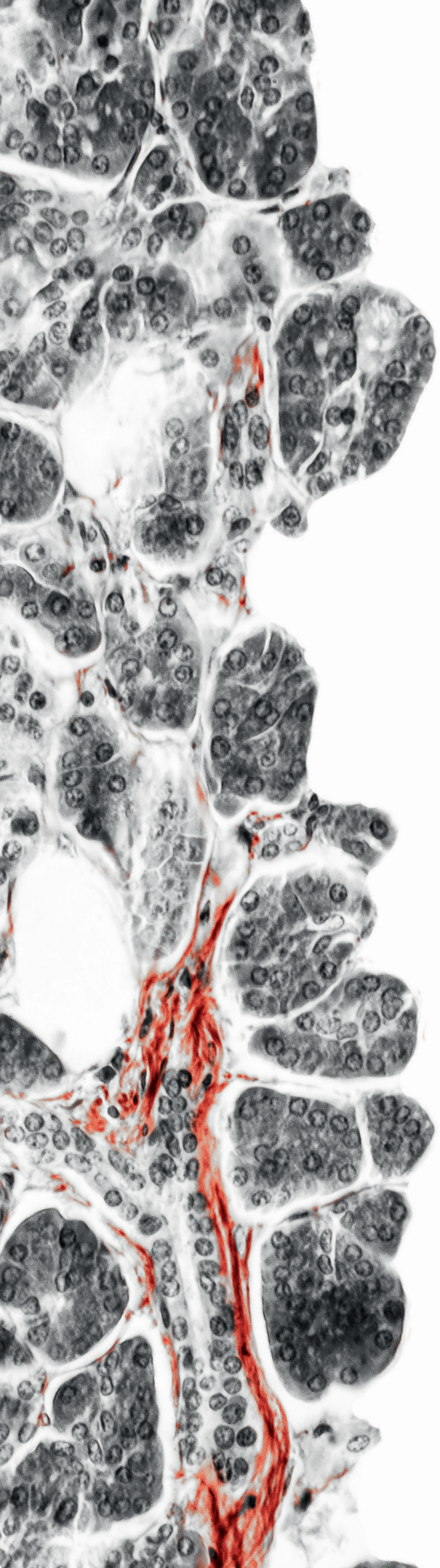

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IT IS WHAT WE KNOW ALREADY THAT OFTEN PREVENTS US FROM LEARNING

"Science and opinion; the former begets knowledge, the latter ignorance" – Hippocrates

It is a sobering thought that two of the body's most critical organs – the liver and pancreas – were shrouded in mystery and legend for so long. Although the pancreas was apparently first identified more than 2,000 years ago, its function was obscure; Galen, the Greek physician, claimed it simply to be a "cushion for the stomach". Similarly, many in the ancient world believed the liver was the seat of the "darkest emotions" although Galen offered an alternative theory, claiming that the stomach was surrounded by the liver in order to be warmed, and that this in turn would warm the food!

Gradually, order and science discarded such fanciful notions, and more prosaic work allowed the mysteries to be explained. Claude Bernard, a 19th C physiologist, first revealed some of the vital functions performed by the liver and pancreas. Although he courted controversy with his research methods, he made important contributions to medical science. Amongst other achievements, he showed that pancreatic secretions were vitally important for digestion, and he contributed to the understanding of glycogenesis in the liver. A fastidious scientist, he once declared "It is what we know already that often prevents us from learning" – an observation which presumably resulted from his unwillingness to accept conventional wisdom and pursue deeper knowledge, and which still speaks to us today. We may, for example, be content with our understanding of liver and pancreatic diseases, but we must be prepared to verify what we think to be correct, and seek the latest knowledge – which is what we strive for in this issue of *Veterinary Focus*.

Ewan McNEILL
Editor-in-chief

• **Focus on** *Veterinary Focus*

Chronic hepatitis is a not-infrequent problem in dogs and can have an insidious onset; **many cases are initially subclinical,** with the disease picked up on routine blood screening, and a suspect diagnosis should be pursued at this stage.

p02

Exocrine pancreatic insufficiency is commonly seen in dogs, yet it is often underdiagnosed, not helped by the fact that the clinical signs can be non-specific, concomitant disease may also be present, and laboratory results can be difficult to interpret.

p26

p38

Successful treatment of feline diabetes requires a holistic approach, and particular emphasis must be placed on the feeding regime, along with attention to the cat's lifestyle.

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ROYAL CANIN

DIAGNOSIS AND TREATMENT OF CANINE CHRONIC HEPATITIS

Chronic hepatitis is a common disease in dogs but can often go undetected, especially in the early stages; Cynthia Webster presents an overview of the disease, with an emphasis on the diagnostic and treatment options.

KEY POINTS

1. An accurate diagnosis of chronic hepatitis (CH) requires pathologic evaluation of multiple hepatic biopsies – preferably obtained by laparoscopy – from different liver lobes.
2. All liver biopsy specimens should be evaluated for quantitative copper concentration, since excess hepatic copper is an important and treatable cause of CH.
3. Significant hepatic inflammation can be present in dogs that have no clinical or diagnostic imaging signs of liver disease.
4. In dogs with idiopathic CH where a meticulous search for other causes has been undertaken, a trial of immunosuppressive medication is indicated to determine if immune-mediated hepatitis is present.

Introduction

Chronic hepatitis (CH) can occur in any breed of dog, and the onset can be insidious. It progresses to end-stage cirrhosis when significant fibrosis and nodular regeneration develops, and is defined histopathologically by certain key features, as outlined in **Box 1** (1). It is critical to differentiate CH from a histologic diagnosis of non-specific reactive hepatitis, where mild-to-moderate inflammatory infiltrates in the portal, lobular and centrilobular regions are present without evidence of cell death or degeneration. These infiltrates are due to the escape of inflammatory cytokines and endotoxins from disease elsewhere in the splanchnic bed (2).

Box 1. Key histopathologic features of chronic hepatitis.

- Moderate-to-marked portal, lobular or centrilobular lymphocytic, plasmacytic and/or granulomatous inflammation
- Interface hepatitis (inflammation that breaches the limiting plate and spills over into the lobule)
- Varying degrees of hepatocyte cell death (apoptosis or necrosis)
- +/- Bile duct proliferation
- +/- Fibrosis
- +/- Nodular regeneration

Etiology

In the majority of dogs with CH the etiology cannot be determined, so-called idiopathic CH (3,4), but various causes or potential causes are worthy of note.

Several studies have failed to identify hepatotropic viruses in dogs with CH, but histopathological and/or serologic evidence of *Leptospira* bacteria have been identified in laboratory colonies of dogs, and more recently molecular means have identified leptospiral organisms in dogs with granulomatous hepatitis (5). Whether it is the organism or an immune reaction to the organism which causes the CH is unknown. Leishmaniasis is associated with granulomatous CH, whilst other bacterial (*Bartonella*), rickettsial (*Ehrlichia, Anaplasma*) and protozoal (*Neospora, Toxoplasma, Sarcocystis*) infections may cause canine CH. These infections, however, are more often acute to subacute, and part of a more systemic disease process.

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Dr. Webster graduated from Cornell University in 1985 and after working in private practice returned for residency training at Cummings School of Veterinary Medicine. She was board-certified in small animal internal medicine in 1993 and then did a post-doctoral fellowship in hepatocyte transport biology. Currently Professor and Associate Chair in the Department of Clinical Sciences at Tufts Veterinary School, she has authored over 100 peer-reviewed manuscripts as well as several book chapters. Most recently, she chaired the ACVIM Consensus Panel on the diagnosis and treatment of chronic hepatitis in the dog.

Several drugs and supplements have the potential to cause CH in the dog, and clinicians should be vigilant in obtaining a complete medication history (6). Most drugs can potentially cause acute liver injury, but a few, including anticonvulsants (phenobarbital, primidone and phenytoin), oxibendazole, lomustine (CCNU), amiodarone, mitotane and NSAIDs can lead to chronic hepatic inflammation.

Copper toxicity is also a potential etiology. Normally, many dogs consume excess copper (Cu) in their diet. Copper entering the liver must bind to Cu-binding proteins or be excreted in the bile, since free Cu causes oxidative stress leading to hepatocellular death. Normal hepatic Cu concentrations in the dog are 120-400 μg/g dry weight (DW) (7). Hepatic damage (as evidenced by increased serum alanine aminotransferase (ALT) activity and morphologic changes) begins when levels exceed 1000 μg/g DW, and damage is invariably present with values of 1500 μg/g DW or higher (7-9). There is, however, considerable phenotypic variability in an individual dog's response to excess Cu. Some dogs have toxic hepatic Cu levels but no evidence of liver damage, while others have only mild elevations in Cu and severe damage (9-11). Although any breed of dog can accumulate copper, several breeds exhibit a predilection **(Table 1)** (7). In some dogs, *e.g.*, the Bedlington Terrier, copper accumulation is due to genetic aberrations in copper-handling proteins. Accumulating evidence, however, suggests that dietary copper excess also contributes to the increasing incidence of copper-associated CH (Cu-CH) reported in the last two decades (10,11). Some 20 years ago many petfood companies switched dietary supplementation from copper oxide (which has a very poor bioavailability) to the more bioavailable copper chelates. This change, coupled with the fact that the US National Research Council has not established a maximum limit for dietary copper, has resulted in some commercial diets containing excess amounts of highly bioavailable copper (12,13). In Europe FEDIAF[1] has established a maximum value for copper concentrations in canine diets, although studies suggest that dogs, particularly those with breed predilections, may accumulate hepatic copper when fed diets with copper concentrations below this level (14,15). Several studies have now demonstrated that dogs (both with and without CH) over the last two decades have higher hepatic copper concentrations compared to similar populations of dogs pre-1998 (10,11). A diagnosis of Cu-CH requires evaluation of a hepatic biopsy specimen which will show the presence of CH accompanied by rhodamine-positive copper accumulation, primarily in centrilobular hepatocytes, and elevated hepatic copper levels (> 400 μg/g DW, typically greater than 1000 μg/g DW). There are, however, several challenges in making the diagnosis of Cu-CH. These include lobe-to-lobe variability in copper concentration, the presence of significant fibrosis which can decrease copper levels, the challenge that regenerative nodules lack copper accumulation, and the fact that later-stage inflammatory/fibrotic changes complicate determination of lobular distribution.

Table 1. Breed predispositions to chronic hepatitis.

Breed	Etiology	Genetic basis
Bedlington Terrier	Copper	Yes, *COMMD1* (majority) or *ABCB12*
Dalmatian	Copper	Yes, but no gene identified
Labrador Retriever	Copper (1/3 of cases) Idiopathic/immune	Yes; *ATP7B* in about 1/3 dogs
Doberman Pinscher	Copper Immune	Unknown
English and American Cocker Spaniel	Idiopathic/immune	Unknown
English Springer Spaniel	Idiopathic/immune	Unknown
West Highland White Terrier	Copper Idiopathic	Yes, but no gene identified

A diagnosis of immune-mediated CH is often considered when no other etiology has been identified. Although specific criteria for such a diagnosis have not been developed, an immune basis in dogs with idiopathic CH is suggested by the presence of a moderate-to-marked lymphocytic infiltrate on histopathology, positive serum auto-antibodies, a familial history of CH, an association with other autoimmune diseases (*e.g.*, hypothyroidism, atopy, inflammatory bowel disease), gender (females are generally more likely to be affected) and a favorable response to immunosuppressive therapy (13). A presumptive clinical diagnosis of immune-mediated CH requires

[1] Fédération européenne de l'industrie des aliments pour animaux familiers

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Figure 1. Chronic hepatitis can occur in any breed of dog, although certain breeds are more prone to it; a male predisposition has been noted in Cocker Spaniels.

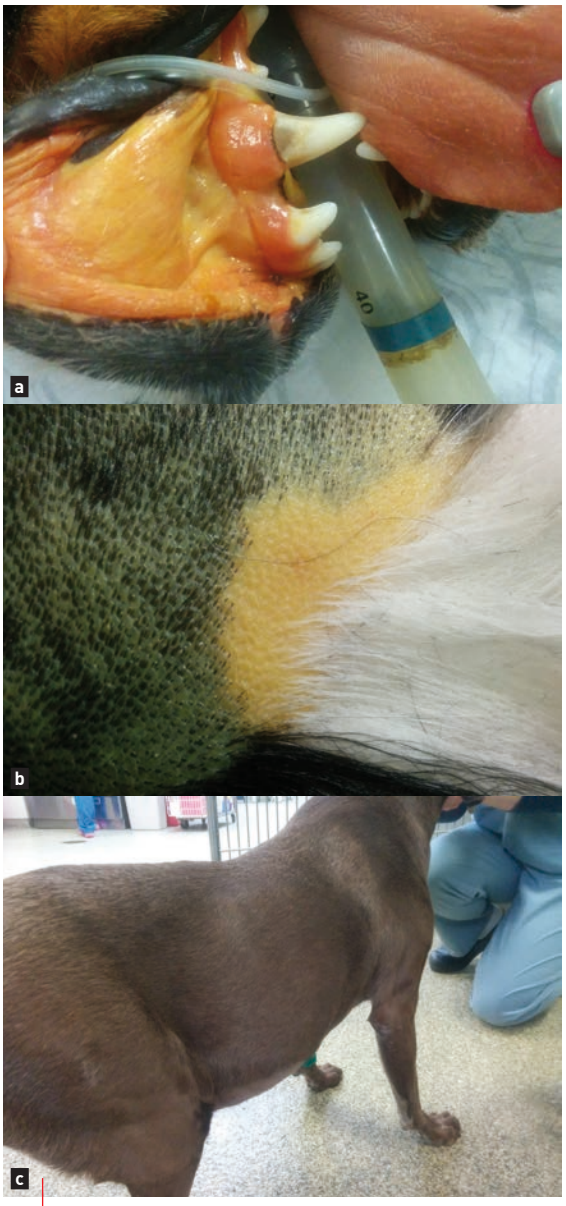

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Figure 2. Late clinical manifestations of chronic hepatitis in the dog. **(a)** Icteric mucous membranes. **(b)** Icteric shaved skin. **(c)** Ascites causing abdominal distension.

the meticulous elimination of other potential etiologies (infectious, environmental or foodborne toxins, drugs).

Signalment and clinical signs

Chronic hepatitis can occur in any dog including cross-breeds, but several breed predilections exist **(Table 1)** (16). Chronic hepatitis is generally a disease of middle-aged dogs, but cases have been reported as young as 5 months and as old as 17 years. There is a female predisposition in Labradors, Dobermans, Dalmatians and English Springer Spaniels, and a male predisposition in Cocker Spaniels **(Figure 1)**.

The most common clinical signs in affected dogs are non-specific and may include lethargy/depression and anorexia. Polyuria and polydipsia (PU/PD) are two of the earliest signs. More specific signs of liver disease, such as jaundice, hepatic encephalopathy and ascites, are less common and typically indicate the presence of advanced disease **(Figure 2)**.

Because of the reserve capacity of the liver, many dogs with CH are subclinical, with the disease picked up on routine blood screens that show increased serum liver enzyme activity. It is at this stage that diagnosis should be pursued, as therapeutic intervention in advanced disease is often less successful.

Clinical pathology

Serum alanine aminotransferase (ALT) is the best screening test for CH, although its sensitivity is only around 70-80%. Significant histological lesions can therefore exist in the absence of accompanying ALT elevation. The magnitude of the ALT elevation activity is typically greater than that seen for serum alkaline phosphatase (ALP) activity, and elevations in ALP occur later in the disease. In late-stage cirrhosis, serum levels of liver enzymes may fall markedly as hepatocytes are replaced by fibrous tissue. The frequency of other clinical pathologic signs is summarized in **Table 2**.

Table 2. Common biochemical changes in dogs with chronic hepatitis.

Parameter	% of dogs with change	# studies (# dogs)
Increased ALT	85 +/-15	10 (250)
Increased ALP	82 +/-18	10 (250)
Increased AST	78 +/-10	3 (56)
Increased GGT	61 +/-12	5 (121)
Decreased BUN	40 +/-29	5 (65)
Hypoalbuminemia	49 +/-19	15 (323)
Hypocholesterolemia	40 +/-12	4 (118)

Total serum bile acids (TSBA) are not a screening test for CH. Using 20-25 μmol/L as a cut-off, the sensitivity for pre-and post-prandial bile acids to detect CH is only about 50%. Since bile acids are very sensitive to shunting of blood around the liver, the sensitivity for cirrhosis when portal hypertension and multiple acquired portosystemic shunts (MAPSS) exist increases to almost 100%. It is ill-advised to wait until TSBA are elevated before proceeding to hepatic biopsy, as by this point significant and perhaps irreversible hepatic changes have occurred.

As PU/PD is a common clinical sign in CH, accompanying isosthenuria is seen on urinalysis. A transient acquired Fanconi syndrome (glucosuria with normoglycemia) is associated with Cu-CH (7).

Imaging

Radiology of the liver in affected dogs is usually normal, so ultrasound is a required part of the routine work-up in all dogs with suspected CH. A summary of the ultrasound changes described in literature is shown in **Table 3**. It is important to note that several studies have shown that there are no ultrasonographic criteria that can predict the presence of CH; in fact the liver may appear normal on a scan, even in the presence of significant disease (17-19).

In advanced CH, the liver may be small and irregularly marginated **(Figure 3)** on ultrasound, with signs of portal hypertension. These include ascites, edema (especially visible in the gallbladder and pancreas), reduced portal flow velocity (mean velocity of < 10 cm/s, as compared to a normal range of 10.5-25.7 cm/s) or hepatofugal flow and the visualization of MAPSS, usually seen as a complex plexus of small tortuous vessels caudal to the left kidney (20).

Biopsy acquisition

The diagnosis of CH requires hepatic tissue sampling. Fine-needle aspirates are not adequate to make a diagnosis, and often result in misclassification of the disease process. Percutaneous ultrasound-guided biopsy with large (14 or 16G) needles can provide adequate samples for diagnosis if multiple cores are taken (21). The diagnostic accuracy of 18G needle biopsies, however, is questionable, as these result in a relatively small sample size, are subject to fragmentation when fibrosis is present, and may not enable sampling of abnormalities located in lobes other than the readily accessible left medial or lateral lobes. This is a problem, since there is often heterogeneity between different liver lobes in terms of histological severity and copper deposition. In general, accurate diagnosis of CH requires the pathologist to evaluate 10-12 portal regions, which is hard to attain unless multiple percutaneous biopsies are procured. Multiple biopsies can, however, increase the risk of bleeding.

Table 3. Ultrasound changes seen in chronic hepatitis.

Abnormality	% dogs showing change
Microhepatica	39
Ascites	29
Heterogenous/non-homogenous/ mottled	23
Hyperechoic	18
Nodular	17
Irregular margins	17
Normal	14
Hepatomegaly	7.8
MAPSS (multiple acquired portosystemic shunts)	4.3
Enlarged hepatic lymph nodes	2.8
Hypoechoic	2

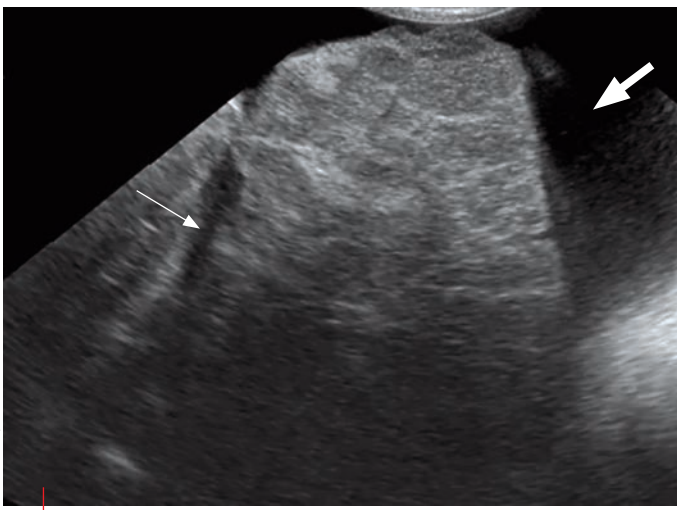

Figure 3. Ultrasound of the liver of a 5-year-old Rottweiler cross that presented for lethargy and decreased appetite. The dog has had a progressive increase in serum liver enzymes over the last 2 years. A moderate amount of abdominal effusion is noted (large arrowhead). The liver was reduced in size with irregular hyperechoic margins (small arrowhead) and many ill-defined hypoechoic nodules. These features are commonly seen in cirrhotic liver.

Laparoscopy is the preferred technique to obtain hepatic biopsies. This enables gross evaluation of the entire liver, the extrahepatic biliary system and surrounding structures while permitting acquisition of multiple large specimens that consistently result in samples with a mean of 16-18 portal triads per

Box 2. Assessment of bleeding risk for hepatic biopsy.

