats, large-cell intestinal lymphomas in dogs are mostly of T-cell origin.[67–69,73] All documented small-cell lymphomas in dogs are of T-cell origin and mostly affect the small intestine.[74] Interestingly, rectal lymphomas in dogs appear to be mostly of B-cell origin and are associated with a significantly better prognosis.[75]

#### 11.3.3.2 Clinical presentation

The median age reported for dogs diagnosed with intestinal lymphoma was between 7 and 10 years (range 1.5–15 years)[67–69,73] with no reported sex or breed predilection. Clinical signs are usually non-specific and include vomiting, hyporexia, weight loss, diarrhea, or lethargy. Physical examination may reveal abdominal pain and/or mass(es), hepatomegaly, splenomegaly, a poor body condition, pale mucous membranes and/or icterus, or peripheral lymphadenopathy. Some dogs present with pyrexia or other signs of bacterial translocation and sepsis. Laboratory abnormalities are non-specific, and the most common findings are hypoalbuminemia, hypoproteinemia, or hypocalcemia (due to hypoalbuminemia).[68] Hypofolatemia and hypocobalaminemia have been described in dogs with intestinal lymphoma.[74] Diagnostic imaging studies will show changes to the gastrointestinal tract and/or the mesenteric lymph nodes in most cases. These include pleural and peritoneal effusion, lymphadenomegaly, diffuse intestinal thickening with or without a loss of wall layering, intestinal masses, and hepato- or splenomegaly.[68] However, the absence of ultrasonographic abnormalities does not rule out lymphoma, and a significant subset of dogs with gastrointestinal lymphoma have no documented imagining abnormalities.[68,74]

#### 11.3.3.3 Diagnosis

In dogs with localized lesions, abdominal and/or peripheral lymphadenopathy or organomegaly, a diagnosis of large-cell lymphoma can often readily be made by cytological examination of fine-needle aspirates. In addition to sampling abdominal lesions, fine-needle aspirates of the liver and spleen can be a minimally-invasive way of confirming large-cell lymphoma even if these organs appear normal on ultrasound (▶Fig. 11-13). In cases with diffuse disease, lesions not accessible by fine-needle aspiration, or non-diagnostic cytological samples, a diagnosis can be reached by histopathologic examination of biopsy specimens collected via endoscopy (in diffuse lesions) or laparotomy/laparoscopy. Similar to cats, diagnosing small-cell intestinal lymphoma in dogs poses the same diagnostic challenges and the collection of biopsy specimens should be pursued. Immunohistochemistry and clonality testing may aid in the differentiation of severe inflammation from lymphoma.[74,76] A recent study investigated the use of a novel PARR (ePARR) analysis as a molecular diagnostic tool for the discrimination of lymphoid malignancies in dogs from benign processes.[76] The technology can be applied to formalin-fixed paraffin-embedded samples, flow cytometry pellets, or fine needle aspirates and has shown a ≥92% sensitivity and specificity. However, the study did not discriminate between large- and small-cell lymphomas. As mentioned, large-cell lymphomas usually do not present a particular diagnostic challenge, and thus, it remains to be determined whether ePARR might be helpful in differentiating small-cell lymphoma from inflammatory lesions in dogs.

#### 11.3.3.4 Treatment and prognosis

The prognosis for GI large-cell lymphoma in dogs is generally guarded to poor with a median reported survival times between 13 and 77 days (95% CI: 34–120 days).[68,69,77] Multiagent chemotherapy protocols, including CHOP (cyclophosphamide, doxorubicin [hydroxydaunorubicin]), vincristine sulfate (Oncovin), and prednisone, COP (cyclophosphamide, vincristine, prednisone), and lomustine (as a single agent or as part of a multiagent regiment) have been used with or without mass resection.[68,69,77] The presence of anorexia, diarrhea, septic peritonitis, and involvement of extraintestinal sides, including abdominal lymph nodes, have been shown to be negative prognostic indicators.[68,69,77]

Exceptions to this are canine intestinal small-cell lymphomas and rectal lymphomas. A study in dogs with intestinal small-cell lymphoma found a median survival time of 628 days (range 12–1079 days) in dogs treated with corticosteroids, alkylating agents (chlorambucil, cyclophosphamide, lomustine), or a combination thereof.[74] The presence of weight loss or anemia was associated with a poorer outcome. Rectal lymphoma in dogs appears to be associated with a remarkably good outcome. One study reported a mean survival time of 1,697 days (95% CI: 935–2,460 days) in dogs treated with surgical resection, chemotherapy (CHOP or COP-based protocols), or a combination thereof.[75] The median survival time was not reached due to a prolonged survival of the dogs enrolled in the study.

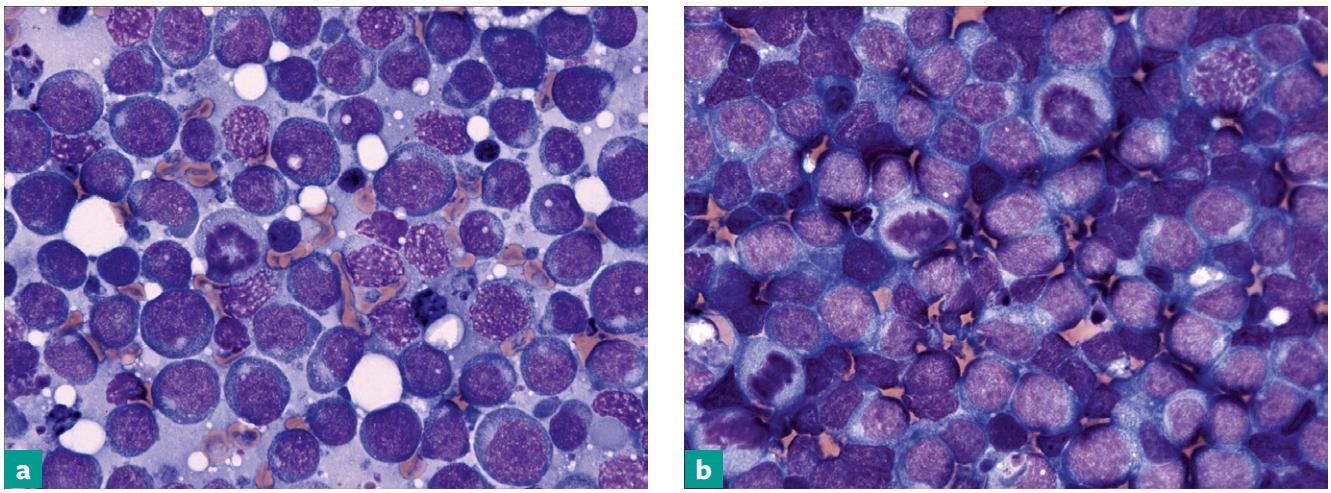



**Fig. 11-13** High-grade large-cell lymphoma in a dog

**a** Cytological examination (60x) of a fine-needle aspirate collected from a jejunal mass. The direct smears are highly cellular and contain a large homogeneous population of large atypical lymphocytes. Cells have a moderate amount of medium to deep blue cytoplasm with a round to ovoid-shaped nucleus with a finely stippled and open chromatin pattern. Multiple variably sized prominent nucleoli and a mitotic figure (center) are seen.

**b** Same as **a**, but this image shows five mitotic figures in one visual field.

(Courtesy of Dr. William Vernau, UC Davis, School of Veterinary Medicine, USA.)

**KEY FACTS**

- While gastrointestinal lymphomas in cats are mostly small-cell, low-grade lymphomas, these are usually large-cell, high-grade in dogs.
- The differentiation between small- and large-cell lymphoma should be a high priority as treatment and prognosis differ significantly.
- In both species, gastrointestinal small-cell lymphomas carry a significantly better prognosis than large-cell lymphomas.
- Most cats with intestinal lymphoma are FeLV-negative.
- Canine rectal lymphoma carries an excellent long-term prognosis.

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
svg.to/9842-11-03

## 11.4 Neuroendocrine tumors of the gastrointestinal tract

Jörg M. Steiner, Cynthia Ward

### 11.4.1 Introduction

The gastrointestinal (GI) tract is the largest endocrine organ of the body, both in terms of the number of neuroendocrine cells, as well as the number of different neuroendocrine substances that are produced. However, relatively little is known about it and only recently has there been renewed interest in the clinical importance of the gut neuroendocrine system as new neuroendocrine substances that regulate metabolism, growth, and even behavior have been discovered.[1] Almost all regulatory substances synthesized in the GI tract are peptides, but several function as endocrine, neurocrine, paracrine, or even autocrine peptides.

In 1902, secretin was discovered as the first GI hormone and, in fact, the first hormone of any kind to be discovered.[1] Since then, more than 100 different regulatory peptides that are released from the gastrointestinal tract have been described.[2] The main functions of the more important regulatory peptides are listed in ▶Tab. 11-7.[3,4]

**Tab. 11-7** Main functions of important gastrointestinal regulatory peptides

This table shows an alphabetical listing of the most important regulatory peptides of the gastrointestinal tract, their location and cell type of secretion, their most important functions, and the stimulatory and inhibitory factors for their secretion.[3,4]

| Regulatory peptide | Location of secretion | Cell type | Most important functions | Stimulatory factors | Inhibitory factors |
|---|---|---|---|---|---|
| Cholecystokinin | Duodenum, jejunum | I | • Stimulation of pancreatic enzyme secretion<br>• Gallbladder contraction<br>• Regulation of pancreatic growth | • Fat, fatty acids, proteins, amino acids, $H^+$ in the intestinal lumen<br>• Bombesin, GRP | • Somatostatin |
| Gastric inhibitory polypeptide (GIP) | Duodenum, jejunum | GIP | • Inhibition of gastric acid secretion<br>• Stimulation of intestinal fluid secretion<br>• Stimulation of insulin release | • All major classes of nutrients in the gut<br>• Bombesin | – |
| Gastrin | Stomach, duodenum, pancreas (during development only) | G | • Stimulation of gastric acid secretion<br>• Trophic effect on acid-secreting gastric mucosa<br>• Stimulation of pepsinogen secretion | • Vagal stimulation and gastrin-releasing peptide in response to digested proteins and amino acids<br>• Gastric distention<br>• Increased intraluminal pH | • Luminal acidification<br>• Somatostatin |
| Ghrelin | Stomach; pancreas | P, D1; E | • Stimulation of appetite<br>• Promotion of fat storage<br>• Stimulation of growth hormone release | • Lack of food intake | • Food intake<br>• Somatostatin |
| Glucagon | Pancreas | A | • Stimulation of glycogenolysis<br>• Stimulation of gluconeogenesis from lactate, amino acids, and glycerol | • Hypoglycemia<br>• High concentration of amino acids or low concentration of free fatty acids in plasma<br>• Ghrelin | • Hyperglycemia<br>• Insulin, somatostatin, GLP-1 |
| Glucagon-like peptide 1 (GLP-1; responsible for the incretin effect) | Small intestine, pancreas | L | • Secretion of insulin<br>• Inhibition of glucagon release | • Food intake | • Somatostatin |
| Insulin | Pancreas | B | • Stimulation of peripheral glucose uptake<br>• Stimulation of glycogen synthesis<br>• Stimulation of lipogenesis<br>• Stimulation of DNA, RNA, and protein synthesis | • Hyperglycemia<br>• Glucagon | • Hypoglycemia |
| Motilin | Duodenum, jejunum | M | • Initiates phase III of the migratory motor complex | • Cyclic release during the fasting state<br>• Intraluminal lipids | - |

**Tab. 11-7** Main functions of important gastrointestinal regulatory peptides (Continuation)

This table shows an alphabetical listing of the most important regulatory peptides of the gastrointestinal tract, their location and cell type of secretion, their most important functions, and the stimulatory and inhibitory factors for their secretion.[3,4]

| Regulatory peptide | Location of secretion | Cell type | Most important functions | Stimulatory factors | Inhibitory factors |
|---|---|---|---|---|---|
| Neurotensin | Ileum, colon | N | • Inhibition of gastric acid secretion | • Intraluminal lipids<br>• Bombesin | – |
| Opioids | Entire GI tract | - | • Inhibition of intestinal water and electrolyte secretion<br>• Modulation of GI motility | • Unknown | – |
| Oxyntomodulin | Ileum, colon | L | • Inhibition of gastric acid secretion<br>• Stimulation of intestinal mucosal growth | • Intraluminal glucose and lipids | – |
| Pancreatic polypeptide (PP) | Pancreas | F | • Inhibition of pancreatic enzyme and fluid secretion | • Intraluminal proteins<br>• Vagal stimulation | – |
| Peptide YY | Ileum, colon | L | • Inhibition of pancreatic secretion<br>• Inhibition of gastric acid secretion<br>• Inhibition of gastric emptying | • Intraluminal lipids<br>• Bombesin | – |
| Secretin | Duodenum, jejunum | S | • Stimulation of pancreatic bicarbonate secretion | • Duodenal acidification | – |
| Somatostatin | Entire GI tract | D | • Inhibition of gastric and pancreatic secretions<br>• Inhibition of intestinal amino acid and glucose absorption<br>• Inhibition of intestinal motility | • Intraluminal lipid, protein, and bile | – |
| Tachykinins | Entire GI tract | – | • Regulation of GI motility<br>• Transmission of pain impulses | • Luminal distension | – |
| Vasoactive intestinal polypeptide (VIP) | Entire GI tract | – | • Relaxation of smooth muscle<br>• Vasodilation<br>• Stimulation of pancreatic and intestinal secretion | • Vagal stimulation | – |

**GRP** = gastrin-related peptide; **GIP** = gastric inhibitory polypeptide; **GLP-1** = glucagon-like peptide 1; **DNA** = desoxyribonucleic acid; **RNA** = ribonucleic acid; **GI** = gastrointestinal; **PP** = pancreatic polypeptide; **VIP** = vasoactive intestinal polypeptide

In general, endocrine disorders are due to a lack (e.g., hypoadrenocorticism) or overabundance (e.g., hyperadrenocorticism) of a hormone. To date, the only syndrome known to be due to the lack of a GI hormone is diabetes mellitus, which is due to an absolute or relative insulin deficiency. Surprisingly, a lack of other GI regulatory peptides has not been identified to cause specific syndromes in any species. However, there is no reason to believe that a lack of GI regulatory peptides would not lead to clinical disease. Furthermore, many chronic GI diseases are considered idiopathic, and it is possible that some of these conditions are actually caused by GI regulatory peptide deficiency.

Disorders related to an overabundance of GI regulatory peptides are well recognized and are caused by neuroendocrine tumors (NET). Gastrointestinal NETs ultimately arise from multipotent stem cells in the pancreatic ductal epithelium, which explains why a NET may be found in a location other than where the neuroendocrine cell is normally located. Overall, gastrointestinal NETs are considered to be rare in humans, with an estimated prevalence of 3–4 cases per million population; however, a much higher prevalence has been reported in autopsy studies.[5] NETs of the GI tract can be divided based on the location of the primary tumor or based on the primary neuroendocrine substance leading to the clinical signs observed. A German NET registry reported 2,009 patients with a NET over a 12-year period (1999–2010).[6] In these patients, 34.6% had a primary tumor localization in the pancreas, 31.0% in the small intestine, 7.0% in the colon, 6.5% in the stomach, 3.8% in the cecum, 3.5% in the lung, 0.7% in the esophagus, and in 12.8% the primary tumor site could not be identified.[6] In the same study, 46.7% of patients were considered to have a functional tumor, 40.8% of which were diagnosed with carcinoid syndrome, 37.8% with an insulinoma, 15.2% with a gastrinoma, 3.7% with a glucagonoma, 2.0% with a VIPoma, and 0.5% with a somatostatinoma.[6] Similar epidemiological data are not available for dogs and cats, and several types of GI NETs (e.g., VIPoma) have not yet been described in veterinary patients. To date, GI NETs described in dogs and cats are limited to insulinomas, gastrinomas, glucagonomas, carcinoids, a single case of a somatostatinoma, and also a single, questionable case of a pancreatic polypeptidoma.

## 11.4.2 Insulinoma

### 11.4.2.1 Introduction

An insulinoma is a pancreatic neuroendocrine tumor causing hyperinsulinism. Insulinomas occur infrequently in dogs and are rare in cats.[7–10] However, as in people, insulinomas are the most common gastrointestinal neuroendocrine tumors in dogs and cats. Insulinoma cells produce a wide variety of regulatory polypeptides, such as insulin, pancreatic polypeptide, somatostatin, glucagon, serotonin, gastrin, and adrenotropic hormone (ACTH).[11] Despite the variety of polypeptides produced by insulinoma cells, almost all patients diagnosed with insulinoma show only clinical signs of hyperinsulinism.[7,9] Insulinomas in humans are sometimes seen in concert with other endocrine neoplastic lesions, a condition known as multiple endocrine neoplasia (MEN). To date, only a few dogs and cats with MEN have been described.[8,12] In dogs, tumors of the adrenal glands and pituitary were the most common, while in cats, the thyroid gland was most commonly affected.[12]

**CLINICAL PEARLS**

None of the combinations of tumors reported in either dogs or cats in one case series resembled MEN syndromes commonly reported in humans.[12] However, a cat described in a single case report was diagnosed with a parathyroid gland adenoma, an adrenal gland cortical adenoma, and an insulinoma.[8]

### 11.4.2.2 Pathogenesis

The etiology of insulinomas remains unknown, and risk factors for insulinomas have not been identified. Beta cells take up glucose through an insulin-independent process, and the intracellular glucose concentration of the islet cells thus mirrors serum glucose concentration. In normal subjects, insulin secretion from beta cells is suppressed when the blood glucose concentration falls below approximately 60 mg/dL. At the same time, secretion of the counterregulatory hormones (immediate response: catecholamines and glucagon; delayed response: cortisol and growth hormone) increases. Insulinomas do not respond appropriately to a falling blood glucose concentration. This results in hypoglycemia, which in turn, can result in central nervous system (CNS) abnormalities. Glucose uptake into the CNS is by facilitated diffusion and is also non-insulin-dependent, so glucose uptake is low at times of hypoglycemia. In addition, the CNS utilizes glucose as its primary energy source, and cannot utilize fatty acids or ketone bodies as can other tissues, including the peripheral nervous system. In addition to CNS disturbances, clinical signs of hyperinsulinism also include signs induced by an increased discharge of the sympathetic nervous system, which is part of its counterregulatory response.

**NOTE**

Insulinoma patients adjust to repeated or chronic states of hypoglycemia and can tolerate extremely low blood glucose concentrations without showing any clinical signs.

In addition to the degree of hypoglycemia, the rate of decrease in blood glucose concentration and the duration of hypoglycemia all determine the extent of the clinical signs.

#### 11.4.2.3 Pathology and natural behavior

Insulinomas most commonly appear as tan nodules in the pancreas (▶Fig. 11-14). They are generally small (i.e., 1 cm in diameter or less). Most often, they appear to be singular, but in a series of 129 dogs, 14% had multiple masses.[7] On histopathology, the tumor cells appear as normal islet cells, forming irregular nests and cords with a variable pattern of dense stromal proliferation.