Assessment parameter	High-risk criteria
PCV	< 30%
Platelet count	< 80,000
PT/aPTT	> 1.5 x upper limit normal
vWF (in susceptible breeds)	< 50%
Buccal mucosal bleeding time (BMBT)	> 5 minutes
Fibrinogen	< 100 mg/dL

biopsy specimen. For the diagnosis of CH, five samples from at least two different lobes are obtained; three for histopathologic evaluation and one each for aerobic/anaerobic culture and heavy metal quantification.

Risks of biopsy include anesthetic complications (especially in patients with advanced liver disease), hemorrhage, air embolism (on laparoscopy), infection, pneumothorax and vagotonic shock. The primary concern is hemorrhage (22). Assessment of the bleeding risk in dogs with liver disease that have deficiencies in both pro- and anti-coagulants as well as in regulators of fibrinolysis is difficult. Prolongations of PT and aPTT occur in about 40% of affected dogs. Decreased fibrinogen, anti-thrombin and protein C activity also occur in many dogs, and mild anemia and thrombocytopenia are occasionally present. Based on the human literature and the limited work to date in dogs, guidelines for bleeding risk assessment are outlined in **Box 2** (13,21,22).

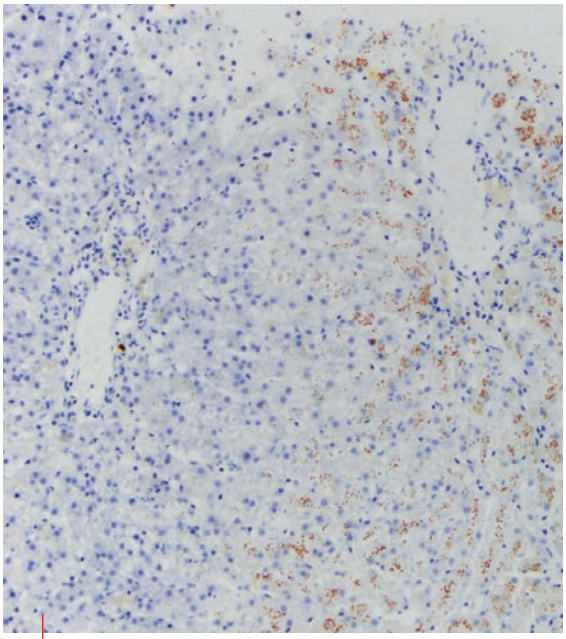

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Figure 5. Rhodamine-stained hepatic biopsy showing prominent centrilobular accumulation of copper which appears as red-brown granules within hepatocytes. This 6-year-old West Highland White Terrier presented with a history of increased liver enzymes. The quantitative copper level was 1170 µg/g DW.

Figure 4. A percutaneous method to obtain a liver biopsy may be suitable in some cases.

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Percutaneous ultrasound-guided liver biopsy **(Figure 4)** carries a greater bleeding risk than techniques in which hemostasis can be controlled locally (*e.g.*, laparoscopy), although the risk of complications (defined as the need for transfusion or fluid resuscitation) appears to be low for both methods, at around 1-5% (13,22).

When high-risk patients are identified, it is unknown if therapeutic interventions – such as administration of blood products or vitamin K – will decrease the risk of hemorrhage following hepatic sampling. The exception is the dog with low von Willebrand factor activity, which should be given cryoprecipitate and desmopressin. Thus the recommendation in high-risk dogs is to pay strict attention to technique and monitor them carefully in hospital after the biopsy procedure for 12 hours, and to be prepared to rescue with blood product support if necessary (13).

Biopsy interpretation

Evaluation of liver biopsy specimens requires H&E, Sirius red or Massons' trichrome (for fibrosis) and Rhodanine (for copper) staining (21).

Table 4. Treatment of copper-associated chronic hepatitis.

Drug and dosage	Mechanism of action and notes
Cu-restricted diet Feed appropriate commercial or home-made diet with < 5 mg/kg dry weight (0.1-0.12 mg/100 kcal) < 0.1 μg/g Cu in water; use distilled water or test water for Cu	Limits intestinal absorption of Cu Available Cu-restricted diets often have unnecessary protein restriction; consider additional protein Most dogs need lifetime low Cu diet With Cu pipes can run water for a few minutes to eliminate Cu
D-Penicillamine 10-15 mg/kg q12H PO on an empty stomach	Cu chelator Common side effects include nausea and vomiting. Rarer side effects include Cu, Fe or Zn deficiency, vitamin B_{12} deficiency, skin eruptions, proteinuria and hematologic dyscrasias. May cause a mild increase in serum ALP and vacuolar hepatopathy. Do not give with zinc
Zinc (zinc gluconate) 50 mg q12H on an empty stomach	Induces synthesis of cytoplasmic metallothionein in intestine and liver, decreasing Cu absorption and protecting the liver. Removes copper slowly, so only appropriate for maintenance Commonly causes nausea and vomiting; hemolytic anemia is seen rarely. Serum levels must be monitored; should be > 200 mg/dL but less than 1000 mg/dL
S-Adenosylmethionine (SAMe) 20 mg/kg PO q24H on an empty stomach	Increases glutathione levels (GSH), promotes anti-inflammatory polyamines and methylation of DNA and membranes to promote cell stability Occasionally causes vomiting; since the compound is unstable, use products with proven pharmacodynamics in the dog
Vitamin E 10 IU/kg PO q24H, not to exceed 400 IU/dog/day	Anti-oxidant: prevents lipid peroxidation of membranes Give with food. Can be pro-oxidant and interfere with coagulation at high doses
Ursodiol 10-15 mg/kg PO q24H given with food	Choleretic, anti-oxidant and anti-apoptotic. Indicated with hyperbilirubinemia or evidence of ultrasound changes in biliary tree. Occasionally causes vomiting. Generic formulations generally have good bioavailability

The pathologist should comment on the type, location and quantity of inflammation, fibrosis, degenerative change (lipidosis, vacuolar change, lipogranulomas), the presence, location and extent of cell death and ductular reaction, and the lobular distribution and amount of copper staining **(Figure 5)**. Special stains for infectious organisms are indicated in some cases, particularly in pyogranulomatous hepatitis. An exchange of information between the clinician and the pathologist may be necessary to maximize the value obtained from biopsies. In some cases, evaluation of samples by a pathologist (and internist) with expertise in hepatic histopathology and medicine should be considered.

Treatment

Treatment is targeted to etiology. Suspected infectious agents should be treated with appropriate antimicrobial therapy, and toxic agents or drugs eliminated from the dog's environment. Any increase in hepatic copper in a dog with CH should be treated. Treatment of Cu-CH is summarized in **Table 4** and involves dietary Cu restriction and methods to chelate Cu or prevent intestinal absorption (penicillamine and zinc) (7). Concurrent administration of hepatoprotectant and anti-oxidant medications is indicated (S-adenosylmethionine, vitamin E +/- ursodeoxycholate). Some dogs with Cu-CH have intense inflammatory infiltrates and may benefit from a short course of anti-inflammatory corticosteroids.

Bedlington Terriers, Dalmatians and young dogs with markedly elevated (> 3000 μg/g DW) hepatic Cu will likely need lifetime dietary therapy combined with Cu chelation. In other dogs, the time necessary to achieve normal Cu balance with penicillamine and low copper diet is poorly defined. Some work in Labrador Retrievers suggests that duration of chelation is related to initial hepatic Cu concentration, with about 6, 9 and > 12 months required for 1000, 1500 and 2000 μg/g DW respectively **(Figure 6)**. Whether this is true for other breeds is unknown. Expert opinion is that some dogs "de-copper" more easily than others and that this is often independent of hepatic Cu concentration (13).

Ideally, re-biopsy with qualitative and quantitative Cu determination should define when chelation can be stopped. If this is not possible then serum ALT is used as a surrogate marker, whilst recognizing that levels can be normal despite ongoing histologic inflammation; chelation should therefore be continued 2-3 months beyond normalization of serum ALT. Although some limited work suggests that fine-needle aspirates stained with rhodamine may be useful in monitoring hepatic copper, this is not recommended until further studies are done.

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Figure 6. Labrador Retrievers are one of the breeds known to have a genetic predisposition for copper toxicity.

In some dogs, normal Cu balance is restored yet serum ALT and histologic evidence of inflammatory disease persists. These dogs either did not have Cu-CH, or the damage has exposed neoepitopes and incited a self-perpetuating immune disease.

Typically, all affected dogs stay on a Cu-restricted diet, but this is often insufficient to maintain normal hepatic Cu, although it is hard to predict which dogs will need additional therapy. In general dogs with high initial hepatic Cu (> 2000 μg/g), dogs with a family history of Cu-CH, and dogs in which serum ALT does not normalize within a 6-8 month period of chelation will often receive an appropriate diet in combination with maintenance penicillamine or zinc therapy.

"As histologic improvement lags behind clinical and laboratory improvement, treatment recommendation adjustments must go beyond laboratory remission by several months before attempting treatment withdrawal."

Cynthia RL Webster

Limited studies suggest that some dogs with idiopathic Cu-CH truly have immune disease and will go into remission on appropriate therapy, although prospective clinical trials of immunosuppression in suspected immune CH are lacking. Corticosteroids, azathioprine, mycophenolate and cyclosporine have been advocated to treat presumptive immune hepatitis in dogs **(Table 5)**, although again none have been evaluated in prospective clinical trials. Often dogs with presumptive immune disease are also placed on concurrent hepatoprotectant medications.

Again, the optimum therapeutic endpoint for judging treatment response is normalization of hepatic histology, but this is often impossible, so ALT activity may be used as a surrogate marker. The timeframe for remission in dogs with immune CH is unknown. Control of enzymes may take 2-3 years in humans, although better long-term response is seen when enzyme activity is controlled within 3 months. As histologic improvement lags behind clinical and laboratory improvement (in humans by 3-8 months), treatment recommendation adjustments must go beyond laboratory remission

Table 5. Immunosuppressive therapy for presumptive immune-mediated chronic hepatitis.

Drug and dosage	Comments and possible side effects
Azathioprine 1 mg/kg PO q24H for 7 days then 1 mg/kg q48H	Increase in serum liver enzymes (typically reversible upon discontinuation) Reversible bone marrow suppression
Prednisolone 2 mg/kg PO q24H (no greater than 40 mg/day) tapered to 0.5 mg/kg q48H	PU/PD/polyphagia GI upset Hypercoagulability Induction of serum ALP and GGT Development of steroid hepatopathy Increased susceptibility to infections (*e.g.*, UTI) Catabolism Sodium retention Use dexamethasone in patients with ascites
Cyclosporine 5 mg/kg PO q12H	Nausea/vomiting Gingival hyperplasia Increased susceptibility to infections (*e.g.*, UTI and opportunistic fungi) Use emulsified preparations only Initial therapy should not be with generic products
Mycophenolate 10 mg/kg PO q12H	Diarrhea

by several months before attempting treatment withdrawal. Stable laboratory data within reference intervals over 12-18 months may be adequate to consider tapering medication. The relapse rate in dogs is unknown but in humans is up to 50%. Recapture of disease control with re-induction of primary therapy is often promptly achieved.

Prognosis and complications

Once diagnosed, dogs with CH typically experience progressive disease. Survival times have been reported in several studies, all of which were retrospective (13), and dogs were treated with a variety of medications and diets. In 10 studies with survival data (n=364 dogs) the mean survival was 561 days +/- 268 days. In dogs with biopsy-proven cirrhosis, survival was considerably less, 23 +/- 23 days (n=39). The clinicopathologic factors associated with a poor prognosis are hyperbilirubinemia, increased PT and aPTT, and hypoalbuminemia. The presence of ascites and the degree of fibrosis on biopsy are also negative prognostic signs; the one exception may be in Cocker Spaniels with CH, where dogs with ascites can have prolonged survival.

Complications of CH in the dog include portal hypertension, ascites, hepatic encephalopathy, gastrointestinal ulceration and coagulopathies (both bleeding and thrombosis) (20,23,24). Bleeding is more common with end-stage disease, and thrombosis occurs more often where other pro-thrombotic factors are involved, such as systemic inflammation, surgery or corticosteroid therapy (20). The incidence of secondary bacterial infection is poorly documented in dogs with CH, but appears to be low at around 5% (24).

CONCLUSION

Chronic hepatitis can occur in any breed of dog and the onset can be insidious; significant histological lesions can exist in the absence of accompanying serum liver enzyme elevation. Multiple biopsy samples are required for a definitive diagnosis, although biopsy can carry some risk for the patient. Targeted treatment is preferred wherever possible, although the causative agent may not be identified in many cases, and therapy should be continued for some months after clinical signs resolve.

REFERENCES

1. Van den Ingh TSGAM, Van Winkle TJ, Cullen JM, *et al*. Morphological classification of parenchymal disorders of the canine and feline liver: Hepatocellular death, hepatitis, and cirrhosis-2 (updated version) In: *WSAVA Standards for Clinical and Histological Diagnosis of Canine and Feline Liver Diseases. Society of Comparative Hepatology.* Available at; http://www.vetvisuals.com/lms/moodle/mod/book/view.php?id=1001&chapterid=52859
2. Twedt DC. Reactive hepatopathies and chronic hepatitis in the dog. *Vet Q* 1998;2:S46-47.
3. Bexfield N. Canine idiopathic chronic hepatitis. *Vet Clin North Am Small Anim Pract* 2017;47:645-663.
4. Poldervaart JH, Favier RP, Penning LC, *et al*. Primary hepatitis in dogs: a retrospective review (2002-2006). *J Vet Intern Med* 2009;23:72-80.
5. Kearns S. Infectious hepatopathies in dogs and cats. *Top Companion Anim Med* 2009;24:189-198.
6. Bunch SE. Hepatotoxicity associated with pharmacologic agents in dogs and cats. *Vet Clin North Am Small Anim Pract* 1993;23(3):659-670.
7. Dirksen K, Fieten H. Canine copper-associated hepatitis. *Vet Clin North Am Small Anim Pract* 2017;47:631-644.
8. Thornburg LP, Rottinghaus G, McGowan M, *et al*. Hepatic copper concentrations in purebred and mixed-breed dogs. *Vet Pathol* 1990;27:81-88.
9. Thornburg LP, Rottinghaus G, Dennis G, *et al*. The relationship between hepatic copper content and morphologic changes in the liver of West Highland White Terriers. *Vet Pathol* 1996;33:656-661.
10. Johnston AN, Center SA, McDonough SP, *et al*. Hepatic copper concentrations in Labrador Retrievers with and without chronic hepatitis: 72 cases (1980-2010). *J Am Vet Med Assoc* 2013;242:372-380.
11. Strickland JM, Buchweitz JP, Smedley RC, *et al*. Hepatic copper concentrations in 546 dogs (1982-2015). *J Vet Intern Med* 2018;32(6):1943-1950.
12. Subcommittee on Dog and Cat Nutrition, Committee on Animal Nutrition, National Research Council. Nutrient Requirements of Dogs and Cats. Washington, DC: The National Academy Press; 2006.
13. Webster CRL, Center SA, Cullen JM, *et al*. ACVIM consensus statement on the diagnosis and treatment of chronic hepatitis in dogs. *J Vet Intern Med* 2019;33(3):1173-1200.
14. Fieten H, Hooijer-Nouwens BD, Biourge VC, *et al*. Association of dietary copper and zinc levels with hepatic copper and zinc concentration in Labrador Retrievers. *J Vet Intern Med* 2012;26(6):1274-1278.
15. http://www.fediaf.org/images/FEDIAF_Nutritional_Guidelines_2019_Update_030519.pdf
16. Watson P. Canine breed-specific hepatopathies. *Vet Clin North Am Small Anim Pract* 2017;47:665-682.
17. Kemp SD, Panciera DL, Larson MM, *et al*. A comparison of hepatic sonographic features and histopathologic diagnosis in canine liver disease: 138 cases. *J Vet Intern Med* 2013;27:806-813.
18. Feeney DA, Anderson KL, Ziegler LE, *et al*. Statistical relevance of ultrasonographic criteria in the assessment of diffuse liver disease in dogs and cats. *Am J Vet Res* 2008;69:212-221.
19. Warren-Smith CM, Andrew S, Mantis P, *et al*. Lack of associations between ultrasonographic appearance of parenchymal lesions of the canine liver and histological diagnosis. *J Small Anim Pract* 2012;53:168-173.
20. Buob S, Johnston AN, Webster CR. Portal hypertension: pathophysiology, diagnosis, and treatment. *J Vet Intern Med* 2011;25:169-186.
21. Lidbury JA. Getting the most out of liver biopsy. *Vet Clin North Am Small Anim Pract* 2017;47:569-583.
22. Webster CR. Hemostatic disorders associated with hepatobiliary disease. *Vet Clin North Am Small Anim Pract* 2017;47:601-615.
23. Rothuizen J. Important clinical syndromes associated with liver disease. *Vet Clin North Am Small Anim Pract* 2009;39:419-437.
24. Wagner KA, Hartmann FA, Trepanier LA. Bacterial culture results from liver, gallbladder, or bile in 248 dogs and cats evaluated for hepatobiliary disease: 1998-2003. *J Vet Intern Med* 2007;21:417-424.

HOW I APPROACH... THE DOG WITH ALTERED HEPATIC ENZYMES

Elevated liver enzymes on routine biochemistry screens are a daily occurrence in small animal practice; Jordi Puig discusses how he decides if such findings are significant or not.

KEY POINTS

1. Liver enzyme levels do not indicate hepatic functionality; this requires evaluating parameters which reflect the liver's capacity for synthesis and/or excretion of compounds, such as bile acids.
2. A single measurement does not provide enough information in most cases, and serial monitoring is much more helpful.
3. The biochemical changes found in patients with a secondary hepatopathy are usually caused by a non-specific reactive hepatitis.
4. Where there is advanced liver disease, such as cirrhosis, any increase in hepatic enzymes may be slight.

Introduction

The correct diagnosis of a hepatobiliary disease can be a difficult task. An increase in liver enzymes is a common finding in all veterinary practices, and we must comprehend its meaning in order to establish a suitable diagnosis and treatment. Understanding the advantages and disadvantages of diagnostic laboratory testing is essential in order to avoid incorrect interpretation of results.

Basic principles of liver enzymology

Most methods used to measure enzyme levels are based on the calculation of their activity. The enzyme unit (U) is the amount of an enzyme that catalyzes the conversion of one μmol of substrate per minute (1). Ranges vary between laboratories and methodologies, and when comparing results it must always be in relation to the magnitude of the increase and not simply with absolute numbers. Additionally, remember that hemolysis, jaundice, or lipemia can alter the sample results, depending on the analytical method used.

The magnitude of the increase in enzyme activity tends to be in proportion to the severity of liver damage; however such tests do not predict liver function, the cause of the problem, or the prognosis. For example, where there is advanced illness such as cirrhosis, the increase in liver enzymes may be slight. Likewise, the duration of any increase depends mainly on the average half-life of the enzyme, the cause of the damage, and the severity of the process. Because of this, a single measurement rarely provides enough information for the clinician, and serial monitoring is much more revealing. Any increase in liver enzymes can be graded into 3 stages (2):

- **Mild:** < 5 times the upper limit of the reference range
- **Moderate:** 5-10 times the upper limit of the reference range
- **Severe:** > 10 times the upper limit of the reference range

The main mechanisms that cause increased serum liver enzymes are cell damage and the induction of enzyme synthesis. The enzymes are mainly found in the hepatocyte mitochondria, cytoplasm, or cell membrane. Where enzymes are elevated due to cell damage, the leaking of enzymes depends on their

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concentration and location within the cell. For example, an increase in enzymes located in the mitochondria suggests greater damage than an increase in enzymes located only in the cytoplasm. Liver enzymes are generally classified into two groups, those that indicate cell damage (alanine aminotransferase and aspartate aminotransferase) and those that indicate enzyme synthesis (alkaline phosphatase and gamma-glutamyl transferase) (3).

Finally, the measurement of liver enzymes is not proof of functionality. The assessment of liver function is based on evaluating parameters which reflect its capacity for synthesis and/or excretion, such as bilirubin, glucose, cholesterol, urea, albumin, or the bile acid stimulation test **(Table 1)**.

Alanine aminotransferase (ALT)

ALT, previously known as serum glutamic pyruvate transaminase (SGPT), is found primarily within the cytoplasm of hepatocytes, with higher levels in zone 1, the periportal area **(Box 1)** (2). It is also found in other organs (heart muscle, skeletal muscle, kidneys and red blood cells), but ALT levels in the liver are 4 times higher than in heart muscle and 10 times higher than in the kidney. If an increase in ALT is seen, it is important to exclude a non-liver-related origin (*e.g.*, hemolysis or severe muscle trauma). The average half-life of the enzyme is estimated to be around 2-3 days.

The release of the enzyme is typically associated with alterations in the permeability of the hepatocellular membrane, and is most commonly caused by toxins, inflammatory processes, hypoxia, tissue trauma, or neoplasia **(Table 2)**. The largest increases are seen with necrosis and inflammation. The magnitude of the increase correlates to the degree of cellular damage, but is not specific for any particular process. In advanced cirrhosis or vascular disease it is common to find only slight elevations. It is important to remember that increased ALT is not always synonymous with primary liver disease; many illnesses can result in elevated liver enzymes and the primary cause can be distant to the liver (*e.g.*, metabolic disease, systemic inflammatory processes). In acute disease, a decrease in ALT levels of greater than 50% during the first few days of illness is considered a positive prognostic factor.