Malignant tumors are defined as tumors that are locally invasive and/or form distant metastasis. In many neoplastic diseases, the malignant potential of a tumor can be successfully predicted by histopathological evaluation. However, this is not the case for insulinomas and other endocrine neoplasia, as these neoplasms often lack many of the typical features of malignancy. Thus, an estimation of the malignant potential of insulinomas based on histopathological findings can be misleading. It is important to note that most insulinomas in dogs are considered malignant, as many have already metastasized at the time of diagnosis.[7] This is in contrast to human insulinoma patients, where 87% have been reported to have a benign insulinoma, which is associated with a 100% survival rate after successful removal.[13]




**Fig. 11-14** Insulinoma

This figure shows an insulinoma in a dog. Note the small size of the tumor. (Courtesy of Dr. Thomas J. Van Winkle, University of Pennsylvania, Philadelphia, PA.)

#### 11.4.2.4 Signalment

Insulinomas mainly occur in older dogs and cats. The mean age of 233 dogs reported in the literature was 8.9 years, with a range of 3.5–14 years in 128 dogs.[7] The sex distribution of 133 dogs with an insulinoma showed 45% males and 55% females.[7] ▶Tab. 11-8 shows the breed distribution of a compilation of 310 dogs with an insulinoma.[7,9,14]

#### 11.4.2.5 Clinical presentation

Dogs presenting with insulinomas generally present with two types of clinical signs: neuroglycopenic signs, such as weakness, ataxia, depression, or seizures or signs related to an increased discharge of the sympathetic nervous system, such as behavioral changes, shaking, trembling, and muscle fasciculations.[7] The incidence of clinical signs reported in 113 dogs with insulinoma is shown in ▶Tab. 11-9.[7] Most patients with insulinoma show only intermittent clinical signs and will have a rather unremarkable physical examination. A few patients will present with status epilepticus or even comatose. Due to the age of the affected population, a number of geriatric comorbidities may be evident that are unrelated to the presence of an insulinoma.

#### 11.4.2.6 Diagnosis

A fasting blood glucose concentration should be part of the workup of a patient with clinical signs suggestive of hypoglycemia, preferably during times when the patient is symptomatic. Most dogs diagnosed with an insulinoma will present with a low blood glucose concentration, even in the absence of clinical signs. If hypoglycemia is confirmed, the causative relationship between the observed clinical signs and the hypoglycemia needs to be established. This is best accomplished by demonstrating Whipple's triad, which consists of:

1. A subnormal blood glucose concentration
2. Presence of clinical signs of hypoglycemia
3. Cessation of clinical signs with a resolution of hypoglycemia

After Whipple's triad has been established, the cause of hypoglycemia must be identified. A basic workup should include a complete blood count, a chemistry profile, and a urinalysis. In insulinoma patients, these basic parameters will usually be within normal limits. Infrequently reported

**Tab. 11-8** Breed distribution of dogs with insulinoma

This table shows the breed distribution of 310 canine patients with insulinoma and the breed distribution of the canine population reported to the Veterinary Medical Database (VMDB) from 1994–2004.[7,9,14]

| Breed | Number of dogs | % of all cases of insulinoma | % VMDB population |
|---|---|---|---|
| Mixed breed | 78 | 25.2 | (20.8) |
| Boxer | 32 | 10.3 | (1.6) |
| German shepherd dog | 22 | 7.1 | (4.1) |
| Irish setter | 19 | 6.1 | (0.3) |
| West Highland white terrier | 17 | 5.5 | (0.7) |
| Collie | 16 | 5.2 | (0.9) |
| Labrador retriever | 13 | 4.2 | (5.9) |
| German shorthair pointer | 13 | 4.2 | (0.6) |
| Golden retriever | 11 | 3.5 | (5.9) |
| Miniature poodle | 9 | 2.9 | (1.3) |
| Standard poodle | 6 | 2.8 | (0.8) |
| Weimaraner | 6 | 2.8 | (0.5) |
| Basset | 5 | 1.6 | (0.9) |
| Other breeds | 63 | 20.3 | (79.7) |

Irish setters, West Highland white terriers, German shorthair pointers, boxers, and collies appear to be predisposed with at least a higher than 5-fold rate of insulinoma cases than of overall cases reported to the VMDB. The 310 cases compiled were seen at many veterinary clinics both in the USA and in Europe. Thus, the VMDB population is not a statistically valid reference population, and the percentages are shown in parentheses.

**Tab. 11-9** Incidence of clinical signs reported in 113 canine insulinoma patients[7]

| Clinical sign | Number of patients | % of patients |
|---|---|---|
| Seizures | 77 | 68 |
| Collapse | 38 | 34 |
| Generalized weakness | 37 | 33 |
| Posterior weakness | 37 | 33 |
| Depression/lethargy | 21 | 19 |
| Ataxia | 21 | 19 |
| Muscle fasciculation | 20 | 18 |
| Abnormal behavior | 17 | 15 |
| Polyphagia | 12 | 11 |
| Exercise intolerance | 11 | 10 |
| Shaking/trembling | 11 | 10 |
| Polyuria/polydipsia | 8 | 7 |
| Weight gain | 7 | 6 |
| All other clinical signs were reported with a frequency of less than 5% | | |

Table reprinted with permission from: Steiner JM et al., 1996.[80]

abnormalities include mild elevations of liver enzyme activities (▶Chap. 1.3.3). Radiographs of the thorax and abdomen are usually within normal limits but may help exclude other causes of hypoglycemia. Abdominal ultrasound is a valuable tool in patients with suspected insulinoma. With the advancement of abdominal ultrasound resolution, the diagnostic sensitivity of this modality has improved, but in one study, only 1/3 of canine insulinomas were identified by ultrasound.[15] In contrast, an insulinoma was identified by ultrasound in three of the four most recently diagnosed cats with an insulinoma.[10,16–18] Even if an insulinoma cannot be visualized by abdominal ultrasonography, this modality is very helpful for assessing the patient for the presence of organ metastasis or mesenteric lymphadenopathy. Contrast-enhanced ultrasonography (CT) may improve the diagnostic accuracy further.[10] As in people with insulinoma, abdominal computed tomography is the imaging modality of choice for the identification of an insulinoma, with a reported sensitivity of 96.3% in one study.[19] However, enhancement patterns can vary, and localization is not always accurate with abdominal CT. [19,20]

The single most reliable diagnostic test for an insulinoma is the demonstration of an inappropriately high serum insulin concentration in the face of hypoglycemia, also referred to as insulin-glucose pair. Serum for the determination of insulin concentration needs to be collected at the time of hypoglycemia. This is accomplished by serial blood glucose measurements, while food is withheld from the animal. It is best to start early in the morning with the patient being closely monitored throughout the day.

**CLINICAL PEARLS**

Blood glucose concentration is measured every 30–60 minutes. When the blood glucose falls below 60 mg/dL, a sample for the measurement of serum insulin concentration is drawn, and the animal is fed. It is important to verify blood glucose concentrations measured by a glucometer through the use of a chemistry analyzer.

Interpretation of the insulin-glucose pair is straightforward if the insulin concentration exceeds the reference interval (the reference interval is dependent on the laboratory used) in the face of hypoglycemia. However, the serum insulin concentration may be within the reference interval and still be inappropriately high with respect to the blood glucose concentration. Several ratios have been evaluated in humans to help document inappropriate insulin secretion: glucose-insulin ratio, insulin-glucose ratio, and the amended insulin-glucose ratio, but none of these ratios improve the diagnostic accuracy. Also, a variety of provocative tests have been suggested to aid in the diagnosis of an insulinoma in people, but none of these have been well-studied in dogs or cats.

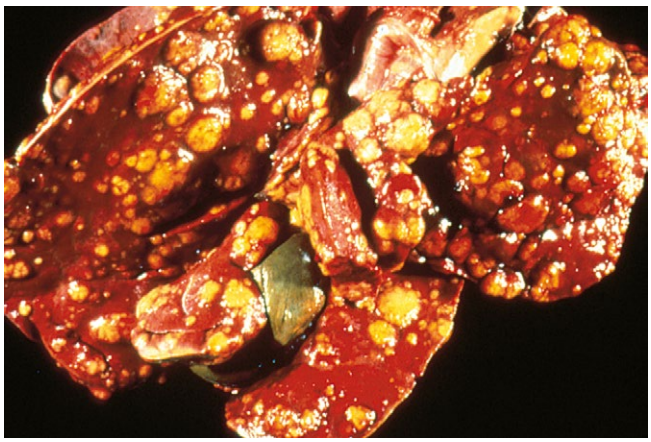


**Fig. 11-15** Insulinoma metastases in the liver

This figure shows a liver with diffuse dissemination of metastatic lesions of an insulinoma in a dog. (Courtesy of Dr. Thomas J. Van Winkle, University of Pennsylvania, Philadelphia, PA.)

### 11.4.2.7 Staging

As with any other neoplastic disease, patients with an insulinoma should be staged. Unfortunately, the available modalities to stage canine and feline insulinoma patients are limited. Abdominal ultrasound can be helpful in demonstrating evidence of local extension and distant metastasis of the disease. Also, abdominal CT can be employed to demonstrate metastatic disease. However, both modalities have been shown to miss most metastatic lesions in either lymph nodes or the liver.[9,15] Thus, the most reliable staging tool for veterinary patients remains abdominal exploration.

In a compilation of 129 abdominal exploratories of canine insulinoma patients, 66 (51%) of the dogs had metastatic disease detected during the exploratory laparotomy.[7] Of those, 29 (22%) had metastatic lesions in the liver (▶Fig. 11-15), 19 (15%) had metastases to regional lymph nodes, 7 (5%) had metastatic lesions in both liver and lymph nodes, and 11 (8%) had metastatic lesions in other locations.[7]

### 11.4.2.8 Treatment

#### 11.4.2.8.1 Emergency treatment

Patients presenting with clinical signs of hypoglycemia need to be treated as quickly as possible. If the animal is able to eat, a well-balanced food should be offered, and this will often correct the clinical signs. If hypoglycemia persists, a dextrose bolus (0.5 g/kg as a 25% solution IV over approximately one minute) should be administered, and a dextrose constant rate infusion should be initiated. Suitable infusion solutions are 5% dextrose or balanced electrolyte solutions with added dextrose. Dextrose infusions should be used with care as insulinoma cells retain sensitivity to glucose and may respond with further insulin secretion. Refractory hypoglycemia in dogs may be treated with glucagon as a 50 ng/kg IV bolus and/or a constant rate infusion of 15 ng/kg/min.

**CLINICAL PEARLS**

It is important to note that the goal of emergency therapy is to eliminate the clinical signs of hypoglycemia rather than to restore euglycemia.

If neuroglycopenic signs persist, cerebral edema should be suspected, and treatment using mannitol and/or corticosteroids should be considered. If seizures still persist, diazepam or other anticonvulsant drugs may be indicated.

#### 11.4.2.8.2 Pancreatic surgery

Surgical exploration with excision or debulking of the tumor and metastases is the treatment of choice for the management of canine and feline patients with insulinoma. It is crucial to stabilize the blood glucose concentration of the patient prior to surgery. Also, the surgeon should be aware that handling of the tumor can lead to increased insulin release. In contrast, removal of the tumor may suddenly lower plasma insulin concentrations, leading to hyperglycemia. Therefore, blood glucose must be monitored closely throughout the procedure.

In order to stage the disease, a careful abdominal exploratory should be performed, and biopsies of suspicious lymph nodes or areas within the liver should be obtained.

Identification of insulinoma can be difficult. In a compilation of 129 abdominal exploratories of canine patients with a suspected insulinoma, a pancreatic nodule could not be identified in 26 patients (20%).[7] Even though some of these cases might have had a rarely described diffuse infiltration of the pancreas, further evaluation of localization techniques seems warranted in canine insulinoma patients. In human medicine, a variety of localization techniques have been described and compared, including endoscopic ultrasonography, glucagon-like peptide-1 receptor single photon emission computed tomography or positron emission tomography (exendin-4 SPECT or PET), somatostatin receptor scintigraphy (SRS), intraoperative ultrasonography, CT, MRI, selective arteriography, intraoperative quick frozen sections, and transhepatic venous sampling.[21,22] Endoscopic ultrasonography and exendin-4 SPECT and PET hold the most promise, but neither have been studied in veterinary patients.[21,22] Thus, intraoperative inspection and palpation remain the primary mode of localization of an insulinoma in veterinary patients. The use of CT has been evaluated for the localization of insulinomas in dogs and allowed visualization of the primary tumor in 26/27 (96.3%) patients.[19] However, the correct location was only identified in 14 of 27 dogs (51.9%).

Somatostatin receptor scintigraphy, that is, the intravenous administration of $^{111}$In-DTPA-D-Phe$^{1}$-octreotide (OctreoScan™, Mallinckrodt Medical) followed by planar scintigraphy or single-photon emission CT, has also been evaluated in canine insulinoma patients.[15,23] In one study, the primary lesion was identified in all five dogs evaluated.[23] However, in the second study, insulinoma was only identified in 6/14 (43%) dogs.[15] This discrepancy can be explained by the fact that the tumor was positive for somatostatin receptor subtype 2 (SSR2), one of the somatostatin receptor subtypes to which octreotide preferentially binds to, in all five dogs in the first study, but only in 43% of the dogs in the other study.[15,23] Thus, while SRS may be useful in identifying and/or localizing an insulinoma, in some cases, if the tumor does not express SSR2, the tumor may not be able to be visualized with this modality.

Extreme care should be exercised when handling the pancreas. After localization of the insulinoma, it can be removed by enucleation, partial pancreatectomy, or total pancreatectomy ± duodenectomy. While the surgical technique for total pancreatectomy has been described for the dog, this procedure is associated with high postsurgical morbidity and mortality and should thus be avoided. Local enucleation has been shown to result in shorter survival times than partial pancreatectomy and should, therefore, only be considered if the tumor is located in the body of the pancreas or very proximally in the right lobe.[24] Use of a bipolar vessel-sealing device has been described and is associated with a significantly decreased surgical time, but the mean disease-free interval was much longer (485 days) for 8 dogs that underwent par-

tial pancreatectomy by the more traditional suture-fracture technique than those with the new technique (138 days).[25] Thus, the surgical procedure of choice is partial pancreatectomy (▶ Fig. 11-16). If the tumor cannot be localized on abdominal exploratory, a small pancreatic biopsy should be taken to evaluate the pancreas for diffuse infiltration histopathologically. Since the right and left lobes are involved with equal frequencies and occult insulinomas are probably the most common in the pancreatic body, random removal of pancreatic tissue should not be performed.

One of the most common postoperative complications of pancreatic surgery is acute pancreatitis (▶ Chap. 10.3.1). However, the risk of postoperative pancreatitis can be minimized by aggressive fluid therapy during anesthesia and gentle handling of the pancreas during surgery. In one study that involved three veterinary centers, the rate of postoperative pancreatitis was 20% of 25 dogs at one center and 0% of 23 dogs at the other two centers, suggesting that either postoperative pancreatitis was underdiagnosed at two of the centers or surgical technique was more aggressive at the other center. Thus, patients should be closely monitored for any sign of pancreatitis postoperatively.[9] Other common postoperative complications are hypoglycemia and hyperglycemia.[9] Persistent hypoglycemia indicates that the insulinoma has not been completely removed and is a poor prognostic indicator.[9] The patient either has to be re-explored, or medical therapy has to be instituted. Hyperglycemia, if present, is most often transient, but some patients may require insulin therapy to control the hyperglycemia.

#### 11.4.2.8.3 Chemotherapy

If surgical exploration is not an option or if it does not lead to the removal of the entire insulinoma, chemotherapy can be considered. Streptozotocin and alloxan have been used in some dogs with insulinoma, but they are highly nephrotoxic and, consequently, are rarely used.[26,27] The use of toceranib phosphate has been reported in a case report, and more recently, in a retrospective multicenter study involving 30 dogs.[28] Most dogs benefited from the use of toceranib at various doses and showed a complete response, a partial response, or stable disease.[28]

#### 11.4.2.8.4 Radiation therapy

Successful treatment of insulinomas with radiation therapy has been described in isolated human patients. However, to date, data for canine or feline patients are not available.

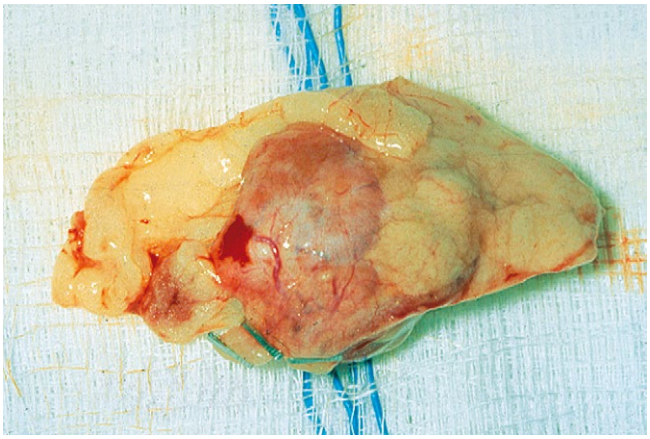


**Fig. 11-16** Insulinoma

An insulinoma after surgical removal by partial pancreatectomy. The size and appearance of this tumor are typical. (Reprinted with permission from Steiner JM et al., 1996.)[80]

#### 11.4.2.8.5 Symptomatic therapy

##### Antihypoglycemic therapy

Symptomatic therapy should be instituted in insulinoma patients when surgical exploration is not an option or is not successful. The dog should be fed a diet low in simple carbohydrates, and high in protein, fat, and complex carbohydrates, divided into multiple small feedings (i.e., 4–6 feedings per day). If the patient shows signs of weakness, a small amount of food should be offered immediately. Owners should also be familiarized with the clinical signs of hypoglycemia and instructed that if signs occur, dextrose solution (e.g., Karo syrup or honey) should be applied on the gums of the patient. Excitement should be avoided, and exercise should be limited to short leash walks.

Glucocorticoids should be administered if frequent feedings alone will not control the clinical signs. Cortisol is an endogenous counterregulatory hormone to insulin. It increases peripheral lipolysis and protein catabolism, increases hepatic gluconeogenesis and glycogenolysis, and decreases peripheral glucose utilization. It also decreases the sensitivity of insulin receptors in the periphery. Prednisone or prednisolone can be started at an oral dose of 0.25 mg/kg q12h. If clinical signs of hypoglycemia cannot be controlled, the dose can be incrementally increased up to 2–3 mg/kg q12h. The development of iatrogenic hyperadrenocorticism or GI side effects (e.g., gastritis, gastric ulceration, or colitis) may warrant the discontinuation of steroid therapy, and additional medical therapy may be required.

Glucagon, one of the counterregulatory hormones to insulin, can be used to increase blood glucose concentrations short-term, but long-term use has not been described to date.[28]

### Antihormonal therapy

Another therapeutic option for insulinoma patients is the treatment with agents that depress insulin secretion. Diazoxide is a non-diuretic benzothiadiazine that has anti-hypertensive as well as hyperglycemic properties. Its hyperglycemic action is due to a depression in insulin release from beta-cells. Diazoxide does not impair insulin synthesis, and it is not cytotoxic to beta cells. Survival times in insulinoma patients treated with diazoxide are rather short. However, this might be due to the fact that in most reports, diazoxide was only administered after previous medical and surgical therapy had failed. A few long-term responders have been reported, the longest being 18 months.[29] The recommended starting dose is 5 mg/kg orally q12h, but the dose can be gradually increased to 30 mg/kg q12h. Since the drug is metabolized in the liver and excreted by the biliary system and the kidneys, dosing should be carefully evaluated for patients with concurrent hepatic or renal disease. Also, care should be taken to avoid hyperglycemia. Thiazide diuretics enhance the effects of diazoxide, and hydrochlorothiazide can be added to the therapeutic protocol (2–4 mg/kg PO q24h). To decrease the frequency of GI side effects, the drug should be administered together with a meal.

Somatostatin (i.e., octreotide acetate) decreases several polypeptides of the gastroenteropancreatic system, including insulin. Octreotide consistently suppresses plasma insulin concentrations in canine insulinoma patients, while it has no effect on counterregulatory hormones, suggesting that it may be useful in the treatment of canine insulinoma.[30] However, in clinical practice, only some of the dogs treated with octreotide showed a response.[31,32] As with SRS, the limited response of canine insulinoma patients to octreotide may be due to a lack of SSR2 expression of insulinoma cells.[32] Doses of 20–100 µg/dog octreotide SC q8–12h have been described in the literature.[31]

#### 11.4.2.9 Prognosis

The long-term prognosis for dogs with insulinoma is grave, although the short-term prognosis is good. In a compilation of 114 dogs with insulinoma, which had been treated with surgery and with symptomatic therapy after the recurrence of clinical signs, the mean survival was 11.5 months.[7] Results may be more favorable as 31 dogs were alive and asymptomatic at their last follow-up visit, and time to relapse or death could not be determined in these patients. It should also be noted that the mean age of dogs presenting with insulinoma is 9 years, and therefore many patients may die for other reasons. In one study, the mean survival of canine insulinoma patients without metastatic disease at the time of diagnosis was 17 months, while it was only 8.4 months for dogs that did have metastatic disease.[33] Thus, the detection of distant metastases at the time of the abdominal exploratory may serve as a prognostic indicator. In one study, tumor size was identified as a prognostic indicator for disease-free interval and Ki67 for both survival and disease-free interval, but there was significant overlap for both parameters, suggesting that neither parameter is useful to predict prognosis in clinical patients.[34]

**CLINICAL PEARLS**

A canine insulinoma tissue microarray has been used to evaluate various immunological prognostic markers in dogs with insulinoma and may prove clinically useful in the future.[14]

## 11.4.3 Gastrinoma

### 11.4.3.1 Introduction

A gastrinoma is a rare neuroendocrine tumor (NET) in small animals, having been reported in about 30 dogs and less than 10 cats, compared with approximately 300 dogs and eight cats with insulinoma.[35–42]

Gastrinomas are most commonly single nodules of small size (▶Fig. 11-17). However, multiple masses have also been reported. In humans, gastrinomas are ultimately malignant, but most grow slowly. When gastrinomas were first described in humans, most were localized in the pancreas, but currently 70–80% of gastrinomas in humans are diagnosed in the duodenum.[43] This is probably due to improved localization techniques. By sharp contrast, a gastrinoma has only been localized in the duodenum in a single dog and no cat.[39] Also, in several canine and feline patients a tumor could not be located in the pancreas. One bile duct carcinoma in a cat was shown to stain positive for gastrin.[44]

Gastrinomas synthesize and release excessive quantities of gastrin (▶Fig. 11-18), leading to gastric acid hypersecretion, hypertrophy of the gastric mucosa, and eventually gastric and duodenal ulceration (▶Fig. 11-19).[42,45,46] Persistent hyperchlorhydria also leads to a decrease in duodenal pH, which in turn leads to mucosal injury and inactivation of digestive enzymes with subsequent maldigestion.

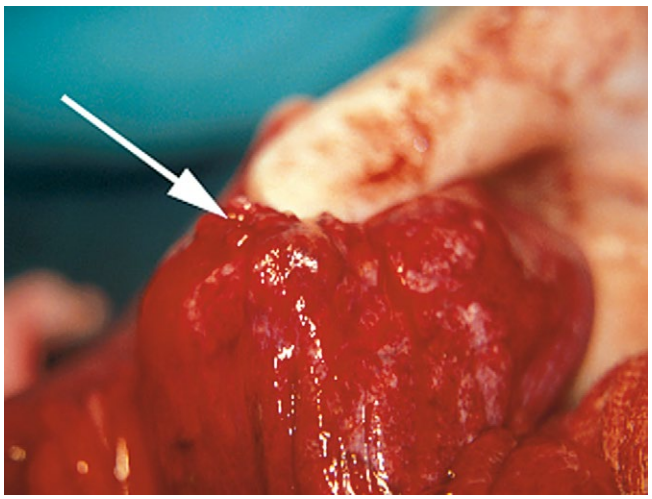


**Fig. 11-17** Gastrinoma

This figure shows a small tumor (**arrow**) in the pancreas of a dog. This tumor is barely visible and was identified as a gastrinoma by immunohistochemistry. (Courtesy of Dr. Kenneth W. Simpson, Cornell University, Ithaca, NY.)

### 11.4.3.2 Clinical presentation

Gastrinomas usually develop in middle-aged to older dogs (age range 3.5–12 years in 21 dogs reported) and cats (age range of five reported cats: 7–12 years).[35] In dogs, females are anecdotally more commonly affected than males, but this may be a reflection of the small number of cases reported.

The most common clinical signs observed in 25 of the reported cases in dogs included vomiting (92%), weight loss (88%), anorexia (72%), lethargy (64%), and diarrhea (60%). In addition, polydipsia, melena, and abdominal pain were noted in approximately 25%, and hematemesis, hematochezia, fever, and ravenous appetite in approximately 10% of cases each. Clinical signs in cats are similar with vomiting, weight loss, and poor body condition being reported most consistently.

Routine laboratory tests do not reveal any specific changes, but up to 50% of affected dogs and cats have a regenerative anemia, indicating ongoing blood loss. Many patients also show a neutrophilia with a left shift. Hypoproteinemia with hypoalbuminemia, hypokalemia, increased serum hepatic enzyme activities, hypochloremia, and hyperglycemia are also common. More serious changes may occur in patients with complications, such as pyloric obstruction due to mucosal hypertrophy or ulcer perforation with peritonitis.

Survey abdominal radiographs are unremarkable in most cases. Upper GI contrast radiography, which is rarely performed, may reveal plaque-like defects in the stomach or duodenum, indicating ulceration. In the small number of dogs described, abdominal ultrasonography failed to locate the primary lesion, but abdominal ultrasound may be useful for identifying metastatic lesions. Of five of the cats diagnosed with a gastrinoma, two were evaluated by abdominal ultrasound and in one of these cases the tumor was identified during a repeat ultrasound examination.[37] Gastroduodenoscopy allows for direct visualization of esophageal (▶Fig. 11-20), gastric, and duodenal lesions, but cannot identify the underlying cause of these lesions. In human patients, sensitivities and specificities of different localization techniques for gastrinoma have been

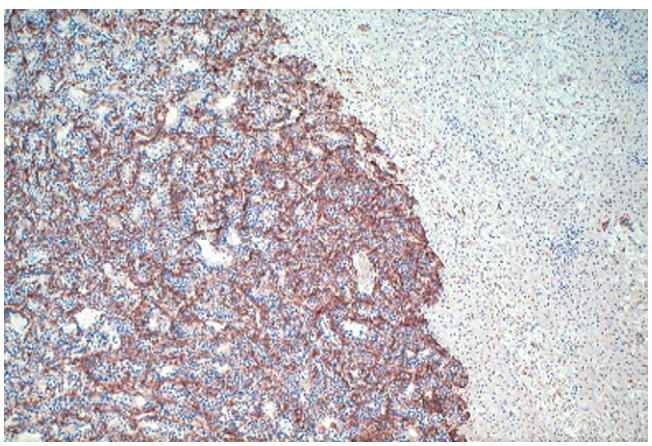


**Fig. 11-18** Immunohistochemistry of a gastrinoma

This image shows a pancreatic tumor that was stained for gastrin. Note the massive degree of brown staining on the left side of the picture. The brown stain shows the presence of gastrin, identifying this pancreatic tumor as a gastrinoma; magnification: 10×. (Courtesy of Dr. Kenneth W. Simpson, Cornell University, Ithaca, NY.)

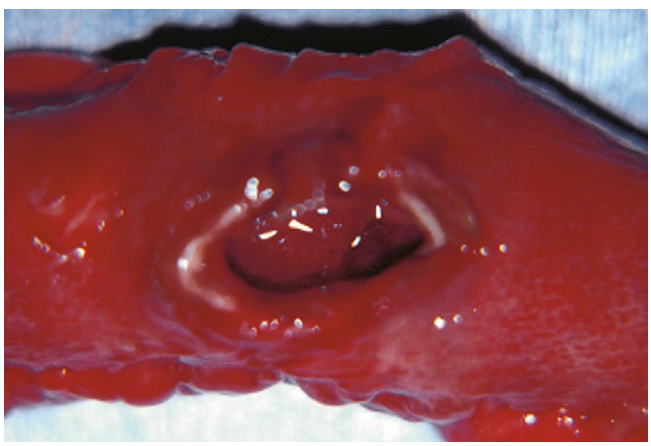


**Fig. 11-19** Duodenal perforated ulcer

This figure shows a perforated ulcer in the duodenum of a dog. This dog was diagnosed with a pancreatic tumor that stained positive for gastrin, identifying it as a gastrinoma. (Courtesy of Dr. Kenneth W. Simpson, Cornell University, Ithaca, NY.)

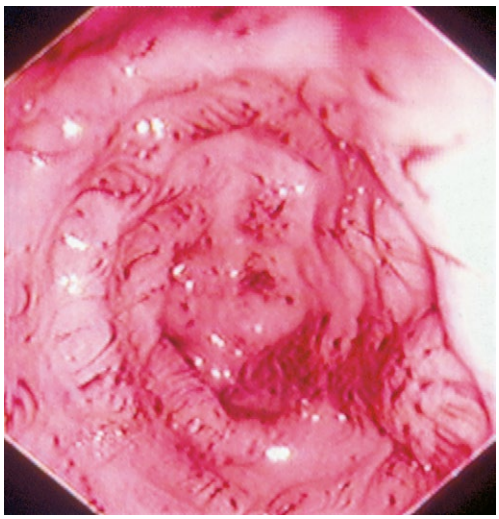


**Fig. 11-20** Esophageal ulceration

This image shows an endoscopic view of severe ulceration of the distal esophageal mucosa in a dog with a gastrinoma. (Courtesy of Dr. Kenneth W. Simpson, Cornell University, Ithaca, NY.)

compared. Abdominal ultrasonography, CT, MRI, or selective angiography all have a rather low sensitivity for the diagnosis of the primary lesion and only larger tumor lesions can be successfully imaged.[45] However, these modalities are all useful in identifying metastatic lesions. Much more promising for localization of the primary lesion are endoscopic ultrasonography and somatostatin receptor scintigraphy (SRS) using either $^{68}$Ga-dotatate positron emission tomography or $^{111}$In-DTPA-ocrteotide single photon emission tomography.[43,44] SRS is the most sensitive technique for localization of both the primary tumor and metastatic lesions in human gastrinoma patients.[43] Currently, endoscopic ultrasonography is not routinely available in veterinary practice. The successful diagnosis of a gastrinoma by SRS using $^{111}$In-DTPA-D-Phe$^{1}$-octreotide (OctreoScan™, Mallinckrodt Medical) has been reported in a single dog.[47]

### 11.4.3.3 Diagnosis

Although rare, gastrinomas should be ruled out in patients with a history of chronic vomiting, weight loss, anorexia, and/or diarrhea when an alternative diagnosis cannot be arrived at. Also, a gastrinoma should be considered in patients with severe gastroduodenal ulceration without any predisposing risk factors.

A definitive diagnosis of a gastrinoma, short of histopathological confirmation, is difficult. A species-specific assay for gastrin is not available and few veterinary laboratories currently offer measurement of serum or plasma gastrin concentrations.[48] In human medicine there has been a lot of controversy concerning serum gastrin assays. This is due to the fact that there are gastrins of different lengths (i.e., gastrin-14, gastrin-17, gastrin-34, gastrin-52) and also sulfated and non-sulfated forms circulating in the blood stream and often times assays only detect some forms or preferentially detect one form over another.[49] Also, some assays cross-react with CCK, which may cause falsely increased measurements.[49] One assay that appears to work fairly well in humans, dogs, and cats is the Immulite® 2000 assay by Siemens Diagnostics.[49] Each laboratory should establish their own reference interval in a number of healthy animals (e.g., the reference interval for serum gastrin concentration at the Gastrointestinal Laboratory at Texas A&M University is <28 ng/L for dogs and <40 ng/L for cats).[50,51] Traditionally, the diagnostic recommendation for humans used to be that a presumptive diagnosis of a gastrinoma can be made when the 24-hour fasting serum gastrin concentration is ten times the upper limit of the reference interval. However, this recommendation no longer holds true due to the widespread use of proton pump inhibitors (PPI), which can lead to extremely high serum gastrin concentrations in humans.[43] Similarly, even short-term administration of omeprazole at standard doses in dogs has been shown to lead to serum gastrin concentrations that can be extremely high.[52] Thus, PPI treatment must be discontinued before serum gastrin concentrations can be fully interpreted. In human patients suspected of having a gastrinoma that have been pretreated with a PPI, discontinuation of therapy is often not possible. Therefore, the recommendation in human patients is to decrease the dosing interval of PPIs, start the patient on a histamine$_2$-blocker, and then try to stop PPI treatment.[43] Also, in human patients, serum gastrin concentrations must be interpreted cautiously as there is a high prevalence of atrophic gastritis, which can also cause severely elevated serum gastrin concentrations. In contrast, in dogs and cats atrophic gastritis is extremely rare and other differential causes of elevated serum gastrin concentrations are much easier to exclude than in humans. These differential diagnoses may include chronic kidney disease, possibly liver disease, gastric outlet obstruction, small intestinal resection, immunoproliferative enteropathy of basenji dogs, other chronic enteropathies, gastric dilatation-volvulus, and administration of proton-pump inhibitors, though the evidence for some of these is more speculative than for others. Therefore, in dogs and cats that are not currently treated with a PPI, a less than 10-fold elevation of serum gastrin concentration after withholding food for 12 hours is sufficient to suspect a diagnosis of a gastrinoma if other differential diagnoses have been carefully ruled out.

In cases where serum gastrin concentrations are less markedly elevated, provocative testing may be useful. Secretin can be injected intravenously at a dose of 2 U/kg after withholding food from the patient for a 24-hour period. Blood samples are collected at 0, 2, 5, 10, 15, and 20 minutes. An increase of serum gastrin concentration to greater than 200 ng/L or a two-fold increase of the serum gastrin concentration at any time point is considered diagnostic for a gastrinoma.[35] Alternatively, calcium is administered intravenously, but neither the secretin- nor the calcium-stimulation test are commonly utilized in dogs or cats.

#### 11.4.3.4 Treatment

##### 11.4.3.4.1 Symptomatic therapy

Symptomatic therapy is started in most cases before a definitive diagnosis can be established and should be continued for several weeks after definitive therapy. The mainstay of symptomatic treatment of human gastrinoma patients is the administration of a PPI. The proton-pump inhibitor omeprazole has also been successfully used in the management of canine and feline patients with a gastrinoma (0.7–1.0 mg/kg PO q12h).[53]

**CLINICAL PEARLS**

The originally recommended omeprazole dose was q24h, but research in both dogs and cats has now clearly shown that effective antacid control requires dosing at an interval of q12h.[38,54]

In patients that do not tolerate oral medication, pantoprazole can be used intravenously at the same dose as omeprazole. Other PPIs, such as esomeprazole (1 mg/kg q24h; if tolerated well q12h), have also occasionally been used in dogs and cats and have demonstrated excellent gastric acid suppression in dogs and cats in general, but not much data concerning their use in gastrinoma patients is available. Initially, sucralfate, a mucosal protectant that adheres to the exposed proteins of the ulcer, should be added to the treatment protocol (1g per dog PO q8h; 0.25–0.5g per cat PO q8h). Histamine$_2$ antagonists, such as famotidine, at double the standard dose can be added if a PPI alone is ineffective. Also, famotidine can be administered as a CRI in hospitalized patients (bolus of 1 mg/kg IV then 8 mg/kg/day).

Octreotide, a long-acting somatostatin analogue, acts by inhibiting gastrin release and by decreasing gastric acid secretion directly and may inhibit tumor growth, thus affording more than just symptomatic relief. In human gastrinoma patients it has been demonstrated that most gastrinomas (both the primary tumor as well as metastatic lesions) express SSR-2, which is the somatostatin receptor type that octreotide binds to most effectively.[55] In contrast, only 58% of human insulinomas express this receptor type.[55] Octreotide has been shown to effectively increase progression-free survival in two placebo-controlled trials in patients with non-functioning well-differentiated advanced NETs and is recommended for use in gastrinoma patients not amendable to surgery. Octreotide has also been used successfully in two canine gastrinoma patients (2–20 µg/kg SC q8h).[31,35] These two dogs survived for 10 and 14 months, respectively, compared with a reported mean survival time of 5.5 months for other dogs with gastrinoma.[35]

###### Staging

Before initiating definitive treatment, the patient should be staged, which involves the localization of the primary lesion and the search for metastatic disease. Metastatic lesions serve as a long-term prognostic indicator, and approximately 85% of all dogs and cats with a gastrinoma have metastatic disease at the time of diagnosis. After localization of the primary tumor and after widespread metastatic disease has been excluded, an exploratory laparotomy should be performed. Even if the primary tumor can be identified easily, the rest of the pancreas and abdominal cavity should be carefully inspected for additional primary or metastatic lesions. This should include careful palpation of the duodenum. If a primary lesion cannot be identified, intraoperative ultrasonography or illumination of the duodenal wall with an endoscope may be useful. In cases where a primary lesion can still not be identified, biopsy samples of pancreas, lymph nodes, and the liver should be collected, but a blind partial pancreatectomy is not recommended. It should be noted that in human patients with gastrointestinal NETs, surgical removal of the primary tumor improves survival, even if metastatic disease is present and metastatic lesions cannot be removed.[56]

##### 11.4.3.4.2 Surgical approach

If the primary tumor can be identified, it is removed by **partial pancreatectomy**. The tumor should be submitted for histopathological examination and immunohistochemical staining for regulatory peptides most commonly found in GI NETs. Metastatic lesions that are present in most cases, should only be removed if this is possible without radical excision. Postoperatively, medical therapy should be continued for at least a few weeks before being slowly phased out.