Aspartate aminotransferase (AST)

AST (which was previously known as serum glutamic oxaloacetic transaminase (SGOT)), is found in the hepatocyte mitochondria at higher concentrations than ALT, and is more predominant in zone 3 of the hepatic acinus **(Box 1)** (2). AST has a lower specificity than ALT and can also be found in muscle and red blood cells. Like ALT, it is important to exclude a non-liver-related origin

Table 1. Liver function tests.

Liver enzymes do not inform us about the functional capacity of the liver. The most common tests employed to determine hepatic function are:
• **Bilirubin**: increased bilirubin levels are seen with liver dysfunction or cholestasis (intra or extrahepatic). Some patients have functional cholestasis, where hepatocytes cannot excrete conjugated bilirubin into the bile ducts due to the presence of inflammatory factors. Any dog with a severe infectious/inflammatory process can have functional cholestasis. At the same time, the inflammatory factors affect transportation of bile acids, which may cause elevated serum levels.
• **Glucose**: hypoglycemia occurs when > 75% of the liver mass is not functional, due to a decrease in glycogen and metabolism of insulin.
• **Cholesterol**: high levels are associated with cholestasis; low levels are due to decreased cholesterol production.
• **Urea and ammonia**: in liver disease alteration of the urea cycle can cause low levels of urea and high levels of ammonia.
• **Coagulation factors**: since coagulation factors are produced in the liver, hepatic disease can lead to delayed clotting times. Cholestasis produces hemostatic defects, attributed to reduced absorption of vitamin K and decreased activation of factors II, VII, IX, and X.
• **Protein C**: this is an anticoagulant protein which helps distinguish between the presence of portal vein hypoplasia and a shunt (4). It is important not to confuse it with C-reactive protein.
• **Albumin**: low levels are due to decreased production when > 70% of the liver mass is not functional.
• **Bile acid stimulation test**: increased levels indicate a liver pathology or a portosystemic shunt.

(*e.g.*, from hemolysis or muscle trauma) if elevated levels are detected, but the differential diagnosis is similar to that of ALT. The half-life of AST in the dog is 5 to 12 hours. In most cases the increase in AST and ALT activity is in parallel, but in some patients AST will normalize before ALT due to its shorter half-life and its mitochondrial location.

Alkaline phosphatase (AP)

AP is codified by two genes: a non-specific tissue gene and an intestinal gene. The non-specific tissue gene transcribes the isoenzymes found in the liver, kidney, placenta, and bone (2); the intestinal gene codes for the intestinal and corticosteroid-induced isoenzymes. The isoenzymes catalyze the same chemical reaction but have a different sequence of amino acids. The half-life of intestinal, kidney, and placenta AP is very short (less than 6 minutes). However, the half-life of AP in the liver and bone and corticosteroid-induced AP is almost 60 hours. In animals under a year old, bone-derived AP constitutes the majority of the total AP (5). In older animals the liver isoenzyme predominates. Corticosteroid-induced AP contributes 10-30% of the total AP level, with the higher percentage in older dogs. Because of this, the specificity of the enzyme is around 51% for hepatobiliary diseases, but its sensitivity is 80% **(Table 3) (Box 2)**.

Liver-derived AP is located in the hepatocyte membrane of the bile canaliculi and sinusoids. The two main mechanisms responsible for an increase in hepatic AP are cholestasis and drug induction.

Cholestasis produces an accumulation of bile acids, which induces the production of AP. Drugs such as phenobarbital and corticosteroids will increase hepatic AP.

Corticosteroid-induced AP is produced in the liver. Levels tend to be increased with hyperadrenocorticism, but the isoenzyme can also be elevated with other conditions such as diabetes mellitus, primary liver disease, or other chronic processes; this limits its use in the diagnosis of hyperadrenocorticism.

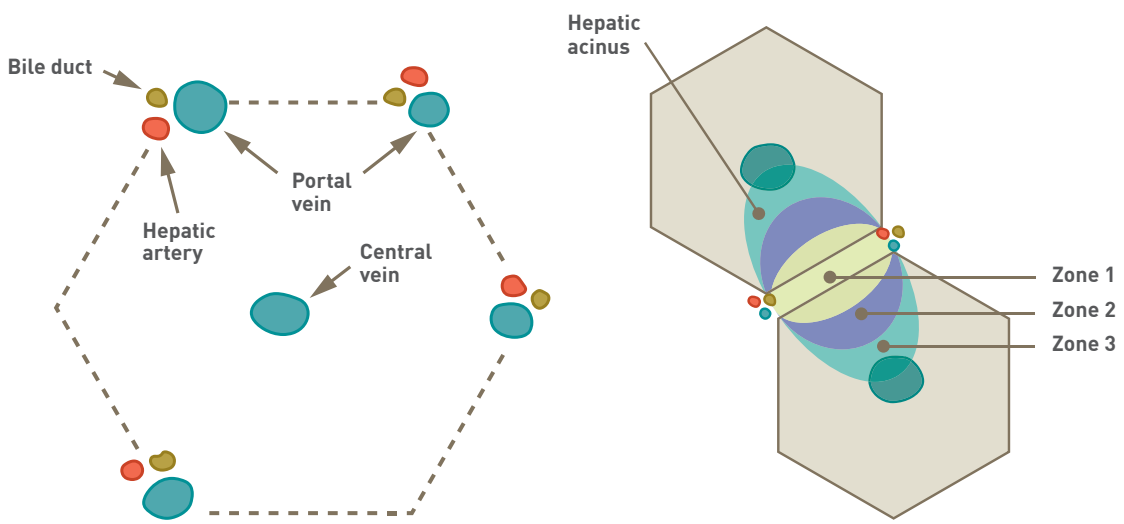
Bone-specific AP is located in the membrane of osteoblasts. Increases in osteosarcoma cases tend to be slight. A benign familial hyperphosphatasemia (with a rise in mainly bone-specific AP) has been described in Siberian Huskies (5).

The most notable elevations in AP can be seen in cholestasis (focal or diffuse), hepatitis, or with corticosteroid use. Certain liver tumors, such as hepatocellular carcinomas, can also cause a significant increase. AP activity levels do not help to distinguish between hepatic cholestasis and post-hepatic cholestasis **(Table 3)**.

Gamma-glutamyl transferase (GGT)

GGT is an enzyme found in epithelial cells of the biliary system and hepatocytes. It is also present in the pancreas, kidney tubules, and epithelial cells of mammary tissue. The half-life in a dog is 72 hours. Elevated GGT is related to cholestasis or biliary

Box 1. Histological division of the liver.



The liver is divided histologically into hexagonal lobules. At the center of each lobule is the central vein, with the portal triads (consisting of a hepatic artery, a portal vein and a bile duct) at the periphery. The hepatic lobule can be described in terms of metabolic "zones" with each zone centered on a line connecting two portal triads and extending outwards to the two adjacent central veins. The periportal **zone 1** is nearest to the entering vascular supply and receives the most oxygenated blood, whilst the centrilobular **zone 3** has the poorest oxygenation; **zone 2** lies between **zone 1 and 3**.

hyperplasia, but corticosteroids will also increase its activity. The enzyme is considered to be more specific (87%) than AP but less sensitive (50%) (3).

Approaching the patient with increased liver enzymes

My main objectives when a hepatobiliary disease is suspected, based on biochemistry screens, are as follows:

- Determine if there is a hepatobiliary disease.
- Evaluate liver function.
- Determine if the origin is primary or secondary.
- Establish the correct diagnosis.
- Monitor the response to treatment.

Although these seem clear in principle, altered liver enzymes are a challenge as clinical signs can be very unspecific and in some cases absent. Furthermore, the liver plays a major role in detoxifying both endogenous and exogenous toxins, and there are many extrahepatic processes which affect it on a secondary level. The liver has a high-reserve capacity and signs of liver dysfunction are only seen in advanced disease processes **(Figure 1)**.

The first step requires integration of the history, clinical signs, and physical examination. It is of utmost importance to obtain an optimal history to identify any possible toxin (diet, drugs, plants, etc.) and determine if there are risk factors for infectious disease (*e.g.*, a poor vaccination schedule). Due to its anatomo-functional situation and its ability to metabolize foreign compounds (xenobiotics), the liver may be exposed to high concentrations of substances which can have toxic effects (6). It is also well recognized that some dog breeds are predisposed to certain liver problems.

Hepatotoxicity due to drugs can be divided into two groups: intrinsic and idiosyncratic. The former causes liver damage in any animal exposed to a given dose of a drug; the latter occurs in individual animals where the liver damage is unpredictable and with no apparent correlation to the drug dosage.

- **NSAIDs** have been associated with idiosyncratic reactions. Most reported cases have been due to carprofen, although all NSAIDs are capable of causing damage. The severity depends on the patient and is typically seen within three weeks of starting the drug. The signs are variable and the increase in liver enzymes severe (especially ALT). Although most dogs recover when the NSAID is withdrawn and given supportive therapy, some can die due to acute liver failure.

- The toxic dose of **paracetamol** in dogs is around 150 mg/kg and is an example of intrinsic hepatotoxicity. The metabolites of this drug (mainly N-acetyl-p-benzoquinone imine, or NAPBQ) are involved in oxidation of red blood

Table 2. Differential diagnosis for increased levels of alanine aminotransferase.

- **Toxicity** from medications or toxins: NSAIDs, azathioprine, *Cycas revoluta*, phenobarbital, lomustine, paracetamol, sulfonamides, xylitol, etc.
- **Inflammation**: this can be infectious (*e.g.*, leptospirosis, cholangiohepatitis/cholangitis, sepsis) or non-infectious (*e.g.*, chronic hepatitis, copper accumulation, reactive liver disease)
- **Cirrhosis**
- **Metabolic**: lipidosis, diabetes, glucocorticoids, hyperthyroidism
- **Hypoxia/degenerative**: anemia, congestion, respiratory disease, portosystemic shunt
- **Trauma**
- **Neoplasia**: primary or secondary
- **Regeneration** of hepatic tissue

Table 3. Differential diagnosis for levels of alkaline phosphatase.

- **Intrahepatic cholestasis:**
  - Nodular hyperplasia
  - Vacuolar hepatopathy
  - Lipidosis
  - Neoplastic: primary or secondary
  - Hepatitis
  - Secondary/reactive to systemic inflammatory illness
- **Extrahepatic cholestasis:**
  - Pancreatitis
  - Biliary disease: mucocele, cholangitis/cholangiohepatitis
  - Neoplastic: bile ducts, duodenum or pancreas
- **Induction:**
  - Corticosteroids
  - Phenobarbital
  - Thyroxine
- **Increased osteoblastic activity: osteosarcoma, bone remodeling**
- **Benign familial hyperphosphatasemia (Siberian Husky)**

Box 2. Sensitivity and specificity.

- **The sensitivity** of a test indicates the proportion of sick patients that are correctly identified as having a given condition. It therefore measures the ability of the test to detect a disease in a population of sick animals. If there are many false negatives (*i.e.*, an animal has a certain disease, but it is not detected by the test), the sensitivity will be low.
- **The specificity** of a test indicates the proportion of healthy patients that are correctly identified as not having a given condition. It therefore measures the ability of the test to ascertain a healthy animal does not have the condition being tested for). If there are many false positives (*i.e.*, an animal does not have a certain disease, but it tests positive for it), the specificity will be low.

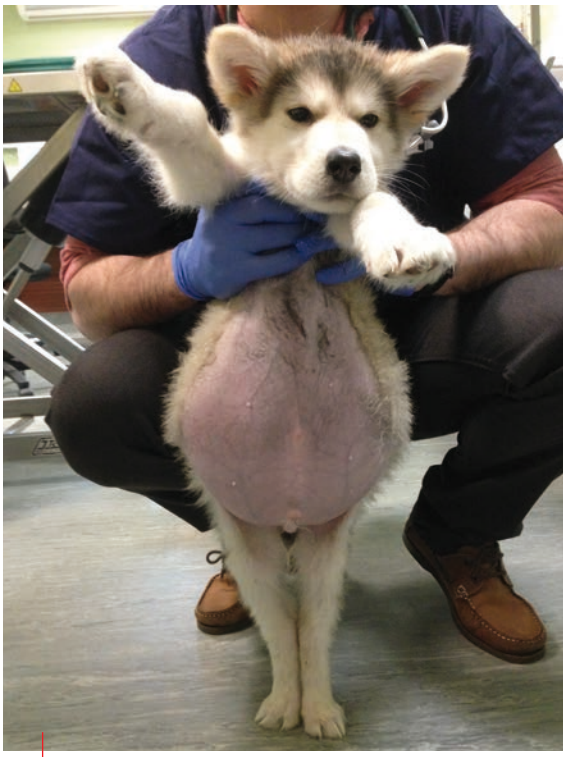


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Figure 1. A 3-month-old puppy with ascites due to portal vein hypoplasia and portal hypertension.

cells and hepatocytes. Laboratory findings include methemoglobinemia, a noticeable increase in ALT, and hyperbilirubinemia in most affected dogs (7). Intravenous acetylcysteine is the treatment of choice for these cases, as it reduces the toxicity of NAPBQ. Cimetidine, vitamin C and S-Adenosylmethionine (SAMe) can also help.

- The hepatotoxicity of **phenobarbital** has been described as both intrinsic and idiosyncratic. Although the most commonly stated theory to explain the increase in AP is induction, this is debatable; liver damage may also occur (8,9). Basically, increases in AP are slight and in some cases there is a mild elevation of ALT. The indications to withdraw phenobarbital treatment include when ALT levels are higher than AP and/or there is evidence of liver dysfunction (hypocholesterolemia, hyperbilirubinemia, increase in bile acids, or hypoalbuminemia). Although clinical and histopathological changes may be severe, some patients can recover their liver function (10).

- **Azathioprine** is a purine analog widely used to treat immune-mediated disorders. Its ability to cause hepatotoxicity (defined as > 2 times the increase in ALT activity) has been described in 15% of treated dogs, generally without clinical signs (11). Hepatotoxicity normally occurs during the first two weeks of therapy, before myelotoxicity (which on average can take 53 days to develop) and it is suspected that German Shepherd dogs are predisposed to it. However, in some cases, the enzyme increase occurs later. Where there is a slight elevation in ALT, it is wise to monitor the patient regularly, but for moderate or severe increases, it is recommended to reduce the dose or stop the medication.

- The increase of AP in dogs treated with **glucocorticoids** is variable and normally not associated with liver damage. However, in some cases, the appearance of a severe vacuolar hepatopathy may cause signs of cholestasis and cell damage. The effects are minimized by reducing the dose, although full remission may take months. It is not unusual to see slightly elevated bile acids in patients receiving glucocorticoids in the absence of liver disease. Administering liver protectants such as SAMe does not influence either the histopathology or the altered enzyme levels in animals on glucocorticoids (12).

- **Lomustine** (CCNU) is an alkylating compound with hepatotoxicity reported in 6% of treated dogs. The toxic effects have been described as delayed in the course of treatment, accumulative, dose-dependent, and irreversible. Enzyme alteration ranges from moderate-to-severe ALT, with an average of 11 times the upper limit of the reference range. The prognosis is serious due to liver failure, but administration of SAMe and silibinin during treatment may help minimize liver damage (13).

What other tests can be performed?

In dogs with increased liver enzymes, I always obtain a complete blood count (CBC) and general biochemistry profile, and urinalysis. Findings from the blood count can be quite variable. If anemia is present, this is usually non-regenerative, although intestinal bleeding secondary to a

"The magnitude of the increase in hepatic enzyme activity tends to be in proportion to the severity of liver damage; however it does not predict function, the cause of the process, or the prognosis."

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coagulopathy can also occur. Microcytosis is frequently seen with portosystemic shunts. In patients with liver failure or portosystemic shunts, it is common to find ammonium biurate crystals in the urine sediment.

Radiography can help determine the size, shape, position, opacity, and edges of the liver, and will also detect the presence of any gas or mineralization **(Figure 2)**. Ultrasound helps to determine the extent of hepatic injury (focal, multifocal, or diffuse), as well as evaluation of vascularization, and can aid sampling (for cytology, culture, and biopsy) **(Figure 3)**. Remember that the absence of ultrasound changes is not synonymous with a healthy liver.

Liver cytology is mainly of value when dealing with multifocal or diffuse metabolic or neoplastic processes (*e.g.*, round cell tumor, vacuolar hepatopathies) **(Figure 4)**. However, sensitivity is low when compared with histopathology, but since the process is fast, minimally invasive, and safe, I recommend it in many cases as a first step for taking liver samples. Ultrasound-guided cholecystocentesis is another useful minimally invasive test, with few associated complications (14).

Histopathology is necessary to distinguish malignant and benign neoplasia, identify vascular abnormalities (portal vein hypoplasia), cirrhosis, inflammatory processes, or liver disease due to copper accumulation or other metals/substances **(Figure 5)**. Following coagulation tests, it is essential to always obtain multiple samples of the liver lobes, and various methods (Tru-Cut©, laparotomy, or laparoscopy) may be employed. It is extremely important that the pathologist follows the World Small Animal Veterinary Association (WSAVA) guidelines for liver histopathology[1] when interpreting the samples.

Hyperbilirubinemia

When presented with a jaundiced dog, it is crucial to determine the origin of the hyperbilirubinemia (pre-, post-, or hepatic) via blood sampling and ultrasound imaging **(Figure 6)**. Recent studies have shown that bacterial cholangitis and cholecystitis in dogs are possibly more common than was previously thought (15). The most typical clinicopathological findings are an increase in liver enzymes, hyperbilirubinemia, and neutrophilia. The most frequent ultrasound findings are distension of the bile duct, thickening of the gallbladder wall, distension of the gallbladder, and the presence of bile sediment or mucocele. Bile sampling is important to check for potential antibiotic resistance, and the preferred treatment for the condition is usually cholecystectomy, which also allows for biopsies/cultures to be obtained. Other common conditions of the gallbladder and bile ducts are mucocele, cholelithiasis, and neoplasia.

[1] https://www.wsava.org/Guidelines/Liver-Disease-Guidelines

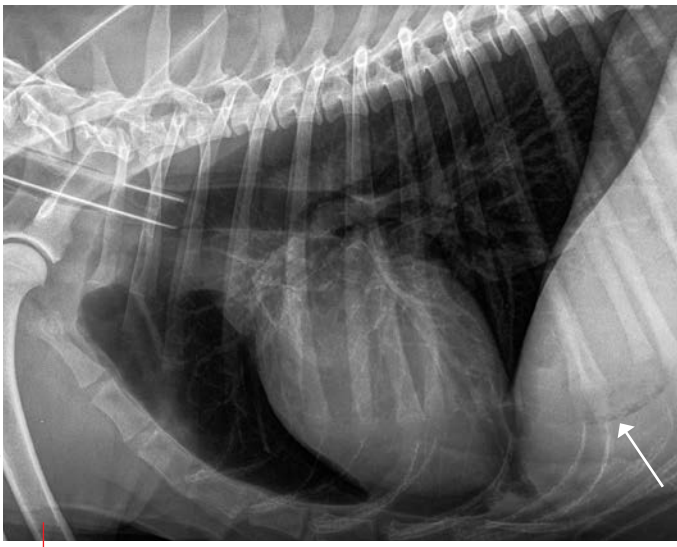

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Figure 2. A lateral radiograph of a dog's thorax and anterior abdomen; there is gas in the gallbladder (arrowhead) due to emphysematous cholangitis.

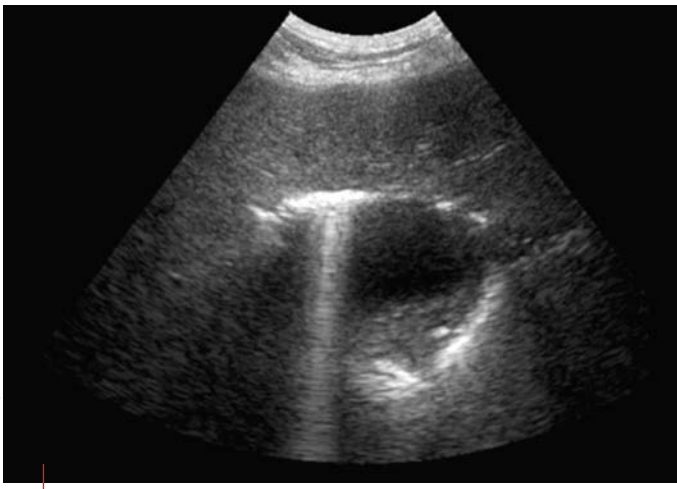

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Figure 3. An abdominal ultrasound of a dog with gas in the gallbladder due to emphysematous cholangitis.