#### 11.4.3.4.3 Alternative therapeutic approach

If the primary tumor cannot be localized and removed during surgery or if extensive metastatic disease is present, an alternative therapeutic approach should be considered. The use of chemotherapy has not been reported in dogs or cats with a gastrinoma and it has a low success rate in human patients. Also, radioactively-labeled somatostatin analogues have been used in the treatment of human gastrinoma patients, but at this time there have been no reports in either dogs or cats with a gastrinoma.[57] Medical therapy as described above may prove useful.

### 11.4.3.5 Prognosis

The long-term prognosis for dogs and cats with a gastrinoma is grave. However, with appropriate medical management the short-term prognosis and quality of life can be good. Several canine and feline gastrinoma patients have been successfully managed for several months, one even for over 2 years after diagnosis.[38,53] With increasing awareness, leading to an earlier diagnosis, improved localization and staging techniques, and advanced treatment options, survival times are likely to increase further.

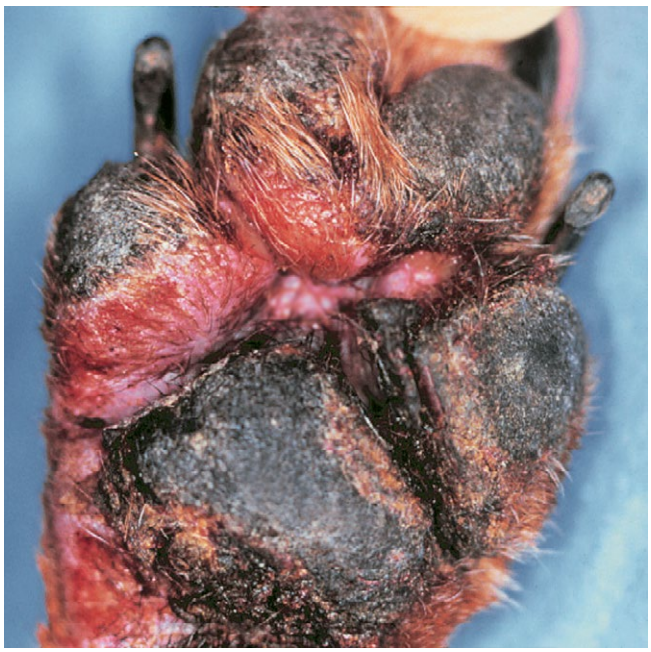


**Fig. 11-21** Foot pad lesion of a dog with necrolytic migratory erythema (NME)

This dog shows severe crusting lesions on his foot pads with significant interdigital ulceration. A biopsy must be collected to confirm the presence of canine NME. Most dogs with canine NME do not have a glucagonoma, but another condition, such as hepatic disease. (Courtesy of Dr. Sandy Merchant, Louisiana State University, Baton Rouge, LA.)

## 11.4.4 Glucagonoma

### 11.4.4.1 Introduction

The first human patient with dermatitis, mild diabetes mellitus, and increased serum glucagon concentrations that was attributed to a neuroendocrine tumor (NET) of the pancreas was described in 1966.[58] To date, only approximately 10 cases of glucagonoma have been described in dogs, and this syndrome has only been reported in a single cat.[59–60]

### 11.4.4.2 Clinical presentation

Glucagonomas in humans are associated with typical skin lesions characterized by marked erythema, destruction of the superficial epidermis, and a tendency to heal and progress to other areas of the body. These skin lesions are descriptively termed necrolytic migratory erythema (NME).[58] Similar skin lesions have been reported in several dogs and were originally descriptively termed superficial necrolytic dermatitis, but are now also referred to as canine NME.[59] As in humans, the majority of patients with NME do not have a glucagon-secreting NET, but instead they are diagnosed with hepatic disease, administration of phenobarbital or primidone, the ingestion of mycotoxin, or gastroenteritis.[62–66]

Human patients with glucagonoma can present with NME, weight loss, diabetes mellitus, glossitis, stomatitis, cheilitis, and a tendency for thromboembolic disease.[58] The small number of dogs diagnosed with a glucagonoma have had crusting and scaling skin lesions, most commonly of the footpads, hocks, abdomen, elbows, perineum, nose, and mucocutaneous junctions (▶Fig. 11-21 ,▶Fig. 11-22 ,▶Fig. 11-23). These canine patients also exhibited depression, peripheral lymphadenopathy, and anorexia. Hyperglycemia was reported in 5 of 9 dogs, but was mild in most cases. Also, in some dogs, diabetes mellitus was diagnosed after the diagnosis of the glucagonoma. It is, therefore, appropriate to suspect a glucagonoma in dogs presenting with canine NME that do not show evidence of hepatic disease, even if they do not concurrently present with diabetes mellitus.

The single cat reported with a glucagonoma presented with vomiting, anorexia, and NME.[61]



**Fig. 11-22** Ear lesion of a dog with necrolytic migratory erythema (NME)

This figure shows severe crusting and ulceration on the concave pinna of a dog. A biopsy must be collected to confirm the presence of canine NME. (Courtesy of Dr. Sandy Merchant, Louisiana State University, Baton Rouge, LA.)



**Fig. 11-23** Skin lesion of a dog with necrolytic migratory erythema (NME)

This image is a close-up of crusting with ulceration on a pressure point area of a dog. A biopsy must be collected to confirm the presence of canine NME. (Courtesy of Dr. Sandy Merchant, Louisiana State University, Baton Rouge, LA.)

### 11.4.4.3 Diagnosis

Most dogs with a glucagonoma are severely hypoaminoacidemic.[60] Measurement of serum or plasma glucagon concentrations may be helpful in confirming a diagnosis. While a glucagon assay has been validated for use in domestic animals, to the author's knowledge, no veterinary endocrine laboratory currently offers this assay commercially. However, samples can be submitted to a human laboratory. In such cases, the laboratory must be contacted for special submission instructions. Caution is advised in interpreting high serum or plasma glucagon concentrations, as they have also been reported in human patients with other conditions, such as chronic kidney disease, diabetic ketoacidosis, starvation, acute pancreatitis, hyperadrenocorticism, and sepsis. Also, similarly to gastrin, there are several different isoforms of glucagon and not all of them are biologically active and not all of them are measurable by all glucagon assays.[58]

Glucagonomas are usually very small, even though, both in humans and dogs, they have often metastasized by the time they are diagnosed. For example, the primary glucagonoma in the pancreas of one of the dogs reported was only 3 mm in diameter.[59] Therefore, routine imaging, such as abdominal ultrasound or computed tomography rarely reveal the location of the primary tumor, but more frequently would be expected to reveal metastatic lesions in the liver, spleen, or lymph nodes.[59] In contrast, at least in humans, glucagonomas usually strongly express SSR-2 and SSR-5 receptors, and the sensitivity of somatostatin receptor scintigraphy for the diagnosis of a glucagonoma has been reported to be 97%.[59,67]

If a glucagon assay is not available, the diagnosis of canine NME is confirmed by histopathology of a skin biopsy after other potential causes for canine NME have been ruled out. SRS scintigraphy or an exploratory laparotomy should then be considered for definitive diagnosis and treatment.

In the single cat with a glucagonoma, a large tumor, that later stained positive for glucagon was located in the liver by abdominal ultrasonography, but no mass was identified in the pancreas.[61] The authors speculated that in this cat the primary tumor was located in the liver, but a small primary nodule may have been missed in the pancreas.[61]

#### 11.4.4.4 Treatment

The same treatment guidelines for localization and surgical exploration discussed for other NETs also apply for glucagonomas. As for gastrinomas, metastatic disease at the time of diagnosis is common in dogs with a glucagonoma. Since most patients with a glucagonoma have hypoaminoacidemia preoperatively, total or partial parenteral nutrition may improve the overall condition of the patient, but have shown little effect in improving the skin lesions.[59,60] An exploratory laparotomy has been reported in four dogs diagnosed with a glucagonoma and a mass was removed in three, two of which died or were euthanized within 3 days of surgery because of postoperative pancreatitis. One dog survived for 9 months before the skin lesions returned and the patient was euthanized.[68]

Medical management should be considered if abdominal exploration is not an option in cases of a metastatic glucagonoma or in recurrent cases. Medical management using exogenous insulin, intravenous infusion of essential amino acids and fatty acids, or zinc supplementation may be used to treat clinical symptoms, but clinical efficacy has not been clearly demonstrated. Similar to humans with glucagonoma, one dog with a glucagonoma responded well to octreotide therapy with complete resolution of the skin lesions within just a few days of initiating therapy.[59,69]

**CLINICAL PEARLS**

A starting dose of octreotide of 2 µg/kg q12h has been reported in two case reports, but as in humans, octreotide has a wide therapeutic range and dose and dosing interval often need to be adjusted (doses up to 20 µg/kg q8h have been reported) to achieve a clinical response while avoiding anorexia, which is the most common side effect.[59]

The long-term prognosis for patients with glucagonoma is poor.

### 11.4.5 Gastrointestinal carcinoids

Gastrointestinal carcinoids are a heterogeneous group of tumors arising from the diffuse neuroendocrine system of the GI tract. In human patients, 90% of gastrointestinal carcinoids are non-functional, while the remainder may release regulatory substances such as histamine, serotonin, tachykinins, and/or others. These regulatory substances lead to carcinoid syndrome characterized by flushing, diarrhea, hypotension, lacrimation, asthma, or heart palpitations.

Gastrointestinal carcinoids have also been reported in dogs and cats, although signs of flushing, hypotension, or bronchoconstriction have not been reported.[70,71] This may reflect a lack of synthesis of regulatory substances by canine and feline GI carcinoids.

One canine patient presented for constipation, tenesmus, and weakness and did well after complete surgical removal of the mass with adjuvant carboplatin therapy.[72] Another canine patient was presented for a cecocolic intussusception and also did well after surgical resection.[73] A feline patient that presented for recurrent emesis and melena was diagnosed with a duodenal carcinoid.[71] The tumor could not be completely removed, and the cat died of continued blood loss.[71] Another cat presented for a perianal carcinoid that had metastasized to regional lymph nodes at the time of diagnosis.[74] This cat was managed with a combination of surgical excision of the primary mass and the regional lymph nodes, as well as radiation therapy and chemotherapy, and survived for at least 13 months after diagnosis, though with progressive disease.[74]

In humans with carcinoids as well as other gastrointestinal neuroendocrine tumors, the somatostatin receptor agonists octreotide, lanreotide, and lanreotide autogel are all effective in prolonging the disease-free interval, but these medications have not been reported to have been used in veterinary patients with GI carcinoids.[75]

Careful evaluation of future cases, including the measurement of urinary histamine and serotonin metabolite excretion, immunohistochemical behavior, and ultrastructural studies of the tumor cells, are required for a better understanding of this disease in dogs and cats.

### 11.4.6 Somatostatinoma

In humans, somatostatinomas are considered extremely rare and only account for approximately 5% of pancreatic neuroendocrine tumors.[76] Human patients with a somatostatinoma often present with vague clinical signs, such

as abdominal pain, vomiting, jaundice, and/or steatorrhea, but with advanced disease, they may present with "inhibitory syndrome," which is characterized by diabetes mellitus, cholelithiasis, and steatorrhea.[76] A single dog with somatostatinoma in the pancreas and a concurrent gastrinoma in mesenteric lymph nodes and the liver has been reported.[77] This dog presented with a 2-month history of weight loss and elevated liver enzyme activities.[77] The serum gastrin concentration was more than 100-fold increased.[77] The dog was treated symptomatically for the gastrinoma but developed an esophageal stricture 2 months after diagnosis and was euthanized without a post-mortem examination.[77] It is unclear whether the somatostatinoma contributed to the clinical signs of this dog, but the authors of this case report speculated that this dog had multiple endocrine neoplasia, similar to many human patients with a pancreatic neuroendocrine tumor.[77]

### 11.4.7 Pancreatic polypeptidoma

Gastrointestinal neuroendocrine tumors in humans often secrete pancreatic polypeptide, but the clinical relevance of this remains unknown.[5] Only a single dog with a suspected pancreatic polypeptidoma has been reported in the veterinary literature.[78] This dog presented for chronic vomiting, anorexia, weight loss, and lethargy. A concurrent insulinoma was diagnosed on the basis of hypoglycemia in the face of a high serum insulin concentration.[78] Baseline serum gastrin concentration was seven times the upper limit of the reference interval but did not rise after a secretin or calcium challenge.[78] Serum pancreatic polypeptide concentration was 3,500 times the upper limit of the reference interval. Multiple pancreatic tumors removed at exploratory laparotomy showed strongly positive immunoreactivity for pancreatic polypeptide and a positive reaction for insulin, but there was no staining for gastrin or other GI regulatory peptides.[78] It remains questionable whether there was a cause-effect relationship between the extremely high serum pancreatic polypeptide concentration and the clinical signs observed in this patient.[78]

### 11.4.8 Other neuroendocrine tumors of the gastrointestinal tract

Several other gastrointestinal neuroendocrine tumors, including CCKomas, VIPomas, GRFomas, ACTHomas, or PTHrPomas, have been reported in human patients but have not yet been identified in dogs or cats.[5,79]

**KEY FACTS**

- Insulinoma is the most common neuroendocrine tumor (NET) in dogs, followed by gastrinoma. All other NETs of the gastrointestinal (GI) tract are extremely rare in dogs. All GI NETs are extremely rare in cats.
- Insulinoma should be suspected in a patient with hypoglycemia with a normal or even increased serum insulin concentration.
- Insulinomas are ultimately malignant in most dogs. However, many dogs can be successfully managed for more than 1 year.
- Localization of NETs of the GI tract can be challenging.
- If a GI NET has been identified, the treatment of choice is the removal of the tumor and medical management of the clinical syndrome.

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
svg.to/9842-11-04

## 11.5 Adipositas/Obesity

Alexander J. German

### 11.5.1 Definition

According to Kopelman,[1] obesity is "a disease in which adipose tissue has accumulated, to the point that health can be adversely affected". Such a definition emphasizes the importance of the clinical consequences of the condition, which goes beyond the quantification of body fat mass, *per se*. Of course, increasing adiposity is a continuum, and the most common clinical metric used to estimate adiposity is body mass index (BMI), which is weight (measured in kg) divided by height squared (measured in cm). In humans, overweight condition (pre-obesity) is classified as a BMI >25, whilst people with obesity typically have a BMI >30 further subdivided into stages (stage I: 30–35, stage II: 35–40, stage III: >40), with each representing a progressive increase in disease and mortality risk. Although easy to quantify, it is an imperfect measure because it may not correspond to the same degree of obesity amongst individuals, not least

because increases in weight might not be the result of fat, but other tissues, such as muscle or fluid. Therefore, other measures of adiposity are also used, such as abdominal girth, and the impact on health status also considered (presence of functional impairment and comorbidities).

Dogs and cats with obesity have a body weight that is >30% above their ideal body weight (IBW), whilst increases in weight of a lesser magnitude are classified as "overweight" (pre-obesity). As in humans, it is recommended that the obesity definition should also include a component of disease or morbidity, given the known associations between excess body fat and various negative consequences.[2–4]

### 11.5.2 Is obesity a disease?

For many years, the medical profession has debated the various reasons for and against defining human obesity as a disease.[1,5] Opponents have argued that obesity is a normal physiological response to excess energy intake as a result of exposure to an abnormal ("obesogenic") environment.[6,7] However, this interpretation conflicts with scientific knowledge about the pathogenesis of obesity.[8] Although the initial expansion of adipose tissue might be seen as a physiological response, continued expansion initiates pathological processes, such as adipose tissue hypoxia, provoking macrophage infiltration, angiogenesis, and abnormal release of adipokines and cytokines. This, in conjunction with fat deposition in other organs, triggers dysregulation of metabolic, hormonal, and inflammatory processes, which are, in turn, linked to adverse health consequences, leading to functional impairment, morbidity, and a worse quality of life. Such a switch from a physiological to a pathological state is also seen in other conditions, considered to be disease states. For example, abnormal triggering of normal immune mechanisms occurs in hypersensitivity diseases, such as atopic dermatitis.

Consequently, an increasing number of national and international professional medical organizations have now formally recognized obesity as a disease. Classifying obesity as a disease has been particularly controversial in Europe but recently, the *European Commission* has published a definition of obesity as a chronic relapsing disease (▶box "Definition of obesity").[10]

**Definition of "obesity" by the *European Commission*[10]**

"Pre-obesity (overweight) and obesity are medical conditions marked by an abnormal and/or excessive accumulation of body fat that presents a risk to health. Obesity is a chronic relapsing disease, which in turn acts as a gateway to a range of other non-communicable diseases, such as diabetes, cardiovascular diseases, and cancer."

This definition has been widely praised, not only for its clarity, but for the particular emphasis placed both on the risk of obesity to health and links to other non-communicable disease. Such a definition also busts many myths that obstruct progress in the field. Most notably, many people try to tie obesity solely to BMI (as discussed above), and then use questions about the validity of BMI to dispute the validity of what obesity is. Similar arguments have been made within the veterinary profession, including criticisms about the use of BCS as a means of defining obesity. A further extension of such arguments is that, because there is inconsistency in terms of when consequences of obesity are observed, applying an arbitrary definition of a disease state on top of this is unhelpful.[6] However, whilst there are undoubtedly flaws in methodology used to quantify fat mass and the predictability of consequences of obesity, such issues do not invalidate the classification of obesity as a disease. In this regard, it is common practice to apply defined diagnostic cut-points to a disease continuum; for example, the staging of the *International Renal Interest Society*[11] has received widespread acceptance for the classification of chronic kidney disease, whereby different stages are delineated with diagnostic criteria (e.g., serum creatinine concentration), whilst various clinical consequences such as hypertension, proteinuria, and uremic syndrome are inconsistent and variable.

### 11.5.3 Prevalence

Obesity is a highly prevalent condition in humans and is recognized as an epidemic of global proportions. The worldwide prevalence of obesity has tripled in the last 40 years, with over 1.9 billion adults estimated to being in overweight condition in 2016, of which 650 million had obesity (this represents approximately 13% of the adult population).[12] More concerning is the increasing prevalence of obesity in children, where over 38 million children under the age of 5 are being classified as obese.

Overweight and obesity are also well-recognized in companion animals, most notably in cats and dogs. Several recent studies have determined the prevalence of excess body weight (overweight and obesity combined) in dogs and cats. For dogs, 11–59% are defined as either overweight or obese, whereas, in cats, the prevalence ranges from 11% to 63%,[13] with differences not only representing differences in when the studies were conducted but also differences in populations and methodology. However, the prevalence has almost certainly increased over recent years. In a survey conducted by the *Association for Pet Obesity Prevention* (*APOP*),[14] 26% of cats in the USA were classified as being overweight (body condition score, BCS 6–7/9), whilst 34% had obesity. By comparison, a similar survey that was conducted by APOP in 2008 revealed a prevalence of 40% and 17% for overweight and obese body conditions, respectively.[15] This makes obesity one of the most common medical disorders identified in veterinary practice. Of even greater concern is the prevalence in young animals, with one recent report suggesting that 37% of juvenile dogs (<24 months) were already in an overweight condition.[16]

## 11.5.4 Etiology and pathogenesis

In all instances, the underlying etiology of obesity is related to energy imbalance, whereby energy intake exceeds energy expenditure for a prolonged period. Energy intake results from the consumption of macronutrients in the diet (namely protein, fat, and carbohydrate), while energy expenditure mainly results from essential metabolic processes (the so-called basal metabolic rate), thermoregulation (heating and cooling), and physical activity. Net energy consumed is mainly stored in white adipose tissue resulting in the expansion of this tissue through both adipocyte hypertrophy (increased cell size) and hyperplasia (synthesis of new cells from preadipocytes), the relative balance of which can vary among individuals. It may also be associated with the metabolic manifestations of obesity (see below). The risk of developing obesity varies amongst animals (and indeed humans) because of many risk factors (see below), all of which alter energy balance. Broadly speaking, such risk factors can be genetic (including common and rare genes, genes of the alimentary microbiome, and epigenetic factors), biological (e.g., signalment factors; endocrine factors, including sex hormones and glucose-regulation; energy metabolism; adipose tissue function; muscle function), behavioral (i.e., animal behavior, including feeding behavior and physical activity; owner behavior; behavior of other in-contact people and animals), and environmental (e.g., food environment; living space; local geography; family environment).

### 11.5.4.1 Risk factors for obesity

As discussed above, there are many factors that are associated with the risk of developing obesity, as detailed below.

#### Genetics

In humans, genetics are thought to account for a significant proportion of an individual's risk of developing obesity, estimated at 40–70%.[17] Single-gene deficits are reported but are rare.[18] Instead, most genetic causes of obesity are polygenic, and over 50 genes have now been identified that are associated with so-called simple obesity. Each of these genes conveys only a minor impact on weight status (typically equating to 1–2 kg of body weight). Thus, the overall risk is associated with the number of obesity-associated genes that an individual possesses. Intriguingly, most of these genes code for proteins active in the brain, which are associated with appetite and satiety. Genetic factors have not yet been widely studied in cats and dogs, and to date, no single-gene disorders have been described in either species. However, recently a mutation in the *pro-opiomelanocortin C* (*POMC*) gene has been identified in some Labrador and flat-coated retrievers, and possession of this variant is associated with increased appetite and weight gain.[19] In cats, genetic factors have not yet been investigated in detail, but some studies do suggest genetic mechanisms.[20] Further evidence for possible genetic influences is demonstrated by known breed predispositions in both dogs and cats. Traditionally, reported breed predispositions for obesity in dogs included cocker spaniels, beagles, Labrador retrievers, golden retrievers, Shetland sheepdogs, Rottweilers, and mixed-breed dogs.[21] However, in keeping with recent changes in popularity, various breeds, notably an increased popularity of small breeds and especially brachycephalic breeds, other breed associations are now recognized. Thus, most recently, the breeds with the greatest reported prevalence of obesity include pugs and French bulldogs. In cats, breed predispositions have not been widely reported, although, in some studies, domestic shorthair cats are reportedly predisposed.[22]

#### Age and early-life factors

Dogs and cats can develop obesity at any time of life, although some studies suggest that the risk increases with age.[23] Other studies have suggested that prevalence is greatest in middle-aged animals and declines thereafter,[21,22] possibly due to the onset of age-related chronic diseases. This finding mirrors some longitudinal studies that have demonstrated that cats tend to gain weight gradually throughout life. Although less

common, overweight conditions and obesity are reported in some growing animals and those in early adult life.[16] In humans, children who grow rapidly during their early years are more likely to develop obesity in childhood and during adulthood.[24] Rapid growth rate is also a risk factor for the development of obesity in both dogs and cats.[25,26]

### Sex and neutering

In cats, male cats are reportedly predisposed,[22,27] but sex associations with obesity are less consistent in dogs. For example, one recent study reported an increased prevalence of obesity in female dogs,[28] whilst the other suggested that male dogs were predisposed.[23] In both species, neutering is a key risk factor,[23,28,29] which is thought to be a consequence of hormonal changes arising after neutering. Such changes are associated with behavioral alterations (i.e., increased food intake, decreased physical activity) rather than there being a decrease in metabolism.[29] Given that neutering, in most dogs and cats, is usually undertaken as an elective procedure, unwanted post-neutering weight gain can arguably be mitigated by instigating preventive strategies at this time (e.g., closely monitoring body weight and adjusting food intake accordingly). Age of neutering might also be a factor, especially in female kittens, where those neutered before 28 weeks are at increased risk.[30] Therefore, in practice, neutering cats early and proactive monitoring of weight after neutering is critical. For example, growth charts can be used to identify any changes in growth rates, enabling corrective measures to be taken (e.g., reducing food intake).

### Comorbidities

Many other diseases can alter energy balance either by increasing energy intake or decreasing expenditure and, as a result, predispose to obesity (▶box right column). Hypothyroidism is thought to be a common endocrinopathy, but studies have revealed a prevalence of <1% and not all affected dogs are overweight. In comparison, 11–59% of all pet dogs are overweight or have obesity.[13] Given the difference in relative prevalence between obesity and hypothyroidism, most dogs in the overweight category that are presented to a veterinary practice are unlikely to have concurrent hypothyroidism. Added to that, hypothyroidism is extremely rare in cats and thus cannot be considered to be a significant risk factor in this species. Some diseases, such as hyperadrenocorticism, can cause polyphagia, and if the animal is allowed to consume more food, weight gain can occur. Furthermore, some therapeutic interventions can also cause an increased appetite, including drugs, such as glucocorticoids and anticonvulsants, as well as ovariohysterectomy to treat pyometra, which is well-recognized as a risk factor for obesity (see above). Finally, some diseases can predispose to obesity by decreasing physical activity, most notable orthopedic diseases, which lead to lameness.[21]

**Diseases that might predispose to inappropriate weight gain by altering energy balance**

- Hypothyroidism decreases energy expenditure by decreasing the basal metabolic rate.
- Hyperadrenocorticism causes polyphagia and can predispose to increased energy intake.
- Side effects of some drugs, e.g. glucocorticoids or anticonvulsants include polyphagia, which might lead to weight gain.
- Neutering is a risk factor for inappropriate weight gain, but may be required for the treatment of certain diseases, such as pyometra.
- Orthopedic diseases decrease the energy expenditure by decreasing physical activity.

### Environment and activity

Both dogs and cats that reside indoors are at greater risk for developing obesity than those who have access to the outdoors, most notably cats that are apartment-dwelling.[31–34] Furthermore, cats that live with one or two other cats or with a dog may also be at increased risk.[32,34] Finally, studies in dogs suggest associations between the level of physical activity, with dogs doing some activity being at a lesser risk of developing obesity than those without any exercise.[23] Another study demonstrated the importance of both frequency and duration of walking: daily exercise and exercising for at least 30 minutes per session were independently associated with lesser odds of having an overweight condition.[35]

### Dietary factors

The influence of food and feeding on the development of both canine and feline obesity has been widely studied, although many findings are contradictory. A summary of some key findings is shown in ▶Tab. 11-10.

**Tab. 11-10** Associations between being overweight/obesity in cats and dogs and food-related factors

| Food type |
|---|
| • Grocery store dog foods are positively associated with canine obesity.[21] |
| • Premium cat foods are positively associated with feline obesity.[22] |
| • There is no association between diet type and obesity in either cats or dogs.[28,32,36] |
| • Dogs fed a mix of commercial and home-made food are at greater risk of obesity than dogs fed either home-prepared food or commercial food alone.[23] |
| • Dry food is associated with being overweight in cats.[73,114,115] |
| • Dietary fats, rather than carbohydrates are associated with body fat mass in cats.[116] |
| • Cats have a ceiling for carbohydrate intake, which limits ingestion when fed high-carbohydrate foods, and prefer a macronutrient ratio of approximately 30%:63%:7% (protein:fat:carbohydrates) based on energy content.[117] |
| • Dogs prefer diets with a macronutrient ratio of approximately 52%:36%:12% (protein:fat:carbohydrate) based on energy content.[118] |
| **Feeding method** |
| • Feeding free choice is associated with obesity in cats.[32,33] |
| • When offering food ad libitum, 45% of cats become overweight and the rest maintain an ideal weight; thus, some, but not all cats can regulate their food intake.[25] In contrast, dogs do not regulate their food intake when offered different diets ad libitum, and most will overeat.[118,119] |
| • Once-daily feeding is positively associated with overweight condition in dogs.[120] |
| • Negative association between the number of meals and overweight condition in dogs.[23] |
| • Feeding of additional snacks (e.g., table scraps, treats) is associated with obesity in cats and dogs.[28,32,33,120] |
| • The cat or dog being present when food is being prepared is associated with obesity.[32,33,120] |
| • Use of a scoop to measure food portions is associated with obesity.[115] |
| • Stealing food from another pet in the household is positively associated with overweight condition in dogs.[115] |

### Owner factors and behavior

Some studies have suggested that overweight status in dogs is associated with a lower income of owners[23,36–38] or gross domestic product of the country,[23] but this is not true for all studies.[28] Furthermore, no association has been reported between feline obesity and owner income in cats.[39] Owners of both overweight cats[39] and dogs[36, 40, 41] are more likely to be overweight themselves, whilst owners of overweight dogs are more likely to be smokers and are more likely to have a negative attitude to sports.[41] Also, there is a positive association between the number of people in a family and overweight status in dogs.[23] Owners of dogs with obesity also tend over-humanize them,[39] are more likely to see their dog as a baby,[42] are more likely to let them sleep on the bed.[42] Owners of overweight cats also have a stronger bond with them, are more likely to use them as a substitute for human companionship, play less with them, and are more likely to reward them with food rather than extra playtime.[39] Furthermore, owners of overweight cats and dogs are less interested in preventive health care, are less likely to see obesity as a disease,[23,41] and are less likely to observe their pet closely during feeding.[36,39]

## 11.5.4.2 Pathogenesis

Obesity has adverse effects on health and well-being (see below), including the development of comorbidities, effects on the function of various body systems, shortened lifespan, and a negative impact on quality of life. Pathogenetic mechanisms can be *mechanically* or *chemically mediated*.

**Mechanically-mediated mechanisms** include an increased load on weight-bearing structures of the musculoskeletal system (i.e., joints, bones, ligaments, and tendons) and local effects on function arising from excess adipose tissue. For example, disruption of respiratory function, as a result of the accumulation of cervical, intra-thoracic, and abdominal fat (affecting breathing function), can exacerbate diseases such as tracheal collapse and brachycephalic obstructive airway syndrome. Furthermore, lower urinary tract function can be disrupted by the deposition of excess intra-abdominal and intra-pelvic fat and exacerbation of lower urinary tract disease (e.g., urethra or urinary bladder, causing incontinence). Other problems that arise as a result of mechanical mechanisms include difficulty grooming and reduced heat dissipation (due to the insulating effect of adipose tissue).

**Chemically-mediated mechanisms** arise as a result of the derangement of endocrine functions of white adipose tissue. In this respect, the term adipokine is used for various cytokines, chemokines, and other inflammation-related proteins that are synthesized by adipocytes and influence the function of an array of organ systems.[3] It is currently postulated that there is an expansion of adipose tissue as a result of a prolonged energy imbalance, leading to tissue hypoxia, which in turn promotes infiltration by macrophages and also increases vasculature. Associated with this, there is a derangement in adipokine synthesis and release. All of this results in a systemic state of chronic mild inflammation, which is causally linked to the clinical consequences. Human studies have shown that increased production of so-called inflammatory adipokines (e.g., leptin, TNFα, IL-6, PAI-1, and haptoglobin) are causally linked to metabolic syndrome and other obesity-related disorders.[3] As described above, adipose tissue expansion in response to energy excess results both from hypertrophy and hyperplasia, but the relative contribution of these two processes varies amongst individuals. If the predominant response is adipocyte hypertrophy, there also tends to be greater deposition of hepatic fat, whilst metabolic disturbances are more marked. These effects likely arise through mitochondrial dysfunction and upregulation of inflammatory pathways in adipose tissue.[3]

Although pathogenetic mechanisms have not been extensively studied in cats and dogs, inflammatory adipokine gene expression has been documented in both canine and feline white adipose tissue, and studies are now highlighting end effects in these species.[3] As with humans, metabolic derangements are most evident. Increased plasma leptin concentrations are independently associated with insulin sensitivity in lean and overweight cats, whilst decreased circulating adiponectin is linked to insulin resistance in dogs and cats with obesity.[3] Increases in serum paraoxonase-1 have also recently been demonstrated[43] and, once again, this is associated with insulin resistance.

#### 11.5.4.3 Pathological consequences of obesity

##### 11.5.4.3.1 Obesity-associated disorders in humans

As mentioned, obesity has many adverse effects in humans, which result from functional impairments (mechanical, metabolic, and inflammatory) as a result of an expanded fat mass. The most important metabolic/inflammatory consequence of obesity is metabolic syndrome, with its associated metabolic and vascular derangements, that predispose to type II diabetes mellitus.[44] Obesity, through metabolic syndrome, also leads to cardiovascular disease, with an associated increased prevalence of coronary heart disease, atherosclerosis, hypertension, and dyslipidemias in those individuals who are overweight. Metabolic and inflammatory mechanisms are also thought to account for the increased risk of kidney disease (especially diabetic nephropathy), gall bladder disease, and certain forms of cancer (e.g., breast, prostate, ovary, colon/rectum, kidney, and esophageal cancer).[8] Furthermore, obesity is now considered to be the most important cause of liver disease, given the increased likelihood of affected patients developing steatosis, cirrhosis, and hepatocellular carcinoma. Finally, obesity is a highly stigmatized condition, and it is increasingly recognized that this can lead to adverse outcomes, not least as a result of increased depression and anxiety, but stigmatization can also impair access to effective obesity care.[8]

##### 11.5.4.3.2 Obesity-associated disorders in companion animals

As in humans, there are many adverse consequences of obesity in cats and dogs, including adverse effects on lifespan and quality of life, as well as effects on various body systems, including comorbidities and functional impairment (▶Tab. 11-11).

###### Lifespan

In a recent epidemiological study involving >50,000 dogs from 12 different breeds, overweight body condition was associated with a net shortening of lifespan, which varied by breed from ~6 months, in larger breeds (such as German shepherd dogs) to over 2 years in smaller breeds (such as Yorkshire terriers).[45] These findings confirm indirect evidence from a lifelong experimental feeding study in a colony of Labrador retrievers, whereby caloric restriction (to approximately 75% of ad libitum) was associated with a leaner body condition score (BCS; 4.6/9 vs. 6.7/9) and an average longer lifespan of almost 2 years (13 years vs. 11.2 years) than dogs fed ad libitum.[46] In the same study, the restricted dogs were less likely to develop hip dysplasia[47] or osteoarthritis, especially of the hip and shoulder joint, later in life.[46] Finally, these dogs showed improved glucose tolerance and lower circulating triglyceride concentrations, compared with the *ad-libitum*-fed and overweight dogs. Associations between BCS and lifespan have also been examined in a recent epidemiological study in

**Tab. 11-11** Diseases associated with being overweight and with obesity in dogs and cats

| Disease category | Species | |
|---|---|---|
| | Dog | Cat |
| Endocrine and metabolic | Diabetes mellitus; insulin resistance; obesity-related metabolic dysfunction; hypothyroidism; hyperadrenocorticism | Diabetes mellitus; insulin resistance; hepatic lipidosis |
| Cardiovascular | Altered cardiovascular function; hypertension (of doubtful clinical significance); portal vein thrombosis; myocardial hypoxia | – |
| Respiratory | Decreased respiratory function (experimental) and oxygenation; increased respiratory disease; brachycephalic airway obstruction syndrome; tracheal collapse | Increased respiratory conditions; increased asthma |
| Musculoskeletal | Osteoarthritis; cruciate ligament disease; humeral condylar fractures; intervertebral disc disease; hip dysplasia | Lameness, musculoskeletal conditions |
| Oncological | Variable neoplasia risk; transitional cell carcinoma; mammary carcinoma (some but not all studies) | Neoplasia |
| Urogenital | Lower urinary tract disease (USMI, calcium oxalate urolithiasis, transitional cell carcinoma); glomerular disease (experimental); dystocia | Urinary tract conditions; lower urinary tract conditions |
| Alimentary | Pancreatitis | Oral cavity disease; gastrointestinal disease; increased risk of diarrhea |
| Integument | – | Increased risk of dermatoses, increased risk of atopic dermatitis |
| Other | Anesthesia risk; dystocia; oxidative stress; undesirable behaviors | Increased risk of allergic disease; increased risk of ophthalmologic diseases |
| Alimentary | Pancreatitis | Oral cavity disease; gastrointestinal disease; increased risk of diarrhea |

**USMI** = urethral sphincter mechanism Incompetence

cats.[48] Cats with a maximum BCS of ≤3/9 and 9/9 (between the ages of 3 and 11 years of age) had the shortest median lifespan. Thus, in cats both being underweight and marked obesity showed an impact on longevity.

### Quality of life effects

In recent studies using a validated questionnaire, health-related quality of life (QOL) was worse in dogs with both overweight and obese body condition compared with non-overweight dogs,[49,50] and many aspects of QOL improved significantly with successful weight reduction.[49] Also, there was an association between the magnitude of fat mass change and improvements in QOL, whilst dogs that ultimately failed to complete their weight loss program had a worse quality of life at the outset than those successfully losing weight.[49] The effects of obesity on QOL in cats have not yet been described; no differences in QOL in cats with obesity were identified using a health-related QOL questionnaire.[51] However, in a large international clinical study, using subjective owner assessment, suggested improvements in QOL as a result of successful weight reduction.[52]

### Musculoskeletal system

Gait analysis studies have revealed functional alterations in the gait of dogs as a result of obesity, including a shorter stride length, increased range of motion during stance, and increased ground-reaction force.[53] Epidemiological studies have also revealed associations between overweight status and orthopedic disease, including cranial cruciate ligament rupture, intervertebral disc disease, humeral condylar frac-

tures, hip dysplasia, and osteoarthritis.[2,21] Furthermore, based upon force plate analysis, weight reduction in obese dogs with osteoarthritis can lead to a substantial improvement in mobility[54] as evidenced by subjective improvements reported when dogs with obesity lose weight.[55] Although functional studies are lacking, epidemiological studies in cats revealed an association between overweight condition and musculoskeletal disorders, with cats having a BCS of 9/9 having four times the odds of cats with a BCS 5/9.[56]

### Endocrine and metabolic system

Many experimental studies have explored the impact of obesity on insulin sensitivity and glucose regulation in dogs and cats, with evidence in both species suggesting significant insulin resistance in obese animals, which improves after successful weight reduction. In a recent study of naturally occurring obesity in pet dogs, percentage body fat correlated with severity of insulin resistance, and insulin sensitivity improved significantly upon successful weight loss.[57] Other metabolic impairments have also been recognized, suggesting an obesity-related metabolic dysfunction.[58] Similar findings have also been seen in cats.[43] Further, epidemiological studies in both species have identified associations between overweight body condition and diabetes mellitus. However, the pathogenetic mechanisms are unknown and are likely to differ between species.