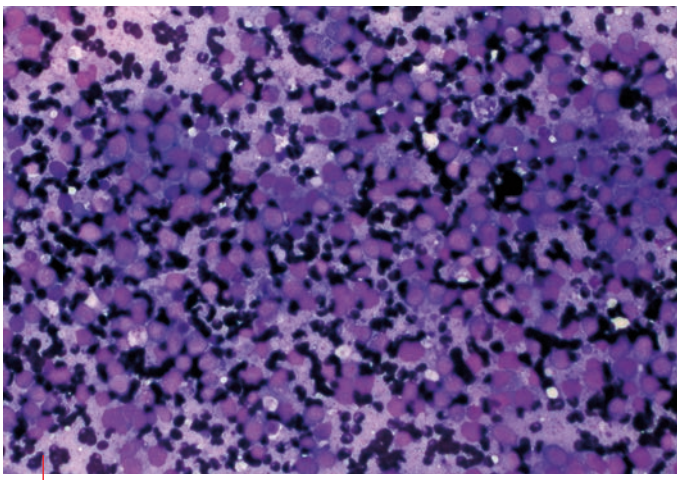

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Figure 4. A liver cytology sample showing mononuclear proliferation with prominent nucleoli, compatible with lymphoma.

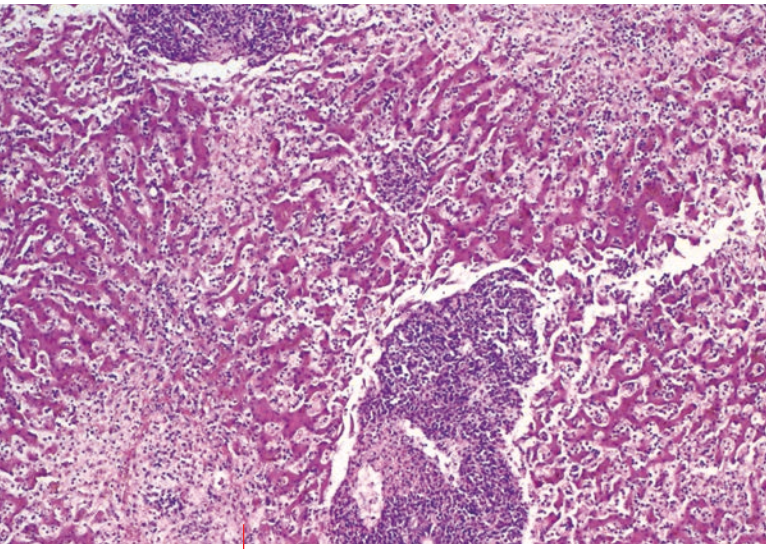

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Figure 5. Histopathology of liver tissue stained with H&E showing dense aggregates of monomorphic round cells expanding into the portal tracts and centrilobular areas, as well as circulating in sinusoids and interrupting hepatic cords. This is compatible with lymphoma.

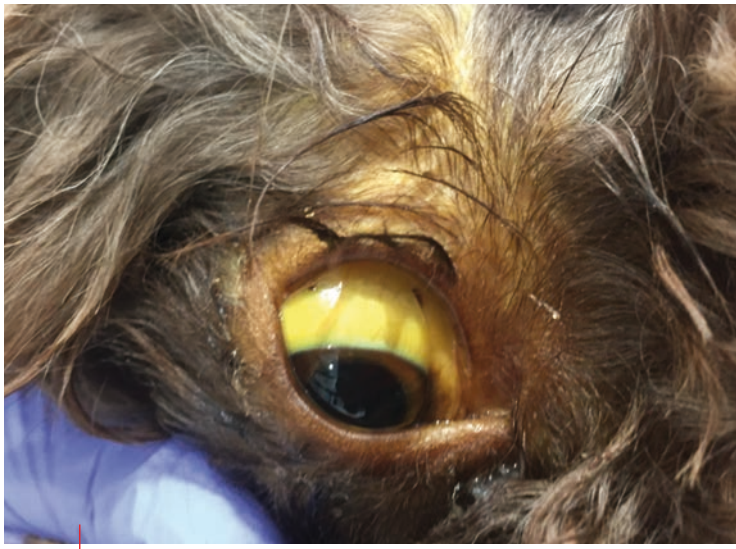

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Figure 6. Severe jaundice in the sclera of a patient with cholangitis.

Secondary liver disease

It is possible that the most difficult part of approaching a patient with increased liver enzymes is distinguishing between primary or secondary liver disease. The changes found in patients with secondary liver disease are typically due to a non-specific reactive hepatitis. Most cases show increased enzyme levels compatible with cell damage (ALT and AST) and enzyme induction (AP and GGT). However, altered liver function is rare except with functional cholestasis. Biopsy will demonstrate an inflammatory infiltrate in the portal areas and parenchyma, without signs of liver necrosis. Other changes can also be seen, such as vacuolar degeneration, lipidosis, or cholestasis, the latter being the most common histopathological finding in biopsies. Patients with primary liver disease are more likely to have more serious clinical signs, such as hepatomegaly, microhepatica, jaundice, or hepatic encephalopathy.

"It is possible that the most difficult part of approaching a patient with increased liver enzymes is distinguishing between primary or secondary liver disease. The changes found in patients with secondary liver disease are typically due to a non-specific reactive hepatitis."

Jordi Puig

Chronic hepatitis

Chronic hepatitis often presents in dogs with vague clinical signs and increased liver enzymes. At the histopathological level, it is characterized by apoptosis or necrosis associated with an inflammatory infiltrate (mixed or lymphoplasmacytic) which tends to progress to fibrosis and cirrhosis with liver failure. The etiology is diverse (copper storage disease, infectious agents, drugs, etc.) although in many cases the cause is unknown (idiopathic chronic hepatitis). Some breeds are predisposed to chronic hepatitis; the most studied ones are those prone to copper storage hepatopathy. It is important to remember that to quantify the amount of hepatic copper, a large sample (1-2 grams) of liver biopsy tissue is required. Various infectious agents can also cause chronic hepatitis, including *Leptospira*, *Leishmania*, *Babesia*, and *Ehrlichia spp*. The most common histopathological finding in animals with leishmaniasis is a granulomatous inflammation or multifocal pyogranulomatous inflammation in the hepatic portal areas.

What about the asymptomatic patient?

It is common to detect elevated liver enzymes in an asymptomatic patient; one study in a group of healthy dogs of differing ages revealed significant numbers of animals had increased levels of ALT, AST, AP, and/or GGT, at 17%, 11%, 39%, and 19% respectively (16). My first step in this situation is to confirm the results (by repetition of the tests or by obtaining a second sample, avoiding hemolysis or lipemia) to exclude laboratory error. Obtaining a clinical history is important in order to detect causes such as drug administration (including topical treatments or drops) or signs not recognized by the owners beforehand. Age is important; young animals can show mild increases in AP, and in older animals enzyme increases tend to be compatible with benign processes (nodular hyperplasia), neoplasia, or vacuolar hepatopathies. One of the most important steps is to determine the origin of the enzyme change, since in many cases the primary pathology is distant to the liver. Diagnosis and resolution of the primary cause will often result in normalization of the enzymes; for example, 50% of dogs with tracheal collapse have increased liver enzymes and bile acids, possibly due to hepatic hypoxia. Although treating the respiratory problem reduces the bile acid levels, hepatic enzymes tend to remain high (17).

An increase in AP detected during an annual check-up or a pre-anesthetic analysis is a common finding. Since increased AP could be due to an isoenzyme, obtaining the clinical history must be exhaustive. The most common endocrine diseases associated with an increase in AP are diabetes, hyperadrenocorticism, and hypothyroidism. 90% of hyperadrenocorticism cases have increased AP, due to enzyme induction and vacuolation of the hepatocytes with glycogen, causing cholestasis. In diabetes mellitus, there is vacuolation of hepatocytes with lipidosis and cholestasis. As noted above, the most common causes of increased AP in asymptomatic older dogs are vacuolar hepatopathy, nodular hyperplasia, or neoplasia.

Vacuolar hepatopathy may be linked to endogenous or exogenous corticosteroids, and this can sometimes be severe, with cholestasis and cell damage leading to an increase in ALT (18). In 50% of the cases described, there is no evidence of adrenal disease or exogenous administration of corticosteroids, and the exact cause is unknown.

Nodular hyperplasia is characterized by multiple nodules in the liver parenchyma and is a benign condition in older dogs. The etiology is unknown, but the WSAVA categorization of liver disease classifies it as a neoplastic process. It is important to distinguish hyperplasia from tumor-related processes or cirrhosis. The increase in AP may be accompanied by slight increases in ALT, but liver function in these cases is normal. There is no specific treatment, although a biochemistry check-up and regular ultrasound every 6-12 months is recommended.

CONCLUSION

Elevated hepatic enzymes are a common finding in small animal practice but such results do not tell us about the functional capacity of the patient's liver. There are numerous causes for such findings, and the clinician must take into account other diagnostic tests, the patient's history and the clinical signs to make an appropriate diagnosis and thus enable correct treatment.

REFERENCES

1. Stockham SL, Scott MA. Enzymes. In; *Fundamentals of Veterinary Clinical Pathology*. Iowa; John Wiley & Sons 2008;639-674.
2. Center SA. Interpretation of liver enzymes. *Vet Clin North Am Small Anim Pract* 2007;37(2):297-333.
3. Chapman SE, Hostutler RA. A laboratory diagnostic approach to hepatobiliary disease in small animals. *Vet Clin North Am Small Anim Pract* 2013;43(6):1209-1225.
4. Toulza O, Center SA, Brooks MB, *et al*. Evaluation of plasma protein C activity for detection of hepatobiliary disease and portosystemic shunting in dogs. *J Am Vet Med Assoc* 2006;229(11):1761-1771.
5. Fernandez NJ, Kidney BA. Alkaline phosphatase: beyond the liver. *Vet Clin Pathol* 2007;36(3):223-233.
6. Weingarten MA, Sande AA. Acute liver failure in dogs and cats. *J Vet Emerg Crit Care (San Antonio)* 2015;25(4):455-473.
7. Stewart JE, Haslam AK, Puig J. Pathology in practice; acetaminophen (paracetamol) toxicosis. *J Am Vet Med Assoc* 2016;248(9):1009-1011.
8. Müller PB, Taboada J, Hosgood G, *et al*. Effects of long-term phenobarbital treatment on the liver in dogs. *J Vet Intern Med* 2000;14(2):165-171.
9. Gaskill CL, Miller LM, Mattoon JS, *et al*. Liver histopathology and liver and serum alanine aminotransferase and alkaline phosphatase activities in epileptic dogs receiving phenobarbital. *Vet Pathol* 2005;42(2):147-160.
10. Dayrell-Hart B, Steinberg SA, Van Winkle TJ, *et al*. Hepatotoxicity of phenobarbital in dogs: 18 cases (1985-1989). *J Am Vet Med Assoc* 1991;199(8):1060-1066.
11. Wallisch K, Trepanier LA. Incidence, timing, and risk factors of azathioprine hepatotoxicosis in dogs. *J Vet Intern Med* 2015;29(2):513-518.
12. Center SA, Warner KL, McCabe J, *et al*. Evaluation of the influence of S-adenosylmethionine on systemic and hepatic effects of prednisolone in dogs. *Am J Vet Res* 2005;66(2):330-341.
13. Skorupski KA, Hammond GM, Irish AM, *et al*. Prospective randomized clinical trial assessing the efficacy of Denamarin for prevention of CCNU-induced hepatopathy in tumor-bearing dogs. *J Vet Intern Med* 2011;25(4):838-845.
14. Policelli Smith R, Gookin JL, Smolski W, *et al*. Association between gallbladder ultrasound findings and bacterial culture of bile in 70 cats and 202 dogs. *J Vet Intern Med* 2017;31(5):1451-1458.
15. Tamborini A, Jahns H, McAllister H, *et al*. Bacterial cholangitis, cholecystitis, or both in dogs. *J Vet Intern Med* 2016;30(4):1046-1055.
16. Comazzi S, Pieralisi C, Bertazzolo W. Haematological and biochemical abnormalities in canine blood: frequency and associations in 1022 samples. *J Small Anim Pract* 2004;45(7):343-349.
17. Bauer NB, Schneider MA, Neiger R, *et al*. Liver disease in dogs with tracheal collapse. *J Vet Intern Med* 2006;20(4):845-849.
18. Sepesy LM, Center SA, Randolph JF, *et al*. Vacuolar hepatopathy in dogs: 336 cases (1993-2005). *J Am Vet Med Assoc* 2006;229(2):246-252.

HOW I APPROACH... THE CAT WITH CHOLANGITIS

A jaundiced cat is not a diagnosis, but rather the starting point for the clinician to investigate the possible underlying causes. Professor Craig Webb explains his approach to such cases.

KEY POINTS

1. Cats don't actually present with cholangitis, they present as sick cats.
2. Sick cats don't present with cholangitis, they present with non-specific signs that could be almost anything.
3. Yellow (icterus or jaundice) is a color, not a diagnosis.
4. Feline cholangitis was the motivating disease behind the search for feline triaditis.

Introduction – a historical perspective

As early as 1996, veterinarian Dr. Sharon Center adeptly summarized the peculiarities of the feline hepatobiliary system and highlighted distinct disease differences between cats and dogs, stating that "cholangitis and cholangiohepatitis are more common in the cat than the dog. The anatomic difference in the biliary duct/pancreatic duct anatomy has long been considered an important predisposing factor in this species difference." (1). Dr. Center collected, analyzed, and cited studies in cats going back to the 1980's that described suppurative cholangitis and chronic lymphocytic cholangitis (2,3) and dug deep enough to uncover the description of 47 icteric cats from 1977 (4). She actually anticipated feline triaditis, noting that "although evaluation for inflammatory bowel disease and pancreatitis has not been thorough in every cat reported to date, they appear to be commonly associated [with cholangitis] conditions".

1996 was also the year that the first study was published quantifying the association in cats between inflammatory hepatic disease, inflammatory bowel disease (IBD), pancreatitis, and nephritis (the condition that fell out of the equation, to leave "triaditis") (5). This marked the beginning of a serious and fruitful effort to better understand liver disease in cats, or (as it was then referred to) the feline cholangiohepatitis complex, or feline cholangitis/cholangiohepatitis (6).

Clinical research attempted to characterize feline inflammatory and lymphocytic liver disease using ultrasound, immunohistochemistry, and clinical presentation (7-9). Potential infectious etiologies, such as *Bartonella*, *Enterococcus*, and *Helicobacter*, were described, and the first report of an infectious organism ascending from the gastrointestinal tract to cause cholangitis in a kitten appeared in the literature (10-13).

A decade later the World Small Animal Veterinary Association Liver Standardization Group attempted to categorize the defining features of feline biliary disease and organize the vocabulary for the veterinary profession (14), and the remainder of this discussion will focus on what we have learned since then. But it is important to realize that although our understanding of this condition has been helped by new technologies and diagnostics, the foundation had been laid and the pathway had been paved by those featured in the cited chapter (1), including Dr. Center herself.

The approach

We start with a sick cat. Sick cats present to veterinarians because they are vomiting, or having diarrhea, or eating less (or maybe not eating at all), losing weight, hiding or becoming "clingy", less active, vocalizing and seemingly painful, salivating excessively, or just looking miserable. Reasons for the depth and variety of clinical presentations consistent with feline cholangitis are that I) it's a cat,

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and II) cats frequently bring more than one problem with them to the veterinarian. Although feline triaditis is a named example of this phenomenon, there are a dozen conditions that might easily be associated with cholangitis: these include IBD, pancreatitis, chronic bacterial infection(s) including pyelonephritis, trematode infestation, toxoplasmosis, septicemia, cholelithiasis, extrahepatic biliary obstruction (EHBO) and neoplasia (1). Although there is long way to go before establishing a diagnosis, potentially helpful information to obtain at the outset, with history and physical examination, include:

- Gender and age
- Does the cat live in North America, Europe or elsewhere?
- Does the cat live in an area that is known for liver flukes? (a cause of feline cholangitis which is not covered here)
- How long has the cat been sick (a few days, a few weeks)?
- Has the cat lost weight?
- Is the cat vomiting, does it have diarrhea, is it nauseous, lethargic or anorexic?
- Are the clinical signs consistent, persistent, progressive, or intermittent?
- Is the cat yellow (icteric, jaundice)?
- Is the cat febrile or dehydrated?
- Does abdominal palpation reveal discomfort (and if so where?), organomegaly (and if so what?), or free fluid?

Some notes of caution

1. If, as you gaze into the eyes (or more specifically, the sclera) of the cat on the examination table you notice that the cat is yellow (icteric, jaundiced), do not jump for joy assuming you have arrived at a diagnosis simply by walking into the exam room and looking at your patient, because you should not jump to the conclusion that this cat has liver disease. If the cat is icteric then its total bilirubin will likely be ⩾ 2.5-3.0 mg/dL, and if you had to place a bet, you would in fact bet on primary liver disease. However, it would be much more prudent to first exclude causes of pre-hepatic hemolysis of erythrocytes **(Table 1)**.

2. If, as you gaze into the eyes of the cat on the examination table you notice that the cat is not yellow (icteric, jaundice), do not announce to the owner that their cat's total bilirubin will be normal and liver disease is "off the table", because cats may have a total bilirubin that is above normal without being high enough to turn the cat yellow. Cats with a total bilirubin ⩽ 2.5-3.0 mg/dL but above the normal reference range are hyperbilirubinemic. If you had to place a bet, you would in fact bet on something other than pre-hepatic hemolysis or primary liver disease (*e.g.*, reactive liver disease), but it would again be much more prudent to work through the differentials for other diseases that might impact the liver as collateral damage, which includes almost anything.

3. Although post-hepatic causes of hyperbilirubinemia (extrahepatic biliary obstruction [EHBO]) are rare in cats, they do occur and need to be considered **(Table 2)**.

Table 1. Published and presumed causes of immune-mediated hemolytic anemia (IMHA) in cats.

Primary IMHA
Infectious • *Mycoplasma haemofelis*, *M. haemominutum*, *M. turicensis* • FeLV/FIV/FIP • *Babesia felis* • *Cytauxzoon felis* • *Dirofilaria spp.*
Neoplastic • Lymphosarcoma or leukemia • Myeloproliferative disease
Inflammatory • Abscessation • Cholangitis • Pyothorax • Pancreatitis
Other • Vaccine reaction (polyvalent modified live) • Transfusion reaction • Neonatal isoerythrolysis • Methimazole • Increased osmotic fragility (cats) • Pyruvate kinase deficiency • Hypophosphatemia • Heinz body anemia (due to, *e.g.,* onions, propylene glycol)

Table 2. Published and presumed causes of extrahepatic biliary obstruction in cats.

Anatomic
Intraluminal • Choleliths/choledocholithiasis • Inspissated bile (biliary sludge) • Biliary foreign body (*e.g.*, grass awns) • Biliary mucocele • Common bile duct avulsion (trauma) • Helminth parasites
Extraluminal • Pancreatitis • Neoplasia (*e.g.*, carcinoma, adenocarcinoma) • Diaphragmatic hernia • Congenital
Functional/inflammatory
Pancreatitis/pancreatic abscess Cholangitis Cholecystitis Duodenitis Gallbladder dysmotility

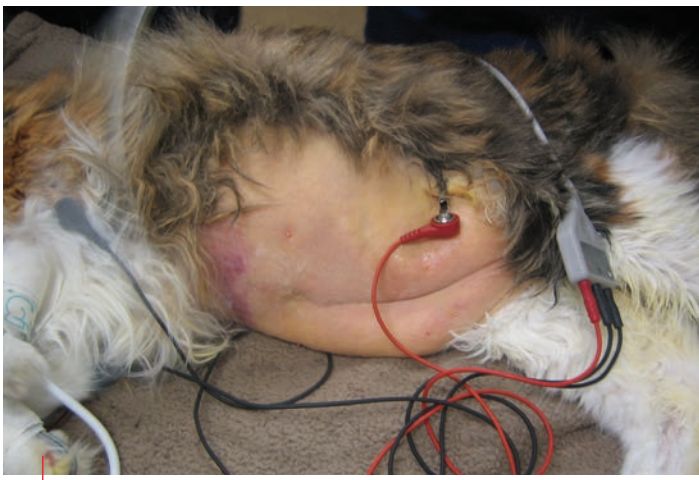

Figure 1. A cat with hepatic lipidosis shaved for an ultrasound scan of the liver; note the easily bruised, icteric abdomen.

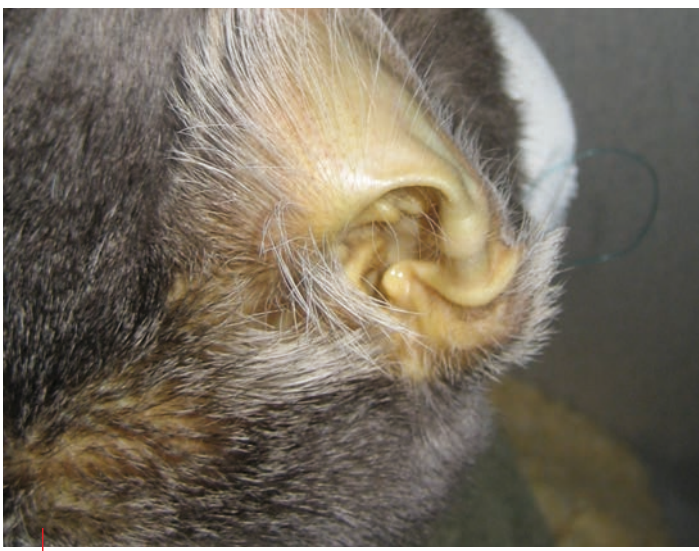

Figure 2. A yellowish tinge to a cat's pinna may be the first sign of jaundice, but the yellow coloration does not automatically indicate liver disease.