Cats are believed to have an insulin-resistant form of diabetes mellitus, akin to human type II diabetes mellitus. Successful weight reduction improves insulin resistance and can significantly reduce the requirement for exogenous insulin therapy, sometimes enabling a cat to enter remission.[3]



Most cases of canine diabetes mellitus are due to absolute insulin deficiency, resulting from progressive beta cell loss such that, once it has manifested itself, lifelong insulin therapy is likely to be needed.[3]

The pathogenesis of beta cell loss in dogs is poorly understood and might not be the same as in human type 1 diabetes mellitus. Putative causes include pancreatitis and autoimmune-mediated beta-cell destruction.

In dogs, but not cats, epidemiological studies have also identified associations between obesity and other endocrinopathies such as hypothyroidism and hyperadrenocorticism.[21] In both cases, it is likely that these diseases predispose to weight gain and obesity, rather than the other way around (see above). In this respect, although obesity can have marginal effects on thyroid homeostasis, the changes are not biologically significant, and are unlikely to affect the interpretation of thyroid function tests.

Experimental studies of canine obesity have also demonstrated increased plasma non-esterified fatty acid and triglyceride concentrations (increased VLDL and HDL; decreased HDL cholesterol), which are associated with insulin resistance.[3] Other studies have demonstrated hypercholesterolemia, hypertriglyceridemia, and increased circulating phospholipid concentrations. Hypercholesterolemia and hypertriglyceridemia have also been reported in clinical studies in dogs with obesity, and these changes improve with weight loss.[59] The clinical significance of these changes is not known. Feline obesity has long been known to predispose to hepatic lipidosis, and epidemiological studies have confirmed this link.[22]

### Respiratory system

Experimental studies have demonstrated that excessive body fat can adversely affect respiratory function in both dogs and cats, although the exact changes vary amongst studies. In dogs, increased airway resistance, decreased tidal volume, increased respiratory rate, increased airway reactivity, and decreased oxygenation have all been reported,[60–62] and there is a significant negative impact on performance during a 6-minute walk test.[63] In cats, there is evidence of decreased tidal volume, minute volume, and both peak inspiratory and expiratory flow.[64] Such adverse effects on function might contribute to the finding that link obesity and certain respiratory diseases, including tracheal collapse, laryngeal paralysis, and brachycephalic airway syndrome in dogs, as well as respiratory conditions and asthma in cats.[56]

### Cardiovascular system

Echocardiographic studies in dogs have suggested alterations is various parameters. In one study, dogs with obesity had increased interventricular septal widths, decreased ratios of peak early to peak late left ventricular inflow velocities and ratios of peak early to peak late mitral annular tissue velocities, as well as increased fractional shortening and ejection fraction percentages.[65] In a second study, dogs with obesity had reduced cardiac wall thickness and lower systolic function

(as indicated by a reduction in ejection fraction, fractional shortening, increased left ventricular internal diameter during systole, and left ventricular end-systolic volume) compared with dogs with a normal weight.[66] In cats, radiography suggested an increased vertebral heart score[67] and increased pericardiac fat.[68] However, echocardiographic changes were less marked in this species, with no differences being identified in one study,[68] and only the left ventricular free wall at diastole being increased in obese cats when compared with cats with an ideal body weight.[67] Mild hypertension does occur in both canine and feline patients with obesity,[67] but this has not yet been shown to be clinically relevant. Finally, obesity in dogs may be associated with portal vein thrombosis and myocardial hypoxia. Therefore, obesity appears to have only a minor effect on cardiac function in both dogs and cats. That being said, overweight status is associated with worse survival in cats[69] but not in dogs[70] with heart failure.

### Urinary system

In experimental dogs, the onset of obesity is associated with glomerular pathology and changes in function, including increases in plasma renin and insulin concentrations, mean arterial pressure, and renal plasma flow.[71] In a more recent study, a number of renal biomarkers were assessed in obese dogs and evidence of subclinical decreases in renal function, which improved after weight loss, were identified.[72] However, it is unclear as to the significance of these changes and, most importantly, whether or not it may predispose to renal disease, as has been shown in humans. Associations have also been demonstrated between obesity and lower urinary tract disease in both dogs and cats.[21,22,56] In dogs, obesity is also associated with cases of urethral sphincter mechanism incompetence.[2]

### Other disorders

Although epidemiological studies have demonstrated an association between obesity and the presence of neoplasia in both dogs and cats, such a link has not been confirmed in all studies. Other studies have examined associations with specific cancer types and although not conclusive, links have been suggested with transitional cell carcinoma and mammary carcinoma. Epidemiological studies have demonstrated associations between feline obesity and oral cavity disease, dermatological disorders, and diarrhea. However, the reasons for these associations are not known. Increased risk of both anesthetic complications or dystocia has also been suggested.[2] Furthermore, dogs with obesity had increased plasma malondialdehyde concentrations, suggesting oxidative stress.[66] Finally, in a recent owner survey, overweight status in dogs was associated with undesirable behaviors, including food guarding and stealing, barking, growling or snapping at strangers and other dogs, being fearful of the outdoors, and not returning when called by the owner.[42]

## 11.5.5 Clinical presentation

As discussed above, obesity is an insidious condition, with weight gain occurring gradually; prevalence is greatest in dogs between 6 and 9 years of age[21] and in cats between 6 and 10 years of age.[22] However, overweight status and obesity are increasingly recognized at a younger age, including in both growing animals and young adults.[16,73] Prevalence tends to decline as both cats and dogs enter the senior life stage.[21,22]

**The clinical signs** that are reported in the history and observed at the physical examination will vary with the severity of obesity as well as the presence of comorbidities. In the author's experience, it is uncommon for an owner to present a cat or dog as the primary problem of obesity. More often, such cases are identified by the veterinary professional at a routine health check. With further questioning, clinical signs potentially associated with obesity can be readily identified. Common signs related to obesity include lethargy, exercise intolerance, altered gait, increased respiratory rate and effort, and abnormal respiratory tract sounds (especially stertor, most often noted when the animal is recumbent or sleeping). An owner may also present their pet for veterinary evaluation as a result of a comorbidity, such as lameness from orthopedic disease, abdominal pain due to pancreatitis, vomiting due to pancreatitis or lipidosis, icterus from lipidosis, polydipsia and polyuria due to diabetes mellitus, coughing due to respiratory disease, or incontinence due to urethral sphincter mechanism incompetence. Changes in appetite are not a consistent finding, but some owners will report that their dog or cat is polyphagic, coprophagic, or liable to steal food and scavenge. However, it is not uncommon for owners to report that their dog has a picky appetite and will not finish the food in their bowl. This is likely to be due to the owner providing food portions significantly greater than maintenance requirements and often tempting their pet with additional palatable food.

**Most primary clinical signs of obesity** are related to the deposition of excess adipose tissue in both subcutaneous and abdominal regions, which has the effect of altering body shape. Such changes are readily apparent on physical examination and can be semi-quantitatively evaluated by

body condition scoring (BCS; ▶Chap. 11.5.7.3). However, there may also be signs of associated comorbidities. Auscultation and abdominal palpation can be challenging given excess pharyngeal, truncal, and abdominal fat deposition. However, adventitious respiratory sounds can sometimes be evident, for example, crackles and wheezes in cats with concurrent asthma and referred sounds in cases presenting with stertor. Poor skin and coat conditions are often present, especially in cats, and perineal fecal soiling can also be seen in this species because of difficulties in grooming. Abdominal palpation is often complicated, especially in dogs and cats with severe obesity, as a result of abdominal adipose tissue deposition. Finally, although it is usually possible to palpate a peripheral pulse in the femoral triangle, excess amounts of subcutaneous fat can make it harder to determine pulse strength and quality.

## 11.5.6 Differential diagnoses

Although obesity is overwhelmingly the most common reason for weight gain in dogs and cats, other reasons include alterations in fluid balance (such as intra-cavitary fluid accumulation) and the development of a large tumor, usually in the abdominal cavity. The cause can usually be differentiated from obesity on physical examination alone. In male cats, one final possibility is acromegaly, where the weight gain is the result of increases in adipose tissue, muscle mass, organomegaly, and bone density.

Once again, such cases can usually be readily distinguished from cases of simple obesity, with key characteristics including coarsened facial features and abdominal organomegaly (e.g., renomegaly) being readily identified during physical examination.

## 11.5.7 Diagnosis

The main diagnostic aims for the clinician are:

- Confirm that weight gain is due to increased adipose tissue mass, rather than weight gain for another reason (e.g., fluid, tumor, acromegaly)
- Determine the severity of obesity
- Determine risk factors and underlying causes (e.g., endocrinopathy or iatrogenic weight gain) that might have predisposed to obesity in a particular case
- Identify possible comorbidities and adverse effects on health (including quality of life), not least because a diagnosis of obesity requires more than simply determining that body condition is abnormal

Such an approach will inform the development of a tailored weight management plan, for example, in determining appropriate ideal weight and target weight, deciding upon key priorities, deciding on what alterations to the weight loss plan might be needed as a result of comorbidities, and also what other therapies might be required for such comorbidities. In patients without comorbidities, few diagnostic investigations may be needed beyond gathering a history and performing a physical examination. However, since most dogs and cats with obesity have at least one comorbidity, additional investigations are usually necessary, with the exact diagnostic approach depending upon individual circumstances.

### 11.5.7.1 History and physical examination

The first stage of diagnosis is to obtain a history and perform a physical examination. In addition to a standard medical history, a full nutritional assessment should be performed (for details, see the WSAVA nutrition guide[74]). Other details of importance include details about physical activity, environment, the family unit (pets and people), lifestyle, and neuter status. Key aspects of the physical examination include quantifying obesity (see below) and determining the possible presence of comorbidities, which might either be a cause of weight gain, a consequence of the obesity or be incidental.

### 11.5.7.2 Body weight measurement

Electronic scales should be used that are appropriate for the size of the patient, for example, large walk-on scales for medium-to-large dogs and small scales for cats and small dogs. Scales should be regularly calibrated for precision and accuracy, which can easily be accomplished by weighing an object of known weight (e.g., a bag of pet food). It is advisable to always weigh a particular animal on the same scale because this will ensure consistency. Adopting a practice policy of weighing all animals at every visit throughout life is recommended, combined with regular BCS assessment (see below). Given that most cases of obesity develop later in life, there may be a historical record of an early adult weight (i.e., 1 year for cats, 2 years for dogs), where the animal was in ideal condition. This can be used to estimate the ideal weight of the patient (▶box "Calculations") and can also be helpful in obesity prevention strategies.

### 11.5.7.3 Body condition scoring

Body condition scoring is the most widely accepted clinical method of assessing body composition in cats and dogs. The technique involves visual assessment and palpation of the patient as a means of semi-quantitatively determining body fat mass. Various systems have been suggested, including 5-, 7-, and 9-unit scales,[75,] and there are other adaptations to the method, such as the body fat index (BFI). Studies have suggested that some BCS systems (e.g., the 9-unit system) correlate well with gold-standard measures of body fat mass, such as dual-energy X-ray absorptiometry (DEXA).[75,76] Visual characteristics alone can also be used to assess BCS from photographs, which can improve the technique's versatility, although performance is inferior to conventional BCS determination.[77] Body condition scoring appears to be relatively repeatable amongst trained assessors,[75] but owner scores are less reliable, with the condition for dogs in overweight and underweight body conditions to be under-estimated and over-estimated, respectively.[40]

The existence of many different BCS systems has created inconsistency (not least in veterinary patient records), and, therefore, both WSAVA and BSAVA now recommend that the 9-point BCS scale be used.[74] With this system, scores of 6–7 and 8–9 represent overweight and obese conditions, respectively. Clinicians can also use the BCS to determine how overweight a particular dog or cat is. Using the 9-unit scale, each unit between a BCS of 5 and one of 9 correlates with ~10% of excess weight, enabling ideal weight to be estimated using a simple calculation (▶box "Calculations"). Of course, such estimates are only a guide, because the proportion of weight change associated with each BCS unit change is variable.[78] Also, in recent times, as the prevalence of obesity has increased, so too has its severity, with many cats and dogs now being classified as being beyond the scale, whereby their excess adiposity is greater than that depicted by a BCS of 9 (▶Fig. 11-24). Such individuals may be challenging to manage because their ideal weight might be over-estimated, meaning that the weight management plan devised for them is inappropriate. To the author's knowledge, there have been no attempts to date of adapting the 9-point BCS scale for beyond the scale animals. Therefore, the author's current approach is to record such animals as BCS 9+, and to consider using different methods for determining the ideal weight in these patients, for example, historical weight records, or DEXA if available (▶Chap. 11.5.7.6).

**Calculations for estimating the ideal body weight in obese cats and dogs**

In published studies, each unit on a 9-point BCS scale equals approximately 10% of excess body weight. Therefore, a simple equation can be used to estimate the ideal weight of a dog or cat from current body weight and BCS. In this example, the dog is estimated to have a BCS of 7:

Ideal weight =
(100 / [100 + (10 × {current BCS - 5})]) ×
(current weight)

This equation can be simplified into 'correction factors' for each BCS, between 6 and 9; dividing the current weight by this factor quickly produces the ideal weight as follows:

- BCS 6: divide current weight by 1.1
- BCS 7: divide current weight by 1.2
- BCS 8: divide current weight by 1.3
- BCS 9: divide current weight by 1.4.

Therefore, the ideal weight of a 42 kg dog with of BCS 7/9 can be estimated as follows:

Ideal weight = 42 ÷ 1.2 = 35 kg.

Please note that, while this is a reasonable guide, due to individual variability, this equation can both over-or under-estimate the ideal body weight.[81] If necessary, as weight loss progresses, adjustments to the estimated ideal weight may be needed.

### 11.5.7.4 Muscle condition scoring

Most clinicians use BCS systems to assess adiposity, but it should be noted that these systems also involve assessments of body components such as muscle mass on a limited basis. In this respect, category descriptions for BCS 1/9 and 2/9 also include a reduction in muscle mass. Despite this, it is advisable to assess muscle condition separately, using a muscle condition score (MCS), since animals with obesity might have a reduced muscle mass, which is obscured by the increase in fat mass. A 4-unit scale is most-commonly recommended.[79]


a


b


c


d


e


f

**Fig. 11-24** Examples of dogs and cats with severe obesity, with characteristics beyond the scale depicted by the 9-unit body condition score scale

**a** Eight-year-old neutered female domestic shorthair cat, weighing 9.8 kg and 49% body fat, as determined by dual-energy X-ray absorptiometry. Estimated ideal weight was estimated to be 4.5 kg, meaning that current weight was ~120% above ideal weight.

**b** Ten-year-old neutered male chihuahua, weighing 15.4 kg and 63% body fat, as determined by dual-energy X-ray absorptiometry. Estimated ideal weight was 5.3 kg, meaning that current weight was ~190% above ideal weight.

**c** Seven-year-old neutered male domestic shorthair cat, weighing 10.5 kg and 55% body fat, as determined by dual-energy X-ray absorptiometry. Estimated ideal weight was 4.5 kg, meaning that current weight was estimated to be ~130% above ideal weight.

**d** Three-year-old neutered female Labrador retriever, weighing 59.8 kg and 52% body fat, as determined by dual-energy X-ray absorptiometry. Estimated ideal weight was 33.0 kg, meaning that current weight was estimated to be ~80% above ideal weight.

**e** Eight-year-old neutered male Siberian husky, weighing 73.9 kg. Its ideal weight was estimated to be 30.0 kg, based on historical medical records, where a previous adult weight was available. Therefore, the dog was estimated to be ~140% above ideal weight.

**f** Three-year-old neutered male Norfolk terrier, weighing 18.0 kg and 60% body fat, as determined by dual-energy X-ray absorptiometry. Estimated ideal weight was 7.7 kg, meaning that current weight was estimated to be ~130% above ideal weight.

(Courtesy of the Royal Canin Weight Management Clinic, University of Liverpool, UK.)

#### 11.5.7.5 Zoometry

Zoometry involves taking dimensional measurements of an animal, usually with a tape measure; some measurements correlate with stature (e.g., head, thorax, and limb length), whilst others better correlate with fat mass (e.g., body weight and body [thorax, abdomen, or neck] circumference) and, together, they can be used to estimate weight status. One example is the Hill's Healthy Weight Protocol (https://www.hillsvet.co.uk/tools/healthy-weight-protocol), which utilizes a combination of four (dogs) or six (cats) zoometric measurements. Although such approaches correlate well with DEXA measurements of body fat mass, equivalent to that of BCS assessment, they are somewhat cumbersome, taking time to complete. This limits their practical application. Furthermore, each measurement can be prone to errors, not least in small patients, leading to imprecision, especially when a different investigator scores the same patient.

#### 11.5.7.6 Advanced body composition measurement

Dual-energy X-ray absorptiometry (DEXA) is said to be the most precise and reliable non-invasive method of assessing body composition and has been used extensively in research studies. Its use has also been described in a referral setting (▶Fig. 11-25), where it can be used to assess the degree of adiposity, calculate ideal body weight, and monitor the weight reduction process, for example, by determining the proportionate loss of fat and lean mass.[80,81] Whilst DEXA provides clear advantages, it is not essential for successful weight management. However, this method should be considered for challenging cases, for example, those patients with severe obesity where the BCS is beyond the scale.

Other imaging techniques can also be used to determine body fat mass, including computed tomography and magnetic resonance imaging. These techniques have also been used in scientific research[82] and have the added advantage over DEXA of being able to determine regional body fat mass. However, the advantage of assessing regional body fat mass, in addition to total body fat mass, has not yet been confirmed in dogs and cats with obesity. Both CT and MRI are widely available in referral settings, but in patients with obesity, these techniques are usually used to diagnose comorbidities rather than assess body composition in clinical cases. Finally, another method of assessment of body composition is an assessment of total body water using isotopes, but these modalities are only widely used in research and not typically in clinical cases.

#### 11.5.7.7 Bioimpedance

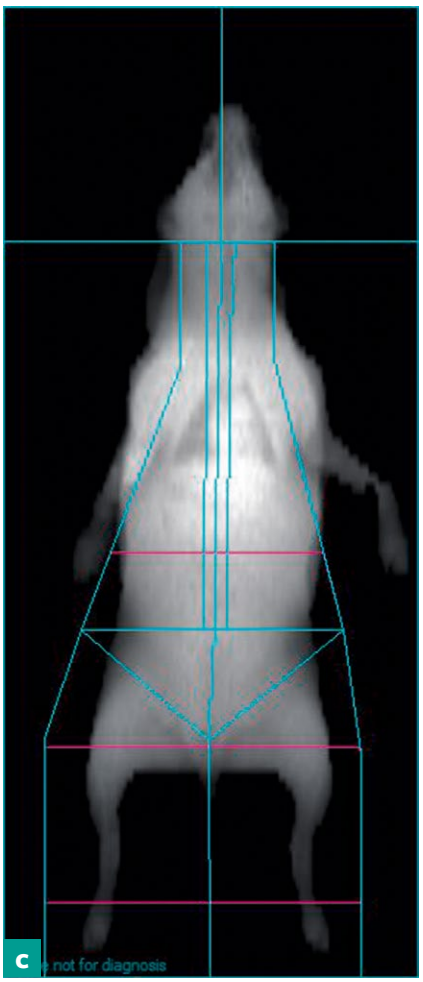
Bioimpedance can be measured non-invasively using handheld units. Unfortunately, such instruments are unreliable and inferior to the use of BCS systems.[83]

#### 11.5.7.8 Photography

Photography can also be used to assess weight loss subjectively, most commonly to highlight success to owners. Photographs should be taken from many angles while standing (i.e., dorsal, lateral, face/chest views, ▶Fig. 11-26). Standardization of lighting, posture, and position is important in order to showcase changes in body shape. Photographs can provide a subjective means of demonstrating long-term changes in body weight to clients (▶Fig. 11-26). As mentioned above, it is possible to determine body condition from photographs, although this is less reliable than using conventional BCS estimation.[77]







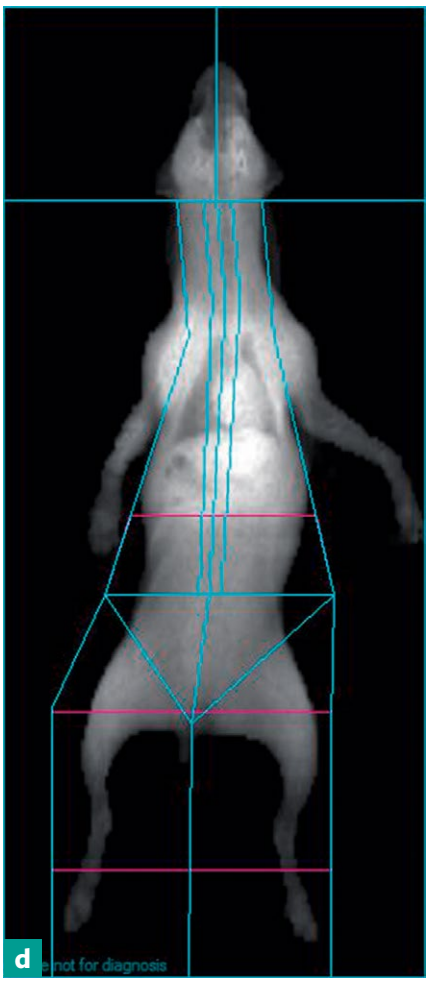




**Fig. 11-25** Dual-energy X-ray absorptiometry (DEXA) as a non-invasive modality for determining body composition

**a** Fan-beam DEXA machine

**b** The associated computer for conducting the analysis

**c** Pre-weight-loss DEXA scan performed on the dog featured in ▶Fig. 11-26; body fat mass was estimated to be 51%.

**d** Post-weight-loss DEXA scan, from the same dog featured in **c** and ▶Fig. 11-26, demonstrating that body fat mass had declined to 36%. Based on the DEXA figures, the estimated composition of the body tissue lost was 83% fat and 17% lean.

(Courtesy of the Royal Canin Weight Management Clinic, University of Liverpool, UK.)

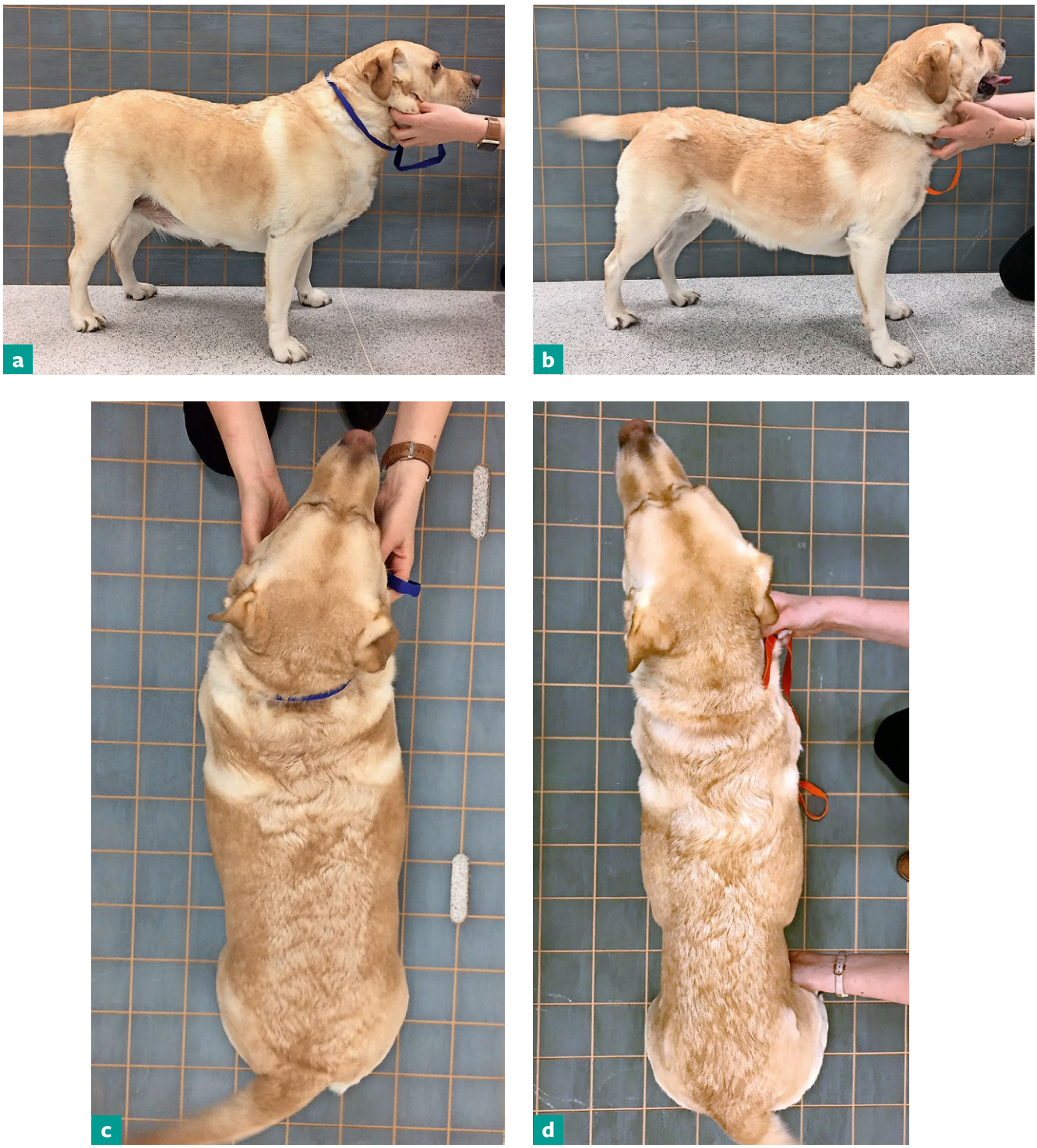



**Fig. 11-26** 5-year-old neutered female Labrador retriever with obesity

**a** and **b** show photographs of the dog with obesity, weighing 49.0 kg (108.0 lb.), and with a body condition score of 9/9.

**c** and **d** show photographs of the same dog, after successful weight loss on a high protein high fiber diet (after 268 days). The body weight had decreased to 33.6 kg (74.1 lb.), and body condition score was estimated to be 5/9. Total weight lost was 31% of the starting body weight, at an approximate rate of 0.8% per week.

(Courtesy of the Royal Canin Weight Management Clinic, University of Liverpool, UK.)

#### 11.5.7.9 Growth charts

BCS systems have not been validated for puppies or kittens. Thus, regular weight measurements are the best way of monitoring weight gain during growth, with reference to evidence-based growth standards.[84] Such standards confirm whether the rate of weight gain is appropriate or excessive, enabling corrective measures to be implemented.[26]

#### 11.5.7.10 Further investigations

In some patients, further investigations are needed, with the main rationale being to determine the overall state of health before starting weight management. Most common tests include hematology, clinical chemistry, and urinalysis, providing general information on health. These investigations are not routinely required and are most often used in older animals, where there is a pre-existing comorbidity or such a comorbidity is suspected based on history and physical examination. Depending upon the patient and how it is presented, additional investigations might be needed, such as blood pressure measurement, assessment of thyroid and/or adrenal gland function in dogs, fructosamine measurement for diabetes mellitus, and diagnostic imaging (e.g., radiography, ultrasonography, and advanced imaging, as required).

### 11.5.8 Management

For people, bariatric surgery is by far the most effective treatment for obesity, leading to significant weight reduction.[85] However, to the author's knowledge, such procedures have not yet been used clinically in dogs or cats and can thus not be considered.[86] Next most effective in humans is drug therapy, with such drugs including orlistat, phentermine/topiramate, lorcaserin, naltrexone/bupropion, and liraglutide.[87] Of all pharmaceuticals, semaglutide appears to be the most promising. In a recent randomized controlled trial, a once-weekly subcutaneous injection of 2.4 mg semaglutide resulted in an average weight loss of 15% of the starting body weight (SBW) over a period of 68 weeks.[88] The main side effects of semaglutide were nausea and diarrhea, but these were mild and subsided with time.[88] This drug has also shown promise in post-weight-reduction maintenance.[89]

As far as the author is aware, none of these drugs have yet been used in dogs or cats. In terms of licensed pharmaceuticals, two drugs (mitratapide and dirlotapide) were previously licensed for dogs but not cats.[90] Both were microsomal triglyceride transfer protein (MTP) inhibitors, exerting a local effect on enterocytes, blocking the assembly and release of lipoprotein particles into the bloodstream, and thereby reducing energy intake.[90] Although there was reasonable evidence of efficacy in clinical trials,[91] results were more disappointing in clinical practice, and they were not widely used. To the author's knowledge, these drugs are no longer available. Thus, in the absence of viable alternatives, most current weight management strategies involve a combination of dietary therapy and physical activity, as detailed below.

Weight management involves two phases: weight reduction and weight maintenance. The aim of the weight reduction phase is for the animal to lose weight in a controlled fashion, with the aim of reaching a pre-determined target weight. This can take a variable length of time, typically 6–18 months, but occasionally longer; in some cases, it may take over 2 years for the weight reduction phase to be completed. Thereafter, animals enter the maintenance phase, where the animal's weight is first stabilized and then controlled in order to ensure that weight regain does not occur.

#### 11.5.8.1 Weight reduction phase

At the outset, a weight reduction protocol should be established, which is tailored to the individual. In setting such a plan, it is important to determine both the ideal weight and the target weight. Although often used interchangeably, these terms are not the same. The **ideal weight** is defined as a weight at which the patient's body fat mass is within the range determined to be optimal[92] and is used to set the initial caloric intake (see below). It can be estimated in various ways, including reviewing historical weight records, to identify a previous weight (typically in early adulthood) where the patient was in optimal condition (e.g., recorded at the same time as a BCS of 4/9 or 5/9). If such a weight is not available, an alternative approach is to determine the ideal weight from the current weight and BCS (▶Tab. 11-10).[52] In this regard, each unit on the scale between 5/9 and 9/9 approximately corresponds to 10–15% of excess weight. Therefore, with a simple calculation, the ideal weight can be estimated (▶box "Calculations"; ▶Chap. 11.5.7.3).

The **target weight** is defined as the weight that the clinician determines to be an appropriate endpoint for the weight reduction phase, usually determined with reference to several factors, including age, comorbidities, and the expected benefits of weight reduction. For some animals (e.g., young adults or those without comorbidities), the target weight and ideal weight may be the same. In other cases (typically older animals and those with comorbidities), the target weight might deliberately be greater than the ideal weight. Such cases will still be in overweight body condition at the end of the weight reduction phase (partial weight reduction).

**Expected benefits** of complete weight reduction, aiming for the ideal weight as the target, is that the greatest beneficial effects on disease prevention and lifespan extension might be expected. However, lifespan effects are likely to diminish as animals age, and the benefits of disease prevention are less relevant in individuals with pre-existing comorbidities. Instead, partial weight reduction might be more appropriate, where the main aim of weight management is to improve the quality of life rather than simply to return a dog or cat to its ideal weight. In this regard, previous studies have revealed that improved mobility[54] and quality of life[52,55] are seen with a modest weight reduction. Partial weight reduction is quicker and, arguably, more appropriate in older animals, especially those with concurrent disease. In humans, an obesity paradox has been identified, whereby an increased BMI is associated with longer survival for patients with some diseases. Examples of a similar obesity paradox have also been seen in animals with chronic kidney disease and cardiac disease, with a recent study demonstrating longer survival times in overweight cats. In such cases, only a modest weight reduction of ~10% would be recommended while aiming to maintain the patient within its overweight range. Such a weight loss protocol will not lead to significant loss of lean tissue but can improve the quality of life.

**The recommended rate of weight loss** is controversial. Historically, and still believed by many today, a rate of loss of 1–2% SBW per week has been recommended. However, such recommendations were based on weight reduction studies undertaken in dogs from research colonies after having gained weight through overfeeding. Such a rate of weight loss is unrealistic for most client-owned dogs and cats. An average rate of loss of 1% SBW per week can often be achieved at the beginning (i.e., first 1–3 months) of the weight reduction phase, with the rate slowing dramatically after that, making it increasingly difficult to maintain this rate over the long term.[4] Instead, an average rate of weight loss of 0.5–1.0% per week is more realistic and appears to be safe.[80,81,93] Whilst uncommon, overly rapid rates of weight loss (>2% per week) are not recommended since there is a potential for complications, such as excessive lean tissue loss.[2] Slower rates of weight loss (<0.5% per week) are also acceptable and maybe more realistic, provided that the inevitably longer duration does not become a source of frustration for the owners.

#### 11.5.8.1.1 Dietary management

##### Diet formulation

Purpose-formulated therapeutic diets are recommended, which usually have a reduced energy density, with the amount of protein (amino acid), and micronutrients increased relative to their energy content. This helps to reduce the risk of nutrient deficiencies as a result of the food restriction that is required for weight reduction.[59,94,95] Supplementing protein, relative to the energy content, helps to minimize the loss of lean tissue mass,[96] an effect that has also been demonstrated with the addition of L-carnitine.[97] Supplementing protein or dietary fiber can improve satiety, with the greatest effect in dogs resulting from supplementing both protein and fiber.[98] There is also some evidence that such a diet can improve the outcome of weight management by speeding up the overall rate, increasing the likelihood of reaching the target weight, and preserving lean tissue.[99]



Cats are more complicated, not least because protein intake does improve satiety and, instead, voluntary food intake is greater when cats are fed diets with an increased protein content.[100] Added to this, there are limits on how much fiber cats will tolerate, because incorporating too much can make a diet unpalatable. Therefore, for cats, the optimal effect on satiety is met when fiber and protein are moderately, rather than markedly, supplemented.

Another consideration is whether to feed wet food, dry food, or a combination of both. Wet food is less energy dense than dry food and, as a result, the owner can feed a greater volume for the same energy allocation. Adding additional water can decrease energy intake further[101] and is associated with increased physical activity in some [102] but not all[103] studies. Although this suggests that wet foods will perform better than dry foods for weight loss, this is not supported by published evidence. In dogs, the odds of reaching the target weight during weight reduction were greater when the animal was fed dry therapeutic foods exclusively, compared with feeding either wet therapeutic foods or a mix of wet and dry foods.[93] In cats, different therapeutic diet types are not associated with a difference in odds of reaching the target weight.[104] Other factors are also important in choosing the diet type, including cost, the preferences of the individual animal, and versatility in how it is fed. For example, dry food is much

easier to be fed using a puzzle feeder. Therefore, the author recommends that veterinarians decide on the type of therapeutic food to be fed after a discussion with the owner, taking into account all factors.

### Calculating starting food allocation for the weight reduction phase

Various methods can be used to determine the starting energy intake to feed to ensure controlled weight reduction, with the amount of food given depending on the energy density of the diet. One suggested approach is to calculate resting energy requirements (RER) from the **current body weight** (i.e., for dogs: RER = 70 kcals × [BW]$^{0.75}$ per day) and then feed 80% of this amount. This is simple but may also be problematic because it does not consider the degree of obesity or sex or neuter status, all of which are known to affect outcomes (especially in dogs). As a result, the initial response is likely to be more variable, with the need to adjust portions at the outset.

The preferred approach of the author is slightly more complicated but has the benefit of better tailoring the starting intake to the individual and improving the chances that the animal will lose weight from the outset. Such early success can increase owner compliance with the overall weight reduction regimen. With the author's preferred approach for calculating the starting energy intake, the ideal weight is first calculated (as discussed above); the animal is then fed a proportion of their metabolizable energy requirement for maintenance (MER), according to their species, sex, and neuter status.[52,55,105] In this respect, the starting energy intake:

- For all cats (male and female, neutered or sexually intact) is either 35–50 kcal per kg IBW or 53 kcal per kg$^{0.711}$ IBW per day
- For sexually-intact male dogs it is 80 kcal per kg$^{0.75}$ IBW per day
- For neutered male and sexually-intact female dogs it is 70 kcal per kg $^{0.75}$ IBW per day
- For neutered female cats it is 60 kcal per kg$^{0.75}$ IBW per day

Further adjustments are made based on individual circumstances, for example, comorbidities (especially orthopedic disease), which typically require a further reduction of ~10% (e.g., a neutered male dog would be started at 55 kcal per kg$^{0.75}$ rather than 60 kcal per kg$^{0.75}$).

The daily food allocation should be offered in two, or if possible, more meals per day, and some of the daily allocation should be reserved for treats. It is also prudent to feed a greater proportion of the daily intake at times when the owner is with the pet (since this is when begging is most likely to occur).

### Accurately measuring food portions

Whatever the method of determining food intake, it is critical to measure daily food allocations accurately, since only this will enable the food offered to be tracked and to ensure that overfeeding does not arise. Measuring cups should not be used for this, because they are imprecise and tend to result in overfeeding.[106] Instead, the author's preference is to use electronic kitchen scales to weigh out food portions. This makes it possible to accurately track the exact amount of food offered, as well as facilitating precise adjustments during the weight management process, as described above.

### Limiting treats and extras

The main sources of extra food intake are scavenging and owners feeding additional food, such as table scraps or treats, although some cats will also hunt. Ideally, consumption of additional food should be limited and regulated during weight management. Some veterinarians recommend limiting additional food to ~10% of MER, if the dog or cat is on a complete and balanced diet, because most commercial foods have a built-in safety factor (in that essential nutrients are present above minimum requirements). By following the 10%-rule, essential nutrient needs should still be met. However, arguably, such a rule is not appropriate for the weight-reduction phase because the food intake of animals is significantly less than MER, and many nutrients are potentially at risk of deficiency.[94,95] Instead, the author recommends limiting intake from extra food to 5% of the daily energy intake, but less if possible. Of course, if a dry therapeutic diet is used, some of the daily intakes can be used as treats or in puzzle feeders. An alternative is to use low-energy treats, with cooked zucchini being the author's favorite, given its low energy density. There is also the added benefit of providing water, which might have additional benefits for weight management, as discussed above.