The liver as the culprit in the cat

Having considered, and appropriately ruled out both pre- and post-hepatic causes of hyperbilirubinemia in the yellow cat, or having settled on the liver as the most likely etiology for the sick cat, we now target that organ with our diagnostic effort.

The terminology

Although hepatic lipidosis is one of the most prevalent conditions diagnosed in yellow cats **(Figure 1)**, it is beyond the scope of this article, as are reactive hepatopathies, neoplastic diseases, and vascular disorders. Chronic cholangitis associated with liver flukes (*Platynosomum concinnum* – also know as *P. fastosum)* (15) is an inflammatory liver disease that will also not be covered. This paper will focus on the two most common WSAVA inflammatory liver diseases (16), namely neutrophilic cholangitis (acute or chronic), and lymphocytic cholangitis, using case reports to identify key features of these conditions and to emphasize the need for a methodical approach to the diagnosis.

Case presentation #1

The patient is an 11-year-old male castrated Norwegian Forest Cat with a 3-month history of progressive vomiting and diarrhea. The cat has a mildly decreased appetite and has lost some weight. The owner perceives a yellowish tinge to the cat's pinna **(Figure 2)** but otherwise the cat appears bright and interactive. Physical examination confirms jaundice and hepatomegaly, but is otherwise unremarkable.

Key features

First, the patient is an icteric Norwegian Forest Cat being seen at a clinic in Europe; this has got to be a clue! A recent survey found that the most frequent liver diseases in cats from the UK, based on histopathology, included neutrophilic cholangitis (20.5% of cases) and lymphocytic cholangitis (6.8%) (17). In another recent study from the Netherlands, 2 of 14 cases of lymphocytic cholangitis used to investigate immunohistochemical markers were Norwegian Forest Cats (18), and the majority of clinical studies on lymphocytic cholangitis

come from Europe (8,19). That being said, 3 of 44 cats undergoing necropsy at the University of Pennsylvania Veterinary Hospital were identified as having lymphocytic cholangitis (20).

This particular patient is an older cat, and although there are generalizations about the age of presentation, it is clear that all forms of feline inflammatory liver disease can afflict a very broad range of age groups. It is noteworthy that this case is chronic and progressive, although the cat is not yet lethargic, anorexic, or febrile. Such a presentation should raise the index of suspicion for lymphocytic cholangitis. The chronicity and course of disease are certainly not pathognomonic, and cats with lymphocytic cholangitis can present as quite ill, with ascites and in poor body condition, but it would be unusual for a cat with acute neutrophilic cholangitis to be handling such an illness as well as this cat is at presentation.

Diagnosis

Going forward with the diagnostic work-up, the complete blood count (CBC) is not likely to be markedly abnormal, although some cats will have a significant lymphocytosis and a mild anemia with chronic disease. The elevation in liver enzymes and total bilirubin will be mild to moderate. Once the bilirubin is elevated enough to turn the cat yellow the bile acids test is redundant – it will be abnormal. FeLV/FIV testing will be negative, clotting times may be somewhat prolonged, but the most striking biochemical abnormality will most likely be a hyperglobulinemia (with gammaglobulins being the predominant peak should you run protein electrophoresis). If present, free abdominal fluid would have a high-protein content (again, increased globulin levels) and contain a variety of inflammatory cells.

Abdominal ultrasound would be a reasonable diagnostic recommendation in this case, not necessarily for what it will show (non-specific hepatic changes and lymphadenopathy), but for what it will not show. The gallbladder and biliary tree in this cat will most likely look unremarkable.

As we will discuss in the next case, fine-needle aspirate (FNA) of the liver is a low-risk procedure, but owners should be warned that it is also often a low-yield diagnostic that frequently produces frustrating rather than fruitful results. If the gallbladder contents, and particularly, the gallbladder wall look normal, studies suggest that aspiration of the gallbladder contents would also be low yield (see next case).

The most compelling argument for obtaining a liver biopsy is, of course, the fact that it is the best way to obtain a definitive diagnosis. In this case, the rule-out that looms largest on the list of differentials would be lymphoma, with FIP perhaps entering the argument in a cat of the appropriate age (high-protein ascites and hyperglobulinemia). In either case, hepatic histopathology would distinguish between these possibilities. The other compelling argument for obtaining a liver biopsy is that you could also obtain biopsy samples of the pancreas and the intestinal tract. The identification and treatment of concurrent diseases is absolutely critical to the successful treatment of a cat with any form of cholangitis.

"Although post-hepatic causes of hyperbilirubinemia (extrahepatic biliary obstruction) are rare in cats, they do occur and need to be considered whenever the clinician is presented with a jaundiced cat."

Craig B. Webb

Treatment

Having arrived at either a definitive (histopathology - **Figure 3**) or speculative (case presentation) diagnosis of lymphocytic cholangitis the treatment targets include non-specific support and an immune-mediated etiology. Non-specific therapy will include vitamin K_1 (5 mg/cat SC q24H) with several doses given in support of the cat's coagulation pathways prior to hepatic FNA or placement of an esophageal feeding tube, and ursodeoxycholic acid (10-15 mg/kg

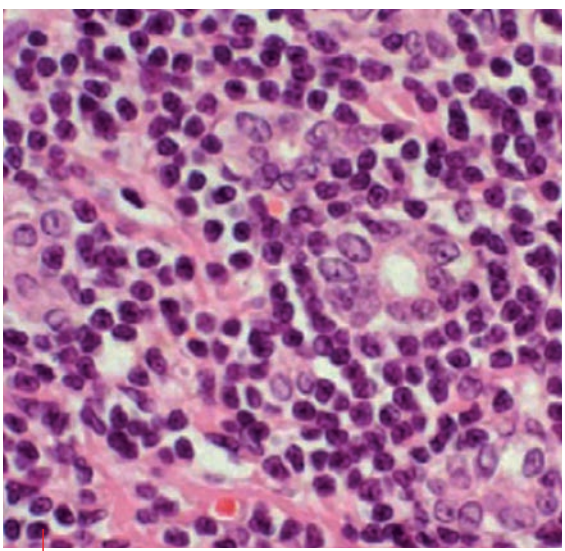

Figure 3. Histopathology of a cat's liver with lymphocytic cholangitis. Note the marked infiltration of small lymphocytes in the portal area and concurrent biliary proliferation.

PO q24H for 2-3 months). This drug is traditionally used to help move bile out of the biliary system, and may have a number of additional beneficial properties for a liver in need (21).

Antibiotics should not be necessary if the disease is an immune-driven infiltration of lymphocytes. Even if the original inciting cause was a bacterial infection, at the time of this case presentation, infection is a historical event. That said, some clinicians recommend a 2-4 week course of antibiotics covering enteric and/or anaerobic bacteria at the beginning of treatment (see **Case 2**), and bacteria may be present, not as the cause, but as a consequence of the immune-mediated disease (19).

Placement of an esophageal feeding tube is recommended as an early and effective intervention in any cat that has stopped eating **(Figure 4)**. It is also an excellent way to empower the owner to better medicate and care for their cat in the comfort of their own home. At CSU we use the 14Fr MILA International, Inc. esophagostomy feeding tube and tunneler[1].

The specific treatment for lymphocytic cholangitis is glucocorticoid therapy, prednisolone being the drug of choice. Some clinicians will start as high as 4 mg/kg/day, many will start closer to 2 mg/kg/day, but all will taper slowly over a 3-month duration.

Clinical signs, mucosal color, and abnormalities in liver enzymes and total bilirubin are all reasonable markers to follow in documenting a response to therapy.

Case presentation #2

This patient is a 6-year-old male castrated domestic longhair seen in the United States. The cat is presenting for a history of vomiting, anorexia, and lethargy for four days. Physical examination reveals an icteric, febrile, dehydrated cat **(Figure 5)** that is uncomfortable on abdominal palpation and may be nauseous and salivating. A biochemical profile shows hyperbilirubinemia, hyperglobulinemia, moderate to significantly elevated ALT activity with a variable elevation in ALP, and non-specific changes associated with dehydration (azotemia), stress or acute pancreatitis (hyperglycemia), and electrolyte abnormalities. In addition to a mild anemia the CBC also shows some significant changes not found in **Case 1**: namely, a lymphopenia, leukocytosis, and a neutrophilia with a left shift.

[1] www.milainternational.com; www.youtube.com/watch?v=qF14Jfajkhw&t=89s

"Cats rarely have a method to their madness, but having a method will help keep you from going mad."

Craig B. Webb

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Figure 4. Placement of an esophageal feeding tube is recommended as an early and effective intervention in any cat that has stopped eating.

Key features

Unlike the previous case in a Norwegian Forest Cat, in the United States we have no geographically specific exotic breeds, and as for age, this is simply an adult cat, although younger than the cat in **Case 1**. (Outside of the US, we might be featuring such breeds as the Burmese, Persian, Siamese, or the British Shorthair). The clinical signs are quite similar to **Case 1**, with the biggest differences being the brief and relatively more severe presentation of the patient. The difference in severity is highlighted by the presence of a fever and an inflammatory leukogram, and a greater number of abnormalities on the biochemical profile. Such a presentation should raise the index of suspicion for neutrophilic cholangitis. The discomfort on abdominal palpation may be the result of an acutely inflamed, infected, and enlarged liver, or the presence of pancreatitis – again, highlighting the commonality and importance of concurrent conditions (including pancreatitis, IBD, EHBO, cholecystitis or cholelithiasis, etc.). It is likely this cat will have some degree of a coagulopathy requiring vitamin K_1, and again, by the time the hyperbilirubinemia is turning the cat yellow the bile acids test will be abnormal and redundant. It is prudent to test a fasted serum sample for fPLI and cobalamin levels.

Diagnosis

Abdominal ultrasound will now be critical for what we do find, and what we take **(Figure 6)**. Imaging the pancreas and intestinal wall thickness/architecture will help in the pursuit of feline triaditis; changes in the hepatic parenchyma will still be non-specific, but the gallbladder will likely serve as the site and source of a diagnosis. It is possible for a cat with neutrophilic cholangitis to present with a biliary system that images normally, but in many cases the gallbladder wall will be thick and irregular, even palisading **(Figure 7)** (22). Sludge **(Figure 8)** or choleliths may be present, and it is important to follow the biliary tract to the duodenum to rule out EHBO. The common bile duct is obstructed in many of these cats. Ascites may be present, in which case aspiration and fluid analysis is warranted.

It is gallbladder aspiration (ultrasound-guided percutaneous cholecystocentesis) for cytology and culture that is most likely to produce a diagnosis, and direct treatment **(Figure 9)** (23). This procedure is most likely to yield abnormal cytology and positive bacterial culture results if the gallbladder appears abnormal on imaging, *e.g.*, if wall thickness is > 1 mm, there is irregular or palisading wall thickness, or significant hyperechoic content ("sludge") **(Figure 10)** (22,24). Note that gallbladder wall rupture and/or leakage of contents and bile peritonitis is a potential risk with aspiration, but there are very few problems when performed by an experienced ultrasonographer in a cooperative and/or sedated patient. However, if the gallbladder wall appears emphysematous, the risks are considerable, and either surgical removal or trial treatment should be considered instead.

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Figure 5. The cat presented as dehydrated and miserable with obvious icterus.

Aspirated bile may appear grossly normal or as a purulent exudate. Cytology is likely to be dominated by neutrophils in various states (*i.e.*, normal to

Figure 6. Imaging the pancreas and intestinal wall thickness/architecture will help in the pursuit of feline triaditis.

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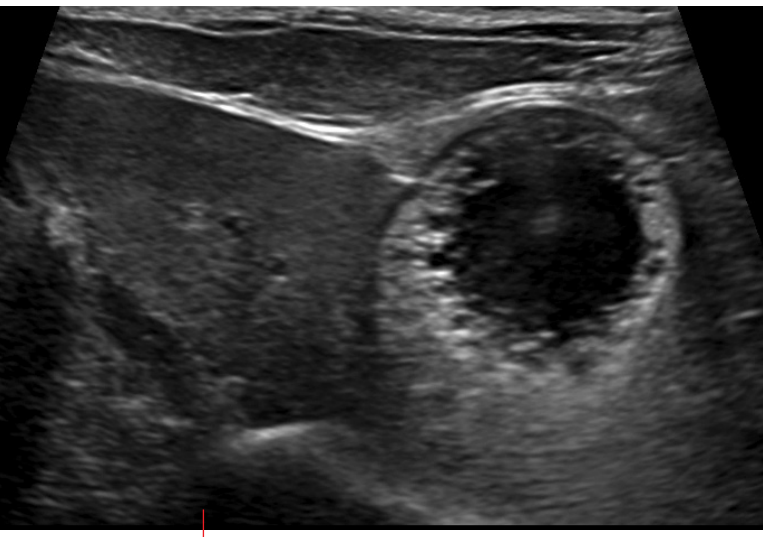

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Figure 7. Transverse ultrasound image of a feline gallbladder demonstrating thickened wall with a palisading appearance, consistent with cholangitis.

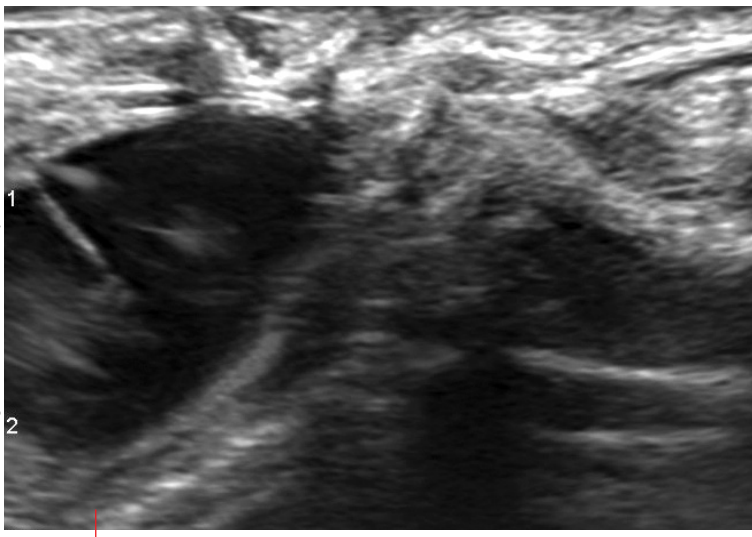

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Figure 9. A feline gallbladder scan showing the aspiration needle as a linear hyerechoic structure in the process of aspirating bile with sludge (swirling hyperechoic material).

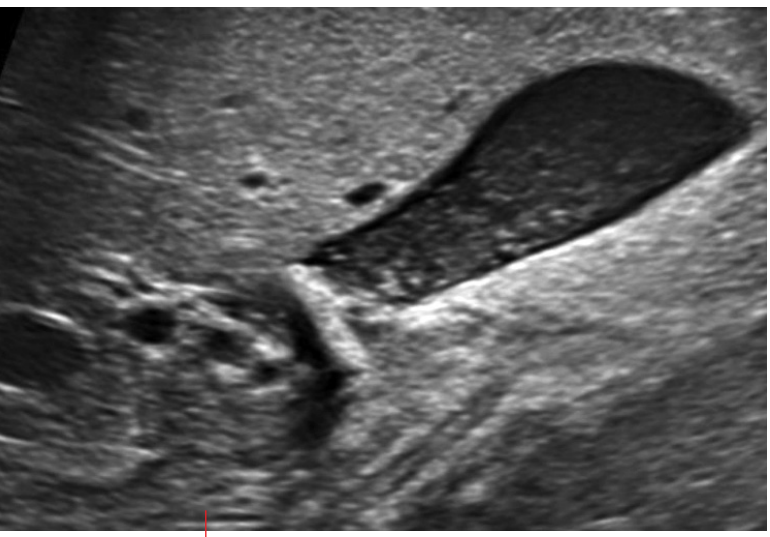

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Figure 8. As with dogs, cats will also present with "sludge" in their gallbladder. This is not necessarily a sign of disease. The architecture and width of the gallbladder wall appears to be a more sensitive indicator of cholangitis.

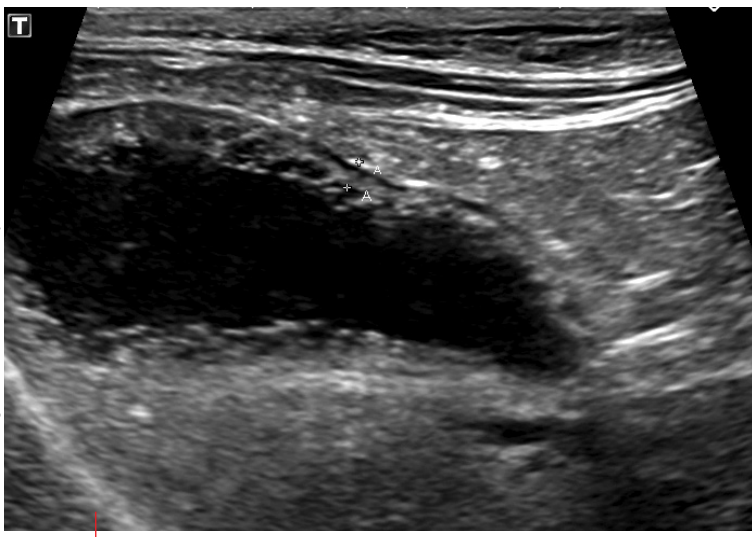

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Figure 10. A longitudinal sonographic image of a feline gallbladder where "calipers" are measuring wall thickness at 1.9 mm. This image also demonstrates the "palisading" like material "growing" off the inner wall into the lumen of the gallbladder.

degenerate) with or without evidence of intracellular bacteria (25). Unsurprisingly, the most frequently cultured organism is *E. coli*, followed by an extensive list of enteric and anaerobic organisms, such as *Enterococcus*, *Streptococcus, Klebsiella, Actinomyces, Clostridium, Bacteroides, Pseudomonas, Staphylococcus,* and *Pasteurella* species, and *Salmonella enterica* serovar Typhimurium.

Again liver FNA is minimally invasive but often of low yield in these patients. At CSU it is rare that we would seek a biopsy sample for hepatic histopathology, although we will perform abdominal laparoscopy on a number of these cats, collect biopsy samples of the liver and the pancreas, and aspirate the gallbladder with direct visualization during this procedure. Although histopathology helps obtain a definitive diagnosis and identify concurrent diseases, cholecystocentesis is most likely to be diagnostically fruitful and therapeutically relevant.

Treatment

These cats are frequently sick enough to benefit from hospitalization, supportive care (fluids, pain management, nutrition, etc.), and IV medications (antibiotics, anti-emetics, etc.).

Bacterial culture and sensitivity results from cholecystocentesis will ideally guide the choice of antibiotic, and cytology with gram stain may help in the initial choice while awaiting culture results. If a selection must be made without the benefit of either of these diagnostics, the choice of antibiotic(s) should be directed at *E. coli* with a spectrum broad enough to cover common enterics, including anaerobes (*e.g.*, clavimox, metronidazole, pradofloxacin, etc.). Recommendations for the length of treatment vary from 4-6 weeks to 3-6 months, following clinical signs and liver enzyme elevations for feedback as to effectiveness.

In addition to chronic neutrophilic cholangitis, one potential consequence of acute neutrophilic cholangitis might well be lymphocytic cholangitis, with infection as the original etiology but also acting as an inciting stimulus for a persistent immune-mediated response. Therefore these cases may go on to require treatment with prednisolone at some point following their course of antibiotics.

Vitamin K_1 and ursodeoxycholic acid, as described in **Case 1**, liver protectants, such as S-Adenosylmethionine, and cobalamin supplementation should also be considered. As with **Case 1**, it is critical to recognize the potential importance of concurrent diseases in these cats.

CONCLUSION

Neutrophilic cholangitis (both acute and chronic forms) appears to be the most common feline inflammatory liver disease in both the United States and the rest of the world, whilst lymphocytic cholangitis seems to show a preference for cats outside of the US, such as the Norwegian Forest Cat and Persian. In both cases, it appears that concurrent diseases are common, and commonly the cause of the demise of the cat. Once again, cats remind us that whether it is diabetic ketoacidosis, hepatic lipidosis or cholangitis, they may ignore the "Diagnostic Parsimony of Occam's Razor" (*i.e.*, the idea that if a patient has multiple clinical signs, a single diagnosis should be sought that accounts for all the clinical features, rather than attributing a different diagnosis to each), and will instead subscribe to Hickam's Dictum, which states "Patients can have as many diseases as they damn well please".

REFERENCES

1. Center SA. Diseases of the gallbladder and biliary tree. In: *Strombeck's Small Animal Gastroenterology*, 3rd ed. Guilford, Center, Strombeck, *et al* (eds). Philadelphia, WB Saunders Co 1996;37;860-888.
2. Hirsch VM, Doige CE. Suppurative cholangitis in cats. *J Am Vet Med Assoc* 1983;182:1223-1226.
3. Prasse KW, Mahaffey EA, DeNovo R, *et al*. Chronic lymphocytic cholangitis in three cats. *Vet Pathol* 1982;19:99-108.
4. Twedt D, Gilberton S. Icteric cats: A survey of 47 necropsied cats. *Anim Med Ctr Lab Newsletter* 1977;48.
5. Weiss DJ, Gagne JM, Armstrong PJ. Relationship between inflammatory hepatic disease and inflammatory bowel disease, pancreatitis, and nephritis in cats. *J Am Vet Med Assoc* 1996;209:1114-1116.
6. Day DG. Feline cholangiohepatitis complex. *Vet Clin North Am Small Anim Pract* 1995;25:375-385.
7. Newell SM, Selcer BA, Girard E, *et al*. Correlations between ultrasonographic findings and specific hepatic diseases in cats: 72 cases (1985-1997). *J Am Vet Med Assoc* 1998;213:94-98.
8. Day MJ. Immunohistochemical characterization of the lesions of feline progressive lymphocytic cholangitis/cholangiohepatitis. *J Comp Pathol* 1998;119:135-147.
9. Gagne JM, Armstrong PJ, Weiss DJ, *et al*. Clinical features of inflammatory liver disease in cats: 41 cases (1983-1993). *J Am Vet Med Assoc* 1999;214:513-516.
10. Kordick DL, Brown TT, Shin K, *et al*. Clinical and pathologic evaluation of chronic *Bartonella henselae* or *Bartonella clarridgeiae* infection in cats. *J Clin Microbiol* 199;37:1536-1547.
11. Boomkens SY, Kusters JG, Hoffmann G, *et al*. Detection of *Helicobacter pylori* in bile of cats. *FEMS Immunol Med Microbiol* 2004;42:307-311.
12. Greiter-Wilke A, Scanziani E, Soldati S, *et al*. Association of *Helicobacter* with cholangiohepatitis in cats. *J Vet Intern Med* 2006;20:822-827.
13. Lapointe JM, Higgins R, Barrette N, *et al*. *Enterococcus hirae* enteropathy with ascending cholangitis and pancreatitis in a kitten. *Vet Pathol* 2000;37:282-284.
14. Rothuizen J, Bunch SE, Charles JA, *et al*. (eds.) WSAVA Standards for Clinical and Histological Diagnosis of Canine and Feline Liver Disease. WSAVA standardization group. Philadelphia PA: Saunders Elsevier; 2006.
15. Carreira VS, Viera RF, Machado GF, *et al*. Feline cholangitis/cholangiohepatitis complex secondary to *Platynosmum fastosum* infection in a cat. *Rev Bras Parasitol Vet* 2008;17 Suppl 1:184-187.
16. Gagne JM, Weiss DJ, Armstrong PJ. Histopathologic evaluation of feline inflammatory liver disease. *Vet Pathol* 1996;33:521-526.
17. Bayton WA, Westgarth C, Scase T, *et al*. Histopathological frequency of feline hepatobiliary disease in the UK. *J Small Anim Pract* 2018;59:404-410.
18. Otte CM, Valtolina C, Vreman S, *et al*. Immunohistochemical evaluation of the activation of hepatic progenitor cells and their niche in feline lymphocytic cholangitis. *J Feline Med Surg* 2018;20:30-37.
19. Otte CMA, Gutiérrez PO, Favier RP, *et al*. Detection of bacterial DNA I bile of cats with lymphocytic cholangitis. *Vet Microbiol* 2012;156:217-221.
20. Callahan CJE, Haddad JL, Brown DC, *et al*. Feline cholangitis: a necropsy study of 44 cats (1986-2008). *J Feline Med Surg* 2011;13:570-576.
21. Floreani A, Mangini C. Primary biliary cholangitis: Old and novel therapy. *Eur J Int Med* 2018;47:1-5.
22. Brain PH, Barrs VR, Martin P, *et al*. Feline cholecystitis and acute neutrophilic cholangitis: clinical findings, bacterial isolates and response to treatment in six cases. *J Feline Med Surg* 2006;8:91-103.
23. Byfield VL, Clark JEC, Turek BJ, *et al*. Percutaneous cholecystocentesis in cats with suspected hepatobiliary disease. *J Feline Med Surg* 2017;19:1254-1260.
24. Smith RP, Gookin JL, Smolski W, *et al*. Association between gallbladder ultrasound findings and bacterial culture of bile in 70 cats and 202 dogs. *J Vet Intern Med* 2017;31:1451-1458.
25. Peters LM, Glanemann B, Garden OA, *et al*. Cytological findings of 140 bile samples from dogs and cats and associated clinical pathological data. *J Vet Intern Med* 2016;30:123-131.

Further reading

Boland L, Beatty J. Feline cholangitis. *Vet Clin North Am Small Anim Pract* 2017;47:703-724.

IMAGING OF THE LIVER AND PANCREAS

Imaging of the liver and pancreas can offer invaluable information when investigating possible diseases linked to these organs; Laurent Blond reviews the options.

KEY POINTS

1. Radiography allows assessment of liver size and contours, but does not allow evaluation of parenchymal changes unless gas or mineralization is present.
2. Ultrasound is a very useful modality to complete evaluation of the liver as it is cost-effective and non-invasive, and in most cases can be accomplished without sedation.
3. Computed tomography requires the patient to be under general anesthesia but is very helpful to image the entire liver, especially in large dogs where ultrasound may be limited.
4. Ultrasound is useful for imaging of the pancreas, although thorough evaluation and interpretation requires some experience.

Introduction

The various imaging modalities now available in small animal practice permit exceptional opportunities for the diagnosis of many conditions involving the liver and the pancreas. This paper briefly reviews the anatomy of both organs and discuss the pros and cons for each technique.

The liver

The liver is the largest organ within the abdomen, occupying most of its cranial aspect. Located between the diaphragm and the stomach, the liver is divided in several lobes: the right lateral and medial lobes, the left lateral and medial lobes, the quadrate lobe, and the caudate lobe, which has a papillar process and a caudate process. The liver has two venous systems, portal and systemic.

The liver is closely associated to the gallbladder, which is located between the right medial and quadrate lobes, and the right kidney is in contact with the caudate process of the liver.

Radiography

Radiographs allow evaluation of liver size and contours, but do not allow evaluation of parenchymal changes unless associated with gas or mineralization. Two orthogonal views of the patient's abdomen are necessary (lateral and ventrodorsal) and should be taken on expiration. It is important to include the cranial margin of the diaphragm on abdominal radiographs to entirely evaluate the liver.

The hepatic silhouette cannot be differentiated from the diaphragm and is delineated caudally by the stomach. The caudoventral aspect of the normal liver has angular margins **(Figure 1)**. The gastric axis may help to evaluate liver size as it should be visible on a lateral radiographic view between a line drawn at 90 degrees to the spine and a line parallel to the last pair of ribs. If the gastric axis is displaced beyond the last pair of ribs, or if the caudoventral margin of the liver extends caudal to the ventral aspect of the stomach, it indicates hepatomegaly. If the stomach is displaced cranially then the liver is probably small, although this can be normal in deep-chested dogs such as the Boxer, Doberman or Great Dane. Hepatic diseases are often associated with ascites which may preclude evaluation of the liver, but the presence of peritoneal fluid, characterized by loss of serosal detail and, in severe cases, a pendulous abdomen, should be easily recognized on abdominal radiographs.

A liver mass may deform the hepatic contour and may induce various mass effects (*i.e.*, the secondary pathological effects caused by a mass pushing on or displacing surrounding tissue). A liver tumor will displace the pylorus caudomedially if coming from the right side, or will distort the cranial contour of the gastric fundus if originating from the center or left side of the liver.

The gallbladder cannot normally be seen on radiography. However, in some cats, the ventral aspect of the gallbladder can project beyond the ventral margin of the hepatic silhouette on the falciform fat, and should not be mistaken for a

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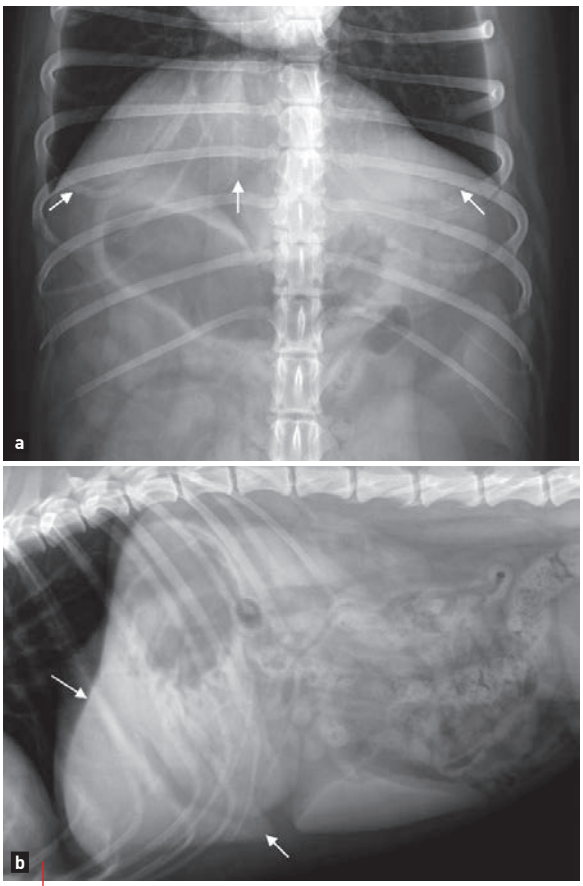

Figure 1. Abdominal radiographs of a dog (ventrodorsal **(a)** and lateral **(b)** projections) showing a normal liver (white arrows). The caudoventral aspect of the normal liver has angular margins.

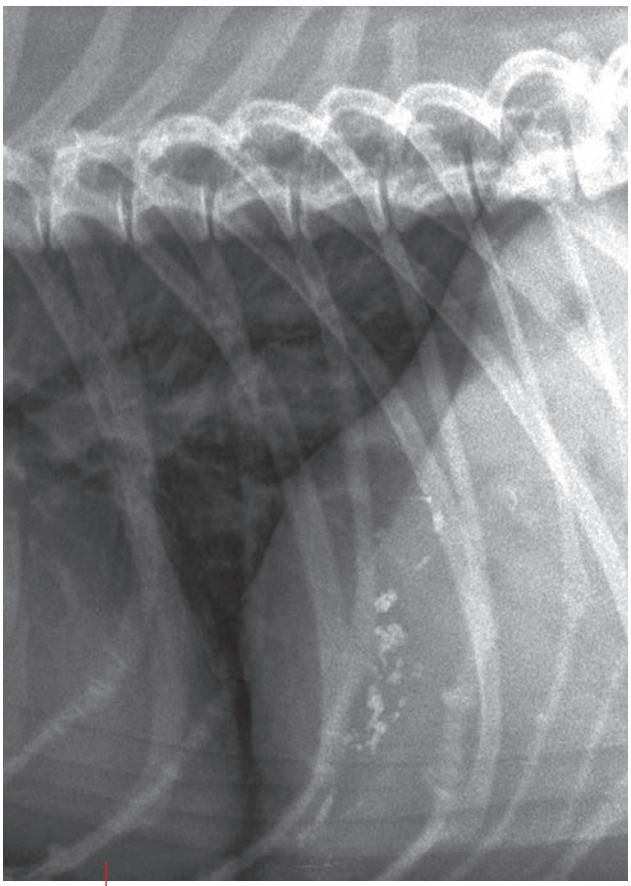

Figure 2. A lateral abdominal radiograph showing cholelithiasis in the intrahepatic bile ducts, with a typical branching appearance.

mass. Cholelithiasis is a common cause of mineralization of the liver, and if involving the intrahepatic bile ducts will have a branching appearance on radiography **(Figure 2)**.

Ultrasound

Ultrasound is a very useful modality to complete evaluation of the liver as it is cost-effective and non-invasive, and in most cases can be accomplished without sedation. Ultrasound is particularly recommended if hepatomegaly or peritoneal fluid is detected on radiography, but its usefulness may be limited in large dogs or if the stomach is markedly distended with gas. The liver can be imaged with the probe positioned just below the xyphoid process, scanning from the left to the right in a sagittal plane, or cranial to caudal in the transverse plane will allow evaluation of the whole organ. Depth has to be set appropriately to include the entire liver. The diaphragm cannot be differentiated from the liver parenchyma, and the diaphragmatic margin will delimit the cranial aspect of the liver, as with radiography. This diaphragmatic margin is characterized by a curved line of reverberation artifacts produced by air within the lungs. A mirror image is a common artifact found on hepatic ultrasound and is characterized by the projection

of the liver image cranial to the diaphragm; this should be recognized and not be confused with a diaphragmatic hernia or thoracic mass.

The liver has a homogenous parenchyma that has a mildly granular echotexture and is hypoechoic to the falciform fat and the spleen **(Figure 3)**, and iso- to hypoechoic to the right kidney (1). The liver contours should be smooth and regular, delineated by a thin hyperechoic capsule. Separation of the liver lobes should be apparent, unless there is free fluid within the peritoneal cavity. The hepatic veins are easily visualized within the liver parenchyma as tubular anechoic structures, and the portal veins are differentiated from the systemic veins by their hyperechoic walls. Additionally, the degree of visibility of the portal vessels may also be used to assess hepatic echogenicity.

As with radiography, liver size will be evaluated subjectively, as the caudoventral aspect should not extend beyond the gastric fundus. The right lobes project more dorsally and are often better evaluated using a caudal intercostal window, between the right 10th or 11th intercostal space. This window is also useful to evaluate the gallbladder, which is normally visible with an anechoic content and a very thin hyperechoic wall. In most middle-aged dogs, mobile echoic material is noted within the gallbladder. This is rather unusual in the cat and if seen may prompt further investigation of the biliary function. Intrahepatic bile ducts are not normally visible.

The main changes that can be appreciated on ultrasound are alterations in liver size (most often hepatomegaly) and echogenicity, or the presence of a nodule or mass. Ultrasound is very sensitive to detect parenchymal changes but not specific, and any change should be interpreted with regard to the clinical signs. For example, hyperechoic hepatomegaly may lead more towards a diagnosis of lipidosis in an icteric cat and will be a common finding in a diabetic dog. In these two particular diseases, the liver parenchyma will also be hyperattenuating **(Figure 4)**. Acute hepatitis can be characterized by a hypoechoic hepatomegaly, whilst in chronic cases the liver may become heterogeneous with irregular margins.

"Ultrasound is very sensitive for the detection of liver nodules, but it is not specific to identify their nature; this is important, as many hepatic nodules can be benign in nature."

Laurent Blond

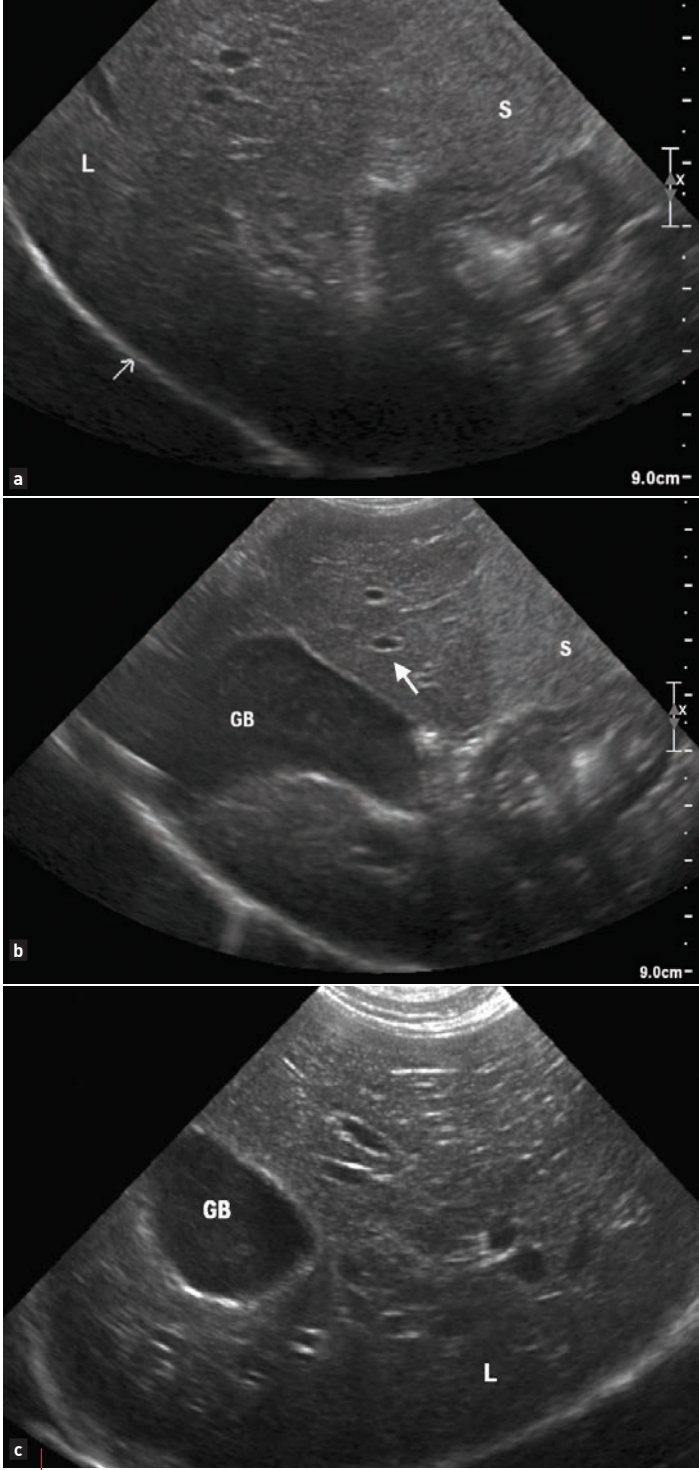

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Figure 3. Ultrasound of a normal canine liver. **(a)** Left aspect of the liver on a sagittal view; the liver has a homogenous parenchyma and is hypoechoic to the spleen **(S)**. The portal vessels (white arrow) have hyperechoic walls. **(b)** Transverse view with the gallbladder (GB) on the right; the portal vessels (white arrow) have hyperechoic walls. **(c)** Right aspect of liver on a sagittal view.

A liver mass may vary in its appearance, but will generally be seen as heterogeneous and can deform the hepatic margin. The portion of the liver

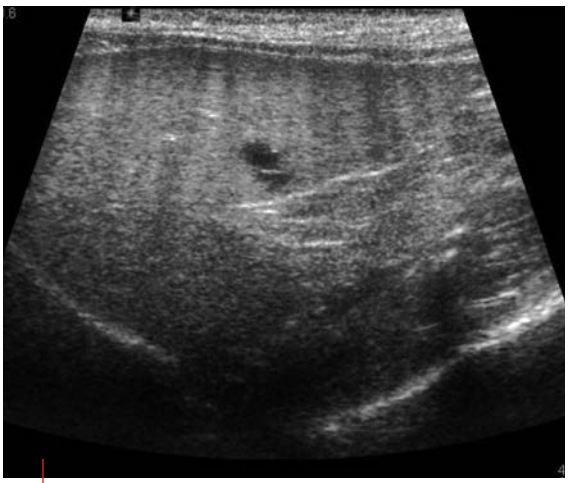

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Figure 4. An ultrasound scan of a liver with hyperechoic parenchyma that is also hyperattenuating (reduced echogenicity in the deep field).

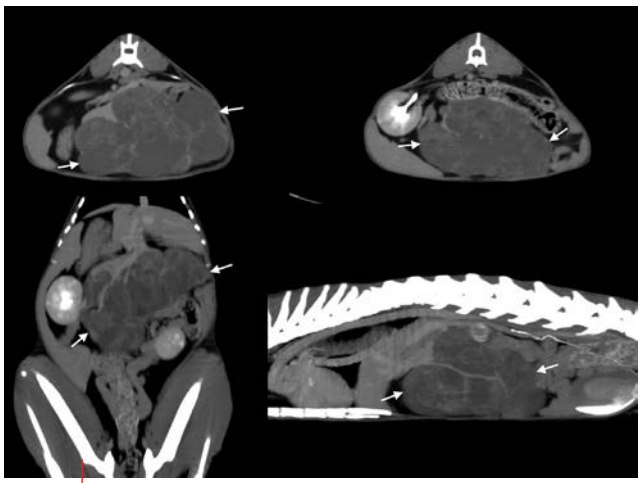

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Figure 5. CT images of a liver tumor in a cat. Transverse images (above) and dorsal and sagittal reformatted images in maximal intensity projection (below). This large mass can be seen in the center of the liver (arrows), with clearly delineated contours which aid planning for surgical removal.

involved can be identified, but it may be difficult to correctly target the exact hepatic lobe affected. On the other hand, ultrasound can be useful to identify the liver when investigating the origin of a large abdominal mass.