### Puzzle feeders

A commonly faced challenge during weight management is that caloric restriction can create hunger, which manifests as food-seeking behavior. Owners can find it challenging to resist giving in to such requests. One solution is to give food portions using an interactive feeding device, either a puzzle feeder or a modified feeding bowl. Such devices have the effect of slowing food intake and, thereby, improving satiety whilst, at the same time, providing mental stimulation. Using such devices is a considerable source of enjoyment for dogs, especially given the fact that dogs (like many animals) are contra-freeloaders, in that, given the choice, will choose to work for food rather than to have it offered freely.[107] These devices have the effect of slowing food intake, thereby improving satiety.

### Adjusting food allocation during weight reduction

For most dogs and cats, feeding the initial food allocation will enable weight loss to occur, for the first week of the process at least. However, as discussed above, it is not uncommon for the rate of weight loss to slow,[4] and adjustments to the amount of food fed will have to be made. Typically, small adjustments (of up to 5%) are made on each occasion. It is easier to make small adjustments to dry food than wet food, especially if an electronic scale is used for measuring food portions.

#### 11.5.8.1.2 Physical activity

Physical activity is commonly incorporated into a weight management protocol. The exact recommendation should be tailored to the individual and take account of any concurrent medical concerns. Suitable exercise strategies in dogs include lead walking, swimming, hydrotherapy, treadmills, and play sessions. Daily (or more frequent) exercise should be included in the weight loss plan and, if possible, sessions should last at least 30 minutes.[35] Cats can be encouraged to increase their activity through regular play sessions with cat toys (e.g., fishing rod toys), motorized units, or puzzle feeders. Short periods of play activity are most used, with the author's preference to be to start with 1–2 minutes at a time, two or more times per day, and build from there.

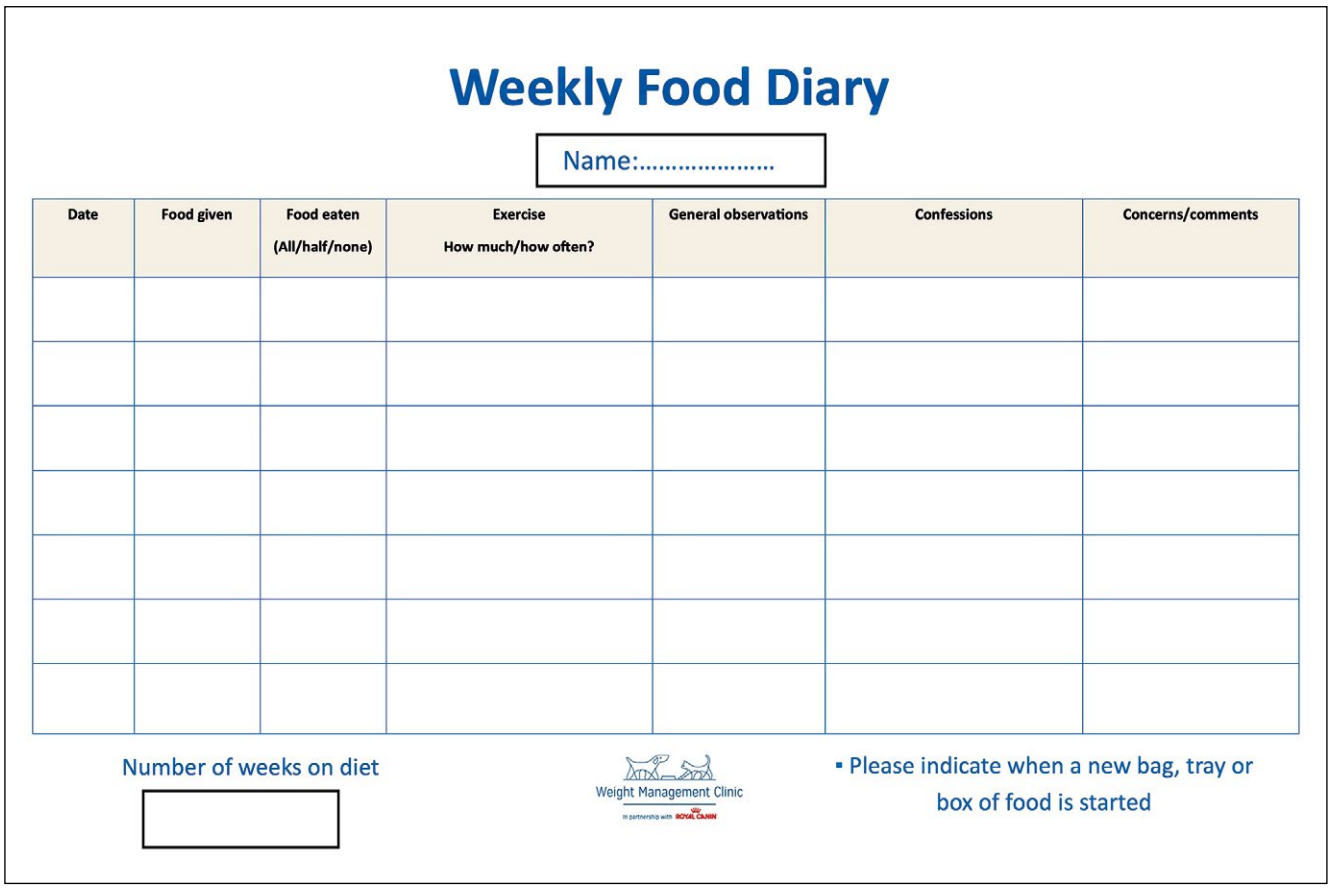
The impact of physical activity on weight loss during weight management is minimal. For example, in a randomized controlled trial, physical activity was less effective than caloric restriction using a therapeutic diet and did not lead to significant weight loss over a period of 7 weeks.[108] Despite that, there are other benefits of physical activity, so its inclusion is strongly recommended. One recent study showed that dogs that only underwent dietary management without exercise lost lean tissue during their weight loss period, while no significant change in lean tissue mass occurred when dogs undertook three underwater treadmill sessions per week in addition to the dietary management.[109] Such an intensive hydrotherapy plan is likely to be difficult for an owner to maintain, not least for the for whole weight reduction phase, which for dogs at the author's clinic, last for a median of about 10 months (see below). Instead, a practical approach for dogs would be to increase the current amount of daily physical activity by 25–33%, if this can be implemented by the owner.

Other suggested benefits of incorporating physical activity into a weight reduction program include improved wellbeing, for both the animal and the owner, not least because it is seen as a positive reward and can be used as an alternative to giving food-based rewards.

#### 11.5.8.1.3 Monitoring the weight reduction phase

It is recommended that veterinary professionals monitoring the weight reduction phase by conducting weight checks at regular intervals. It is usually best for one member of the practice team to take responsibility for monitoring each case. That way, they can get to know the client and build a trusting relationship, improving the likelihood of success. Given that some clients require intensive support throughout the program, it is advisable for staff to be trained in owner counseling.

Initially, checks every 2 weeks are recommended since such an interval should be sufficient for demonstrable weight loss to have occurred but not been too long that owner motivation weans. During the early stage, owners are becoming accustomed to the changes that have been made and might be struggling to maintain motivation. Owners can be counseled, and problems with the program can be addressed. Body weight should be measured at every check, and adjustments to the plan be made if the rate of weight loss is either too quick or too slow. Periodically, it can be sensible to also score body condition and, if desired, perform zoometry (e.g., thoracic and abdominal circumference). On occasion, repeat photographs can help to illustrate changes in body shape as weight loss has progressed. The author also recommends maintaining a diary to record progress (▶ Fig. 11-27) since there is some evidence in human studies that this helps with compliance.[110] Information from the diary can help to identify



Weekly Food Diary

Name:.....

| Date | Food given | Food eaten (All/half/none) | Exercise How much/how often? | General observations | Confessions | Concerns/comments |
|---|---|---|---|---|---|---|
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |

Number of weeks on diet

Weight Management Clinic

▪ Please indicate when a new bag, tray or box of food is started

**Fig. 11-27** Example of a diary to record progress with weight management in dogs and cats with obesity (Courtesy of the Royal Canin Weight Management Clinic, University of Liverpool, UK.)

reasons for the lack of progress (e.g., if the owner has fed additional food or the exercise pattern has changed). The weight reduction phase can take a considerable length of time in many cases, and it can be impractical to ask owners to visit the clinic every 2 weeks. For cases that lose weight consistently, the interval between checks can be extended, but, preferably, it should not be greater than every 4 weeks. However, this is not sensible if progress is slow or if progress with weight loss keeps slowing. Another issue with regular weight checks is the inconvenience of attending the clinic, which can be difficult for clients, particularly owners of cats who are reluctant to travel. Options are available for remote monitoring in these cases by phone call and/or video chat. Owners of cats and small dogs can also readily weight them at home, either using a bathroom scale or a luggage scale and a pet carrier (▶ Fig. 11-28).

#### 11.5.8.2 Maintenance phase

The weight reduction phase ends either when the target weight has been reached or if the owner has had difficulty making progress and does not wish to continue. At the start of the maintenance phase, food intake is gradually increased (typically in increments of up to 5%), and the animal is reweighed every 2 weeks until the body weight stabilizes. From that point on, the interval between weight checks can be gradually extended but should not be discontinued altogether. The author's preference is for animals to continue to be weighed at least every 3 months, if possible. The reason why this is so critical is that weight regain occurs commonly, with approximately half of the animals regaining weight after reaching the target weight.[111,112] This might be because MER after weight reduction is less than the reported MER for pet dogs and cats.[92,113]

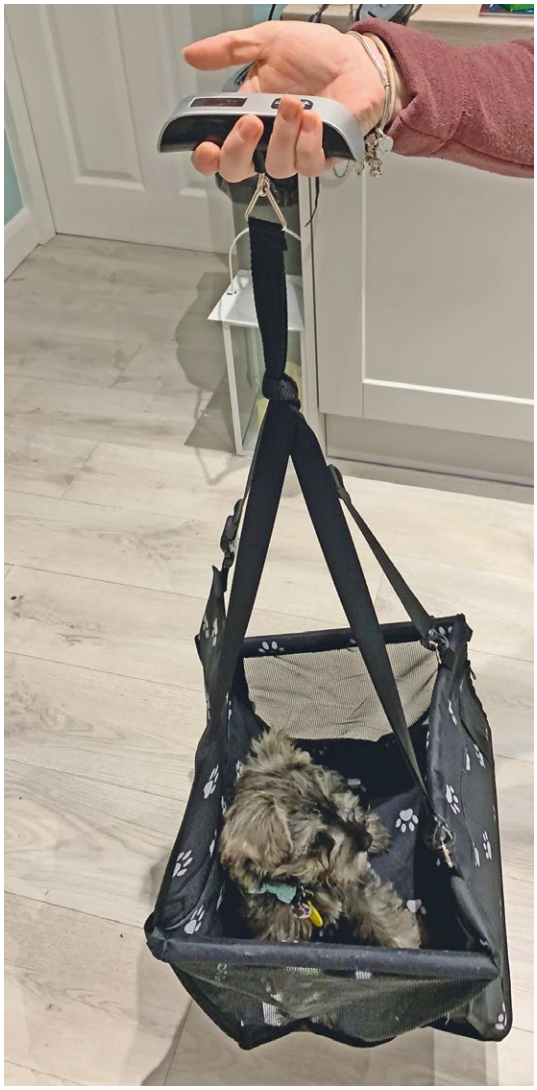


**Fig. 11-28** Use of pet carrier and luggage scales to monitor the progress with weight management at home

A key variable associated with regaining weight is the type of food selected for the maintenance phase.[111] The odds for regaining weight is twenty times less in dogs that remain on the same (therapeutic) diet that was used for the weight reduction phase than when a different diet is used. Thus, owners should be strongly encouraged to continue to feed the weight management diet, albeit at an amount to maintain weight rather than one to achieve further weight loss.

Age is an important variable, with the odds of regaining weight being greater in cats <9 years of age.[112] As a result, close monitoring is recommended for younger cats. Although the reason for older cats being less at risk of regaining weight is not known, it is probably the result of the development of chronic diseases, many of which can lead to insidious loss of weight and body condition.

### 11.5.8.3 Outcomes of weight management

The outcomes of weight management for cats and dogs with obesity have been examined in various studies,[80,81,99] although these can be misleading because many studies only comprise short term weight loss programs (mostly 12 weeks or less). Relatively few studies have examined a complete weight reduction plan (e.g., long enough to return the animal to their ideal body weight). In a recent study, of animals successfully completing and reaching ideal weight, the average weight lost was 18% in dogs and 27% in cats.[80,81] This took an average of 177 and 280 days, at an average rate of loss of 0.9% and 0.8% per week, in dogs and cats, respectively.[80,81] However, these figures are misleading because the study only included dogs that completed their program. In further studies,[93,104] variables associated with failure to reach the target weight included the severity of obesity and the rate of weight loss, with the odds of completion being less in dogs with greater body fat mass and those that lose weight more slowly. These findings are consistent with other research that has highlighted that weight loss becomes increasingly challenging the longer an animal is on their weight loss program.[4] As mentioned above the type of diet may also play a role. Recent work has also suggested that outcomes change over time during weight reduction. During the initial stages (e.g., first 2–3 months), both dogs and cats typically lose weight at ~1% per week. However, beyond that time, weight loss slows dramatically such that, after 12 months, rates of weight loss are usually <0.3% per week. This occurs despite reductions in daily energy intake by 10–20%.[4] Such slowing of progress can be frustrating to owners and, perhaps, explains why compliance, which is good in the first 2–3 months (typically >80% for pet owners of both species) worsens gradually as time passes.[4] Beyond the weight reduction phase, outcomes of weight maintenance are also important and, as mentioned above weight regain is common, affecting 48% of dogs and

46% of cats.[111,112] In dogs, the magnitude of rebound is typically less severe than in humans, with approximately 10% of dogs regaining over 50% of the weight they originally lost.[111] Cats are intermediate, with approximately 1/3 regaining over 50% of the weight they had lost.[112]

**CLINICAL PEARLS**

In the author's opinion, veterinary professionals should focus less on the mechanics of a weight management program (i.e., calculating energy intake, rate of weight loss, ideal weight), and more on the overall point of the process to improve quality of life. As described above, obesity impacts health and wellbeing in many ways by predisposing to comorbidities[21,22] and by reducing lifespan.[45] Therefore, one should focus on whether the animal is happier, has improved function, and whether the impact of comorbidities is lessened (e.g., lameness, diabetes mellitus, respiratory diseases).

There is now good evidence that successful weight reduction improves respiratory function,[62] insulin sensitivity, other metabolic derangements,[3] and overall quality of life.[49,52,55] Most strikingly, force-plate analyses have demonstrated that mobility benefits begin very quickly during the weight loss process, e.g., after 6–9% of body weight have been lost.[54] Studies in primary care practice across many geographic locations have demonstrated that such outcomes are possible, in most dogs and cats, over a period of 12 weeks.[52,55]

### 11.5.9 Prevention of obesity

Given the variable outcome of weight management, as detailed above, prevention of obesity is likely to have a more significant beneficial effect on the health and welfare of all dogs and cats rather than treating the problem once it has developed. The medical profession defines three forms of disease prevention:

- **Primary prevention:** Preventing disease before it develops by avoiding risk factors, modifying unhealthy behaviors, and increasing resistance to disease
- **Secondary prevention:** Reducing the impact of a disease or injury that has already occurred by early detection and intervention
- **Tertiary prevention:** Lessening the impact of an ongoing disease with long-term effects by managing functional impairments, improving quality of life, and increasing life expectancy

Preventing obesity is more challenging than it may appear, not least because the problem develops insidiously, such that it is often missed until it is too late. A lifelong strategy is required, starting early in life and continuing to senior years.

#### 11.5.9.1 Primary prevention strategies

Early-life care is the priority by identifying at-risk individuals early, providing education to pet owners on responsible pet care, and intervening if problems are identified. Risk factors that should alert veterinarians to starting an obesity prevention plan include breed, neuter status (which is under veterinary control), and family factors (e.g., having other family pets with obesity). Most important, however, is the growth pattern, not least because studies both in humans[24] and companion animals[25,26] have shown that these, especially rapid growth and being heavy for a certain age, are associated with a future risk of obesity. Therefore, regular monitoring of body weight throughout growth is strongly recommended, and evidence-based growth charts have recently become available for dogs and cats (https://www.waltham.com/resources/puppy-growth-charts).[26,84] Such charts can be used to record the body weight from initial visits (first and second vaccination), throughout the growth period (at least monthly until 6 months of age, and then at least every 3 months, with additional checks around the point of neutering). To improve compliance, these checks should be coordinated with other preventive medicine visits e.g., deworming, neutering, microchipping, and others. If an animal is being identified as growing too rapidly, the owner can be advised to adjust the feeding plan while the growth trajectory continues to be followed. Once the animal reaches early adult life and is known to be at a healthy weight (verified by performing a BCS assessment), this **early adult weight** should be recorded in the notes and used as a goal weight for the animal to maintain during its adult years.

#### 11.5.9.2 Secondary prevention strategies

Secondary prevention can be challenging because inappropriate weight gain develops insidiously during the adult years, and the early adult years are a particular period of risk. Therefore, veterinary professionals must be proactive in monitoring body weight and body condition throughout life in order to identify unwanted weight gain quickly and correct it. Ideally, veterinarians should record body weight routinely at least twice a year, as well as at any non-routine consultation, and compare this with the **early adult weight record** in the patient's records. Advice on the management

should be given whenever the current body weight deviates more than 5% from the early adult weight.

#### 11.5.9.3 Tertiary prevention strategies

Tertiary prevention is used when an animal already has obesity, and management should follow the above strategies. The author recommends adopting a prevention philosophy, focusing on lessening the effect of comorbidities, improving function, and improving the quality of life, rather than focusing on the numerics of weight loss itself.

**KEY FACTS**

- Obesity is a chronic disease, which is highly prevalent in dogs and cats, and can be difficult to manage, with many individuals either failing to lose weight successfully, or regaining weight after initial weight loss.
- Obesity can have an adverse impact on both health and wellbeing, including increased risk of developing comorbidities, decreased function, decreased quality of life, and decreased lifespan.
- Management of obesity most-commonly involves caloric restriction using a therapeutic diet and increasing physical activity with two phases to the process: weight reduction and subsequent weight maintenance.
- Prevention of obesity is arguably more important than managing it once it has developed and should be started early in life to maximize success; frequent monitoring of body weight, including during the growth phase is critical to this.

**References**

The complete list of references for this chapter can be downloaded from vetline.de:
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