It is important not to interpret gallbladder changes as a hepatic mass, and this is especially true in cases of mucocoele where the gallbladder is filled with heterogeneous, organized and static material.

Ultrasound is also very sensitive for the detection of liver nodules but again is not specific to identify their nature, and many hepatic nodules are benign. A hepatic cyst will appear as an anechoic, rounded structure in orthogonal planes that will induce an acoustic enhancement. Ultrasound-guided fine-needle aspirates or biopsies may be performed if necessary.

Decreased liver size may be a consequence of chronic hepatitis and cirrhosis, and in this case irregular margination may be seen on ultrasound; ascites is often also present. However, a small liver can also be indicative of a congenital portosystemic shunt in younger patients, especially where there is an extrahepatic shunt. An intrahepatic shunt can usually be easily seen as an abnormally large, curved, tortuous vessel within the liver parenchyma that connects the portal flow to the hepatic portion of the caudal vena cava.

Where there is chronic biliary obstruction, intrahepatic bile ducts can be seen on ultrasound as mildly tortuous, tubular anechoic structures; color Doppler technique may help differentiate the ducts from blood vessels.

Computed tomography (CT)

Imaging via CT will require the patient to be under general anesthesia followed by intravenous injection of iodinated contrast medium. It is very helpful to image the entire liver, especially in large dogs in which ultrasound may be limited. Dogs may be placed in either dorsal or ventral recumbency and images acquired in the transverse plane may be reformatted in different planes. The liver will normally have a homogeneous soft tissue attenuation. CT is especially recommended to evaluate the exact location and possible dissemination of a hepatic mass if surgery is to be considered **(Figure 5)**. It is also very useful to evaluate vascular anomalies, and especially portosystemic shunts (intra- or extrahepatic); in this case three post-contrast medium injection acquisition times are required, during the arterial, portal and venous phases (2).

Magnetic resonance imaging (MRI)

MRI of the liver is not frequently used in veterinary medicine and applications are still limited. However, its superior contrast resolution may help differentiate benign from malignant lesions in the liver. It requires general anesthesia of the patient, gadolinum contrast injection and a high-field MRI (at least 1.5 Tesla) to avoid respiratory-induced motion artifacts.

The pancreas

The pancreas is a small organ which can be divided into three anatomic sections; the right lobe is located along the mesenteric border of the duodenum, the body of the pancreas runs along the caudal aspect of the stomach, and the left lobe sits alongside the descending colon. The contours of the organ are typically irregular.

Radiography

The normal pancreas cannot usually be identified on radiography as it is too small. However, in some overweight cats with a large amount of peritoneal fat, the left lobe of the pancreas can be seen alongside the medial aspect of the spleen adjacent to the cranial pole of the right kidney, and should not be mistaken for an abnormality. Radiographs may, however, still be useful if a pancreatic disease is suspected, as pancreatitis may induce indirect changes such as loss of serosal detail in the cranial abdomen, enlargement of the pyloro-duodenal angle, and gaseous dilation of the duodenum due to secondary induction of a functional ileus. Additionally, some pancreatic tumors can be mineralized, and a cranial abdominal mass with foci of mineralization may be of pancreatic origin.

Ultrasound

Ultrasound is quite useful to image the pancreas although thorough evaluation requires some experience. The normal pancreas is discretely heterogenous and generally slightly hypoechoic to the surrounding fat, with ill-defined margins (3). It may be iso-echoic to the surrounding fat in cats and hyperechoic in the Yorkshire Terrier (4). Assessment of the pancreas relies mainly on identification of specific landmarks. To evaluate the right lobe it is important to image the duodenum from the right kidney caudally to the pylorus cranially. In the dog, the pancreatico-duodenal vein can be easily identified as a tortuous, tubular anechoic structure parallel to the medial aspect of the duodenum **(Figure 6a)**; the tissue around this vessel is the pancreas. Color Doppler can be used to better characterize this vessel. In the cat, it is the pancreatic duct that will be visualized in this location, and this will help localize the right lobe of the pancreas. The pancreatic duct is physiologically dilated in the cat (and especially in older cats, up to 3 mm in diameter); it joins the common bile duct at the level of the major duodenal papilla in this species. The body of the pancreas is located caudal to the pylorus and ventral to the portal vein between the stomach and the transverse colon. The left pancreatic lobe can be visualized at the lateral aspect of the descending colon caudal to the gastric fundus, medial to the spleen and cranial to the cranial pole of the left kidney. The pancreatic duct may also help to localize this lobe in the cat **(Figure 6b)**. The thickness of the pancreas can be measured in cats and should not exceed 1 cm (5).

Acute pancreatitis is generally characterized by hypoechoic and heterogenous thickening of the pancreas, surrounded by hyperechoic and hyperattenuating fat. Fluid is also frequently present in the vicinity of the pancreas. The adjacent duodenal wall is often thickened and plicated, with loss of definition of its layers **(Figure 7)**. Abdominal pain can often limit examination of the pancreas and necessitate analgesia or sedation. Concomitant abscessation or cyst formation may occur, and will be identified as a rounded structure filled with hypoechoic to anechoic fluid. Such lesions can be drained via ultrasound guidance. Chronic pancreatitis can be more difficult to recognize and may be characterized by heterogeneous areas within the pancreatic parenchyma and foci of hyperechoic fat adjacent to it.

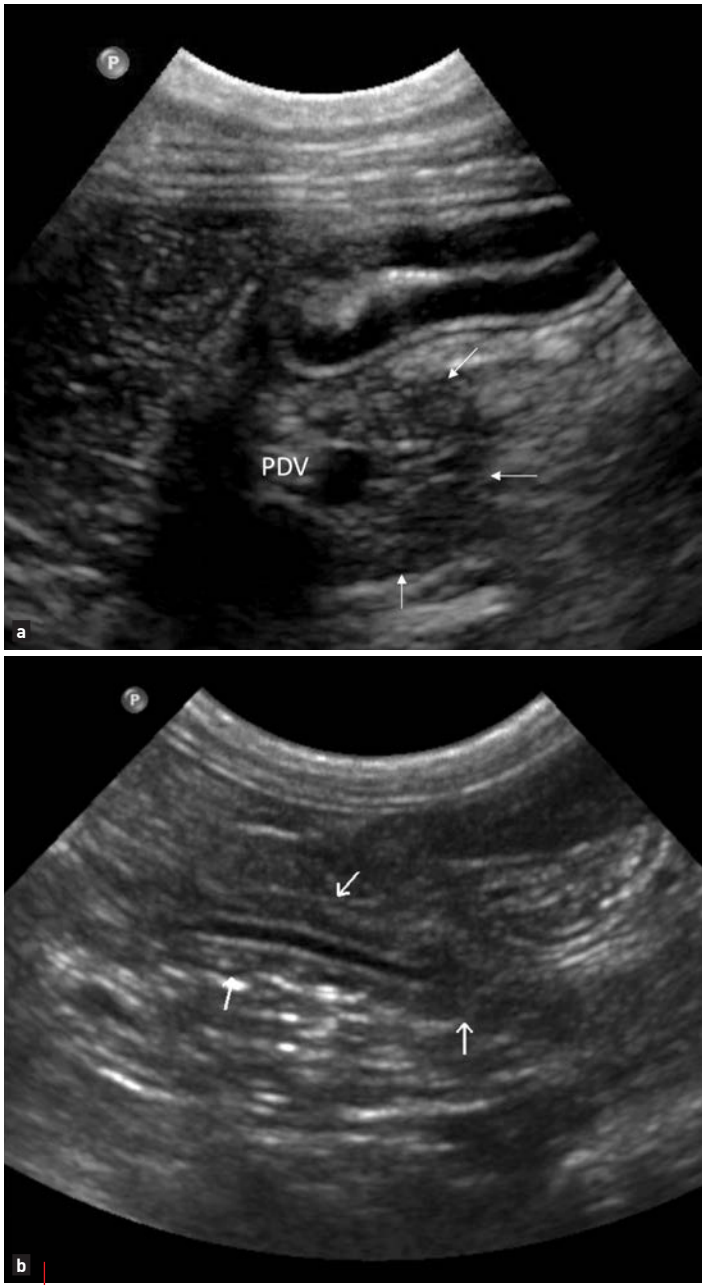

Figure 6. **(a)** Ultrasound of a normal pancreas (white arrows) in a dog. The right pancreatic lobe is found alongside the duodenum and can be localized by visualization of the pancreatico-duodenal vein (PDV). **(b)** Ultrasound of a normal pancreas (white arrows) in a cat; the pancreatic duct can help identification of the pancreas.

Nodular hyperplasia is commonly seen in older cats and is characterized by hypoechoic, well-defined nodules measuring less than 1 cm in diameter (6). Pancreatic tumors are often hypoechoic and slightly heterogeneous, and will distort the pancreatic contours **(Figure 8)**. Pancreatic carcinoma are

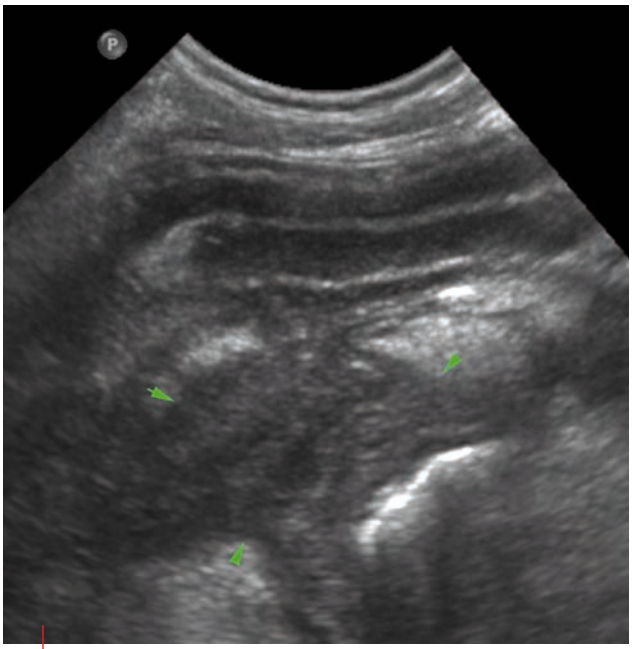

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Figure 7. Ultrasound image of pancreatitis in a dog: the pancreas is thickened and hypoechoic (green arrow heads) and is surrounded by hyperechoic fat. The adjacent duodenal wall is thickened.

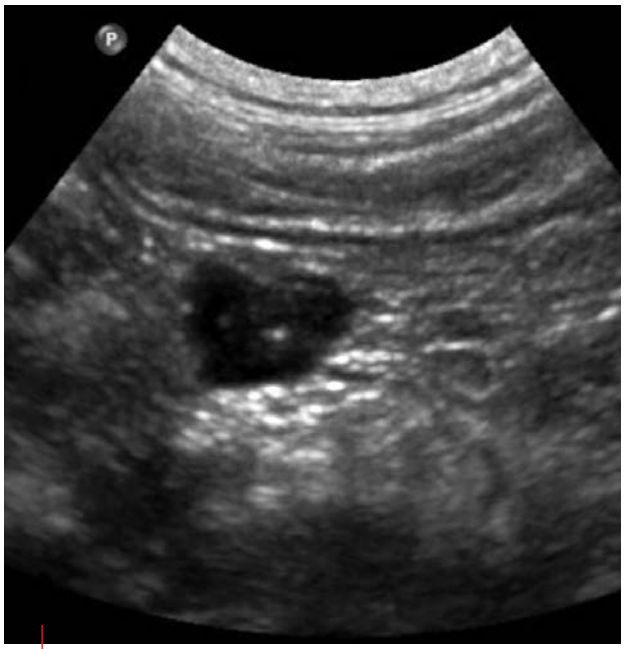

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Figure 8. Ultrasound image of a pancreatic carcinoma in a cat visualized as a well-defined hypoechoic nodule.

often associated with carcinomatosis, which is characterized by peritoneal fluid accumulation and hypoechoic nodules dispersed within the mesentery and onto the peritoneum.

Insulinomas usually appear as small hypoechoic nodules and may be difficult to visualize. Metastases to the liver or adjacent lymph nodes are often detected before the primary tumor is identified.

Computed tomography

CT is useful to fully evaluate the pancreas, which will appear as an irregularly marginated, soft tissue attenuating organ along the landmarks describes in the section above. The technique can be particularly useful to search for insulinomas as it will not be limited by gas in the gastrointestinal tract, and it is more sensitive for the detection of small lesions, although this will usually require dual-phase computed tomography. An insulinoma is characterized on imaging by a hypo-attenuating nodule that will have a strong enhancement during the arterial phase of the study but not during the other phases (7).

CONCLUSION

Imaging can be invaluable when investigating diseases of the liver and pancreas, but it is essential that the clinician be familiar with the normal anatomy and appearance on the chosen imaging modality. It is also necessary to be aware of the limitations when using such diagnostic techniques, but appropriate care and a standardized approach should enable beneficial results in most cases.

REFERENCES

1. Larson MM. Ultrasound imaging of the hepatobiliary system and pancreas. *Vet Clin North Am Small Anim Pract* 2016;46(3):453-80.
2. Zwingenberger AL, Schwarz T, Saunders HM. Helical computed tomographic angiography of canine portosystemic shunts. *Vet Radiol Ultrasound* 2005;46(1):27-32.
3. Hecht S, Henry G. Sonographic evaluation of the normal and abnormal pancreas. *Clin Tech Small Anim Pract* 2007;22(3):115-121.
4. Granger LA, Hilferty M, Francis T, *et al*. Variability in the ultrasonographic appearance of the pancreas in healthy dogs compared to dogs with hyperadrenocorticism. *Vet Radiol Ultrasound* 2015;56(5):540-548.
5. Etue SM, Penninck DG, Labato MA, *et al*. Ultrasonography of the normal feline pancreas and associated anatomic landmarks: a prospective study of 20 cats. *Vet Radiol Ultrasound* 2001;42(4):330-336.
6. Larson MM, Panciera DL, Ward DL, *et al*. Age-related changes in the ultrasound appearance of the normal feline pancreas. *Vet Radiol Ultrasound* 2005;46(3):238-242.
7. Mai W, Cáceres AV. Dual-phase computed tomographic angiography in three dogs with pancreatic insulinoma. *Vet Radiol Ultrasound* 2008;49(2):141-148.

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ACUTE FELINE PANCREATITIS

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Dr. Allenspach qualified from Zurich University in 1994 before undertaking an internship in emergency and critical care at Tufts University. She followed this with a residency in small animal medicine at the University of Pennsylvania and gained her ECVIM Diploma in 2001. She was awarded her PhD for studies in immunology in 2005 and is currently Professor of Internal Medicine at Iowa State University.

KEY POINTS

- Pancreatitis in cats is a common yet often overlooked condition, and diagnosis should be based both on clinical signs and appropriate tests.
- Early intervention in any anorexic cat with pancreatitis is desirable; a high-protein diet given by the enteral route is the preferred method to supplement nutrition.

Feline pancreatitis is one of the most commonly encountered diseases in small animal practice. Professor Allenspach offers a brief overview of the disease and discusses a holistic approach to treatment.

Introduction

Pancreatitis in cats is a very common disease: in one retrospective study, 67% of 115 cats had histological lesions found on post-mortem examination (1). However, the condition is also probably underdiagnosed, as many of the clinical signs associated with feline pancreatitis are very non-specific. The etiology of pancreatitis in cats is, as with dogs, largely unknown; however, unlike the situation in dogs, dietary indiscretion is not a common cause in cats. However, one specific consideration is to include toxoplasmosis as a potential infectious cause of feline pancreatitis (2). Other etiologies that have been associated with acute onset of pancreatitis in cats are recent general anesthesia, hypoxia secondary to acute heart failure episodes, and organophosphate intoxication.

Clinically, cats with pancreatitis show less specific signs than dogs, with anorexia, lethargy, dehydration, weight loss, hypothermia, vomiting, icterus and fever being amongst the most common signs. In a few cases, abdominal pain can be present, and the patient may also have diarrhea. However, it is important to consider the possibility that any cat with suspected pancreatitis could have abdominal pain, and appropriate treatment may greatly improve the clinical demeanor of the cat.

Diagnosis

On hematology, many affected cats show anemia or hemoconcentration; either leukocytosis or leucopenia is also common. The biochemistry profile often includes hypoalbuminemia, which can also be a negative prognostic indicator. Hypocalcemia may also be present (from saponification of the mesenteric fat) and should be treated if present.

On radiography it is occasionally possible to identify bicavitary effusion (*i.e.*, effusion in both pleural and peritoneal cavities) in affected cats. As noted above, hypoalbuminemia is a common finding in feline pancreatitis, and can also contribute to this. Ultrasound is often employed to help with the diagnosis of pancreatitis, but has been shown to have very variable sensitivity, between 10-70%. This is dependent on the experience of the ultrasonographer, as well as the severity of clinical signs. In acute pancreatitis, the sensitivity of ultrasound is much

higher than in chronic cases. Typical signs on ultrasound are hyper- or hypoechogenic pancreatic tissue, free fluid surrounding the pancreas, and hyperechogenic mesenteric fat.

Feline pancreatic lipase (fPLI) or DGGR lipase assay are the laboratory tests that currently offer the best sensitivity and specificity for the diagnosis of pancreatitis in cats, when compared with histological identification of pancreatitis as the gold standard. Since we do not know how relevant histological pancreatitis is in the clinical setting, the results of these tests must be carefully interpreted in light of other clinical findings. In fact, feline pancreatitis is always a clinical diagnosis and diagnosis should never be made on the basis of a single test, but rather based on a combination of clinical signs, laboratory and ultrasound findings.

In a recent large retrospective study of 157 cats with pancreatitis, hypoglycemia, azotemia, pleural effusion and persistent anorexia during hospitalization were the factors most commonly associated with poor outcome (3). This hints towards the importance of nutritional support, which is most often best achieved by naso-esophageal or esophageal tube feeding **(Figure 1)**. Furthermore, withholding antibiotic treatment was associated with a poorer outcome in these cats. This is an important finding, and concurs with recent literature indicating bacterial infections in cats with pancreatitis. It is assumed that bacterial infection of the liver and pancreas is a result of ascending infection from the upper small intestine through the bile and pancreatic ducts. Most commonly, bacterial DNA from *E.coli* species have been found to be present in such cases (4). It is therefore prudent to assume bacterial infection with enteral species in severely sick acute pancreatitis cases, and to empirically treat with antibiotics.

"Cats are able to digest very high amounts of fat, and there is currently no evidence that fat restriction is indicated when dealing with feline pancreatitis."

Karin Allenspach

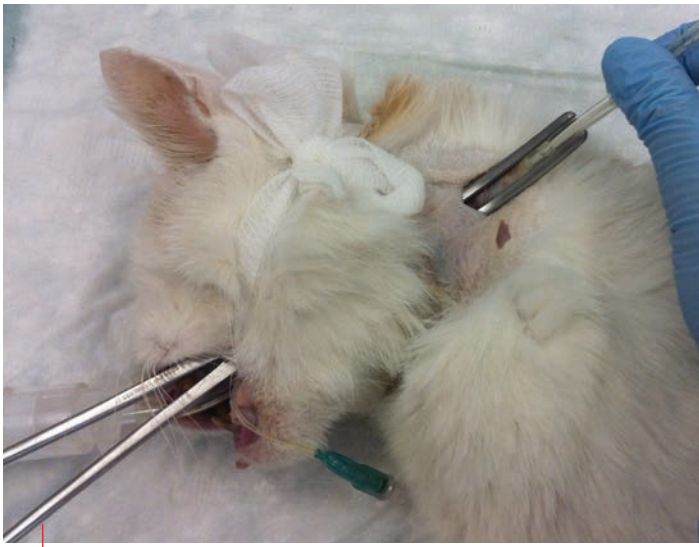

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Figure 1. Placement of an esophagostomy feeding tube. The tube bypasses the mouth and pharynx and can be left in place for many weeks if necessary, but general anesthesia is needed for placement, which may not be ideal in a compromised patient.

Medical treatment

As mentioned above, analgesia is very important for all cats with pancreatitis. The best options are morphine derivatives such as buprenorphine administered parenterally. Anti-emetics should also be given; maropitant and ondansetron, sometimes in combination, have empirically been shown to have good efficacy in these cases. Furthermore, although dopamine D_2 receptors have historically not been reported to occur in cats, metoclopramide may have an effect on functional ileus in feline pancreatitis, and can therefore also play a role in the management.

Nutritional management

In veterinary medicine, the premise that the gastrointestinal tract plays an important role during critical illness, and that enteral nutrition is preferable to parenteral nutrition whenever possible, is well established. Lack of enteral nutrition can lead to decreased gastrointestinal motility, as well as morphological changes to the intestinal anatomy, such as villus atrophy. Such changes have been associated with a higher rate of bacterial and endotoxin translocation into the peripheral bloodstream. Early enteral nutritional support is therefore important in any anorexic cat, but especially if pancreatitis is suspected. In fact, because most cats present when they have already been anorexic for several days, enteral nutrition should be instigated as soon as possible. In one study, nasogastric feeding was assessed in 55 cases of acute feline pancreatitis (5). Treatment

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Figure 2. Naso-esophageal feeding tubes are easy to place without general anesthesia and can be removed whenever required.

with parenteral amino-acid /dextrose infusion was compared to enteral feeding. Nasogastric feeding was very well tolerated in the study **(Figure 2)**, and there were no differences between the groups in terms of clinical variables or outcome. Enteral feeding is only contraindicated in a cat with intractable vomiting, but antiemetics should be tried in such patients. Esophagostomy or gastrostomy provides a good medium- to long-term option; however, since they both necessitate anesthesia in a sometimes debilitated patient, naso-esophageal tubes can be very effective, especially in the first few days of treatment (6).

CONCLUSION

The clinician should be alerted to the fact that pancreatitis in cats can cause vague, non-specific signs, and consequently the disease may be underdiagnosed. Feline pancreatitis is essentially a clinical diagnosis which relies on a combination of clinical signs, laboratory and ultrasound findings. Early and considered intervention should improve recovery rates, and this involves both appropriate medication, including analgesia and antibiotics, and appropriate nutritional support with a high-protein diet given – wherever possible – by the enteral route.

The diet fed to these patients should be high in protein, because of the considerable dietary protein requirement of cats (7). This high-protein requirement also makes them susceptible to lean muscle loss during starvation, which needs to be avoided if at all possible. Furthermore, anorexia can result in decreased intake of certain amino acids such as arginine and methionine, which can lead to hepatic lipidosis, as these amino acids are essential to form apolipoproteins to re-distribute fat from the liver to other organs in the body. In addition, there is accumulating evidence in people with severe illnesses that other nutrients, such as glutamine, tryptophan and fatty acids, may play a role in modulating inflammatory and immune-mediated mechanisms. Supplementation of such critical nutrients have been shown to be associated with reduced hospital stay and lower infection rates (8). Note, however, that cats are able to digest very high amounts of fat, and there is currently no evidence that fat restriction is indicated in cats with pancreatitis.

REFERENCES

1. De Caock HE, Forman MA, Farver TB, *et al*. Prevalence and histopathologic characteristics of pancreatitis in cats. *Vet Pathol* 2007;44(1):39-49.
2. Carpenter D. Histologically confirmed clinical toxoplasmosis in cats: 100 cats (1952-1991). *J Am Vet Med Assoc* 1993;203;1556-1565.
3. Nivy R, Kaplanov A, Kuzi S, *et al*. A retrospective study of 157 hospitalized cats with pancreatitis in a tertiary care center: Clinical, imaging and laboratory findings, potential prognostic markers and outcome. *J Vet Intern Med* 2018;32(6):1874-1885. doi:10.1111/jvim.15317. Epub 2018 Oct 13.
4. Twedt DC, Cullen J, McCord KJ, *et al*. Evaluation of fluorescence *in situ* hybridization for the detection of bacteria in feline inflammatory liver disease. *J Feline Med Surg* 2014;16(2):109-117. doi: 10.1177/1098612X13498249.
5. Klaus JA, Rudloff E, Kirby R. Nasogastric tube feeding in cats with suspected acute pancreatitis: 55 cases (2001-2006). *J Vet Emerg Crit Care (San Antonio)* 2009;19(4):337-346. doi:10.1111/j.1476-4431.2009.00438.x.
6. Doerfelt R. A quick guide to feeding hospitalized cats. *Vet Focus* 2016;26(2);46-48.
7. Jensen KB, Chan DL. Nutritional management of acute pancreatitis in cats and dogs. *J Vet Emerg Crit Care* (San Antonio) 2014;24(3):240-250. doi: 10.1111/vec.12180. Epub 2014 Apr 1.
8. Sakai K, Maeda S, Yonezawa T, *et al*. Decreased plasma amino acid concentrations in cats with chronic gastrointestinal diseases and their possible contribution in the inflammatory response. *Vet Immunol Immunopathol* 2018;195:1-6. doi: 10.1016/j.vetimm.2017.11.001. Epub 2017 Nov 8.

EXOCRINE PANCREATIC INSUFFICIENCY IN DOGS

Exocrine pancreatic insufficiency is a debilitating disease which is underdiagnosed in dogs; María-Dolores Tabar Rodríguez discusses the condition, its diagnosis and treatment.

KEY POINTS

1. Exocrine pancreatic insufficiency (EPI) must be considered in any dog showing one or more of the appropriate clinical signs, but especially if there is small intestinal diarrhea and weight loss.
2. EPI diagnosis is essentially functional and is based on assessment of pancreatic function by measurement of serum trypsin-like immunoreactivity (TLI).
3. Therapy for these patients focuses on the administration of pancreatic enzymes, adequate nutrition, and cobalamin supplementation.
4. Although not all patients show an optimal response to treatment, the prognosis is generally good but requires ongoing treatment and regular monitoring.

Introduction

Exocrine pancreatic insufficiency (EPI) in dogs can cause poor absorption and digestion of food, with affected animals showing a progressive and serious deterioration in their health status. The veterinarian must know which breeds are predisposed to the problem and should be familiar with the clinical presentation, as well as being aware that concomitant disease may also be present. The clinician should therefore be alerted to the possibility of EPI when presented with a dog that shows one or more of the signs typically encountered with the disease, which will allow appropriate diagnostic tests to be instigated.

EPI – an overview

Exocrine pancreatic diseases have a significant prevalence in small animals yet are often underdiagnosed. Diagnosis can sometimes be complicated due to the presence of non-specific clinical signs, the possibility of concomitant disease, and difficulties in interpreting laboratory results and imaging tests. The most common disease processes of the exocrine pancreas are pancreatitis and exocrine pancreatic insufficiency; however, the exocrine pancreas can also be affected by neoplastic processes that, although rare in small animals, can be confused with other lesions such as cysts, pseudocysts, or pancreatic abscesses.

The exocrine pancreas is responsible for the secretion of various substances that contribute to several important functions, including digestion of proteins, carbohydrates, and lipids (via digestive enzymes); helping to neutralize the duodenum (via bicarbonate, chlorine and water); intervening in the absorption of cobalamin (via intrinsic factor); and regulating the bacterial flora of the small intestine (via antibacterial proteins). EPI is a disorder of the gastrointestinal tract characterized by insufficient production of digestive enzymes by the pancreatic acinar cells; clinical signs will appear when over 90% of exocrine pancreatic function is lost.

Causes of EPI

Histopathological biopsy is required to confirm the underlying etiology of EPI, so in most cases a simple diagnosis is usually made based on the patient's history, laboratory results and/or imaging tests. However, literature data points to pancreatic acinar atrophy and chronic pancreatitis as the most probable causes of canine EPI.

Pancreatic acinar atrophy (PAA)

This is the most common cause of EPI in dogs, especially in breeds such as the German Shepherd, the Rough Collie, the Eurasier, and the Chow Chow (1). Studies in these breeds indicate the presence of an autoimmune process in genetically susceptible individuals, with the development of progressive lymphocytic infiltration that causes gradual destruction of the acinar tissue. Endocrine function is usually not affected. EPI is also presumed to be hereditary in nature, although this is not entirely understood at present, with complex multiple genetic and environmental factors likely involved

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in its etiopathogenesis (2). Two stages have been identified in PAA progression: a subclinical phase and a clinical phase. The progression from the first to the second phase is unpredictable, with some dogs taking years to reach the clinical stage whilst others may never show clinical signs. The subclinical phase is characterized by partial acinar atrophy in which the affected dog shows no clinical signs. As tissue inflammation and destruction progresses, severe atrophy of the tissue develops, leading to the second phase in which the clinical signs characteristic of insufficient pancreatic function become apparent. Some authors suggest the term *immune-mediated atrophic lymphocytic pancreatitis* to describe the pathological changes that define the phase that precedes the terminal atrophy of the acinar tissue (1).

Chronic pancreatitis

This is the most frequent cause of EPI in cats and the second most common cause in dogs, especially in breeds such as the Cavalier King Charles Spaniel and Cocker Spaniel (1). Unlike PAA, with chronic pancreatitis there is usually a progressive destruction of both endocrine and exocrine pancreatic tissues. It is therefore necessary to consider the possibility of concurrent diabetes mellitus, chronic pancreatitis, and EPI in these patients, or to be alert to signs of EPI developing after a diagnosis of diabetes.

Congenital pancreatic hypoplasia

This is much less common, but cases have been described in puppies, some of which have concurrent endocrine and exocrine failure, with both EPI and diabetes mellitus. However, some cases of PAA can occur at a very early age (3), making it impossible to evaluate the cause without a pancreatic biopsy.

Pancreatic neoplasia

This is a very rare cause of EPI in small animals.

Clinical presentation

As noted above, EPI can occur in many different breeds of dogs but is more frequently seen in certain breeds including the German Shepherd, the Rough Collie, the Chow Chow, the Cavalier King Charles Spaniel, the West Highland White Terrier, and the Cocker Spaniel (4). For breeds where PAA is the cause, clinical signs usually appear in young adults

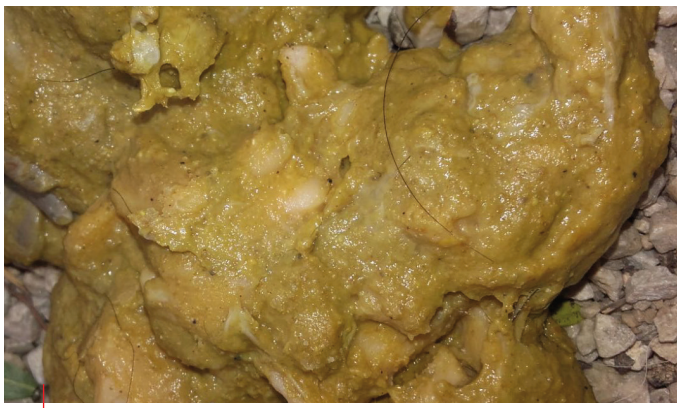

Figure 1. Soft, yellowish feces with the remains of undigested food particles are often seen with EPI.

(before 4 years of age), although in some cases the disease may develop at a later stage. However, when the cause is chronic pancreatitis the age at presentation is typically older, at around 7 years. In some breeds, such as the German Shepherd, the Chow Chow, and the Cavalier King Charles Spaniel, a female gender predisposition has been noted (4).

The most characteristic clinical signs are increased stool frequency and volume, which tends to be yellowish and greasy (steatorrhea), along with weight loss and flatulence **(Figure 1)**. Affected dogs also tend to have decreased stool consistency (*i.e.*, small intestinal diarrhea **(Table 1)**), polyphagia and coprophagia. Some patients may have episodes of abdominal pain, which can manifest as periods of aggression. Affected dogs generally have a poor body and coat condition **(Figure 2)**, often with seborrhea **(Figure 3)**. Atypically, some dogs may occasionally vomit.

It should be noted that although diarrhea, polyphagia and weight loss are the classical signs, not all may be present in all affected dogs. Some studies have reported that 5% of affected dogs did not have diarrhea, 35% had a normal appetite, 12% had a decreased appetite, and 13% had normal or increased weight (5).

For patients with small intestinal diarrhea in which a chronic enteropathy is suspected, it is essential to exclude the presence of EPI, which is one of the main differential diagnoses **(Box 1)**. EPI is the most frequent extra-gastrointestinal cause of chronic diarrhea in dogs (6).

Table 1. Differentiating between small intestinal and large intestinal diarrhea.

Sign	Small intestinal diarrhea	Large intestinal diarrhea
Defecation frequency	Normal or slight increase (3-5 times a day)	Large increase (> 5 times a day)
Stool volume	Normal or increased amounts	Decreased
Mucus in stool	Generally absent	Often present
Blood in stool	Melena	Hematochezia
Tenesmus	Absent	Often present
Urgency	No	Yes
Steatorrhea	Sometimes	Absent
Weight loss	Frequent	Infrequent

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Figure 2. A Giant Schnauzer with poor body condition due to EPI.

Diagnosis

EPI is a functional diagnosis, based on detecting a decrease in secretory capacity via pancreatic function tests. A pancreatic biopsy is necessary to verify the underlying etiology.

The test of choice is the measurement of serum TLI (trypsin-like immunoreactivity). The pancreas secretes trypsinogen into the intestine where it is transformed into the active enzyme trypsin, a potent digestive protease. In addition, small amounts of trypsin can form within the pancreas. Under normal conditions, some of the trypsinogen enters the bloodstream where it can be detected. Trypsin will only be present in the serum when there is pancreatic inflammation. Trypsinogen and plasma trypsin are broken down in the kidneys and by the mononuclear phagocytic system. The TLI test is an immunoassay that detects trypsinogen, trypsin, and trypsin bound to protease inhibitors (7).

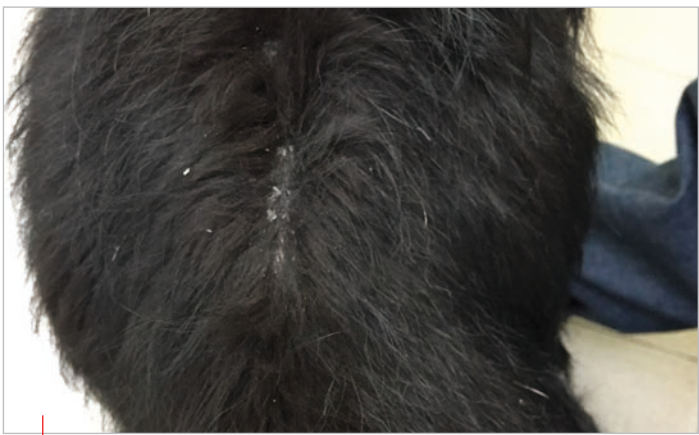

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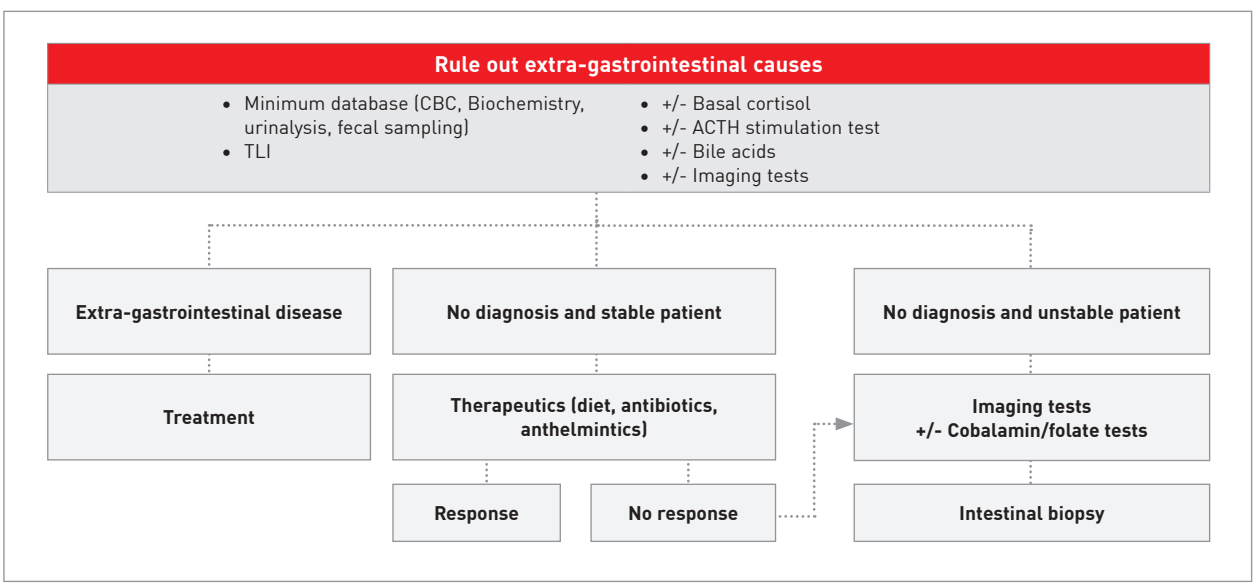
Figure 3. The same dog as in **Figure 2** in which skin changes secondary to EPI, including seborrhea and desquamation, are obvious.

Box 1. The diagnostic approach for a dog with chronic small intestinal diarrhea.



The test is a specific, and species-specific, measurement of pancreatic function, and therefore the definitive technique for the canine species (cTLI) must be used. Levels increase in the postprandial period, so the patient should be fasted for 12 hours before sampling. Some authors have recommended suspending the administration of pancreatic enzymes at least one week before any measurement, on the assumption that it could give erroneous TLI levels. However, several studies have indicated that pancreatic enzyme supplementation does not influence TLI measurement in either healthy animals (8) or in dogs with EPI (9), so it is unnecessary to suspend treatment when dealing with a patient for which a definitive diagnosis is required but which has already been given pancreatic enzymes.

In general, when interpreting the cTLI results **(Box 2)**, values lower than 2.5 µg/L are regarded as confirming the presence of EPI. If equivocal results are obtained (between 2.5-5.7 µg/L), the test should be repeated a month later, since not all dogs in this category will progress to having low TLI levels. Such cases, especially if a breed predisposed to PAA, may be in the subclinical phase where there is still adequate secretory function, and which have not yet progressed towards total pancreatic atrophy when clinical signs become apparent (1).

TLI may be increased in patients with pancreatitis, although it is not a reliable diagnostic test, since it only remains elevated for 24-36 hours after the initial insult; the presence of pancreatitis should be confirmed with other tests. TLI may also be elevated for other reasons; these can include some individuals with intestinal disease, as reported in people and cats with various gastrointestinal disorders (10-12). Some authors also suggest that small amounts of trypsin can be synthesized in the intestine (10), and in humans, trypsin is present in the small intestine, in the biliary epithelium, and in some ovarian and hepatobiliary neoplasms (7).

"Hypocobalaminemia is very common in EPI and can even develop in dogs already on treatment with pancreatic enzyme supplementation; it is therefore essential to monitor cobalamin levels on a regular basis."

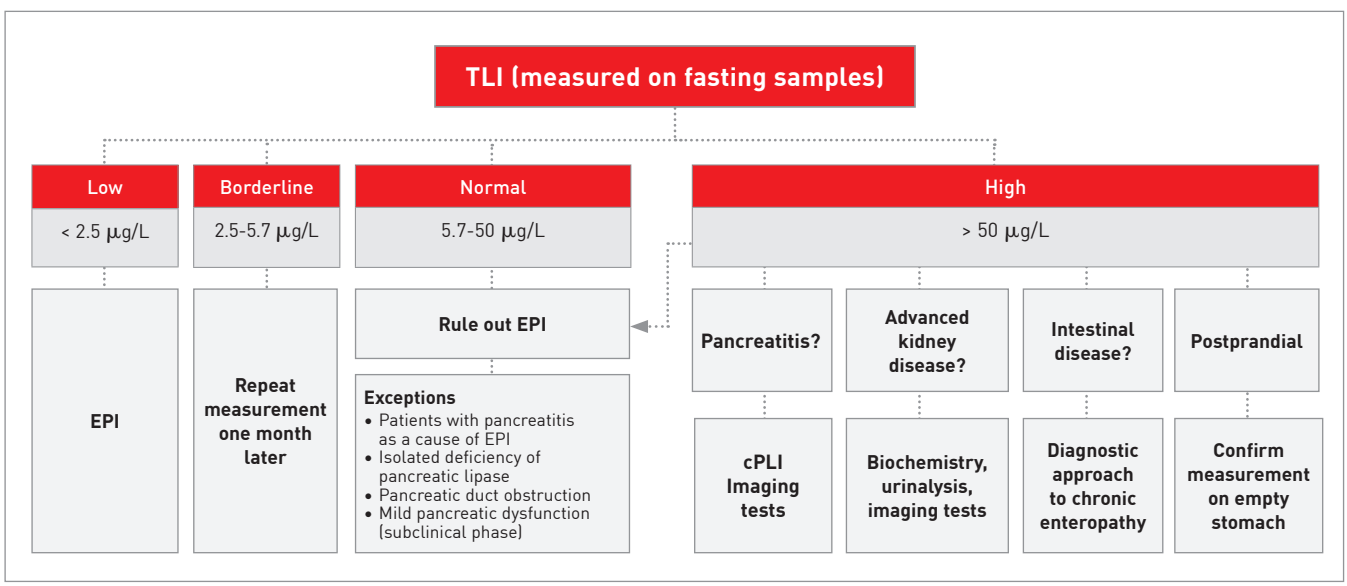
María-Dolores Tabar Rodríguez

In general, a normal TLI result rules out the presence of EPI. Rarely, the TLI result may be normal despite the existence of EPI, for example with a pancreatic duct obstruction (13) or if the patient has a standalone pancreatic lipase deficiency (14).

The interpretation of TLI in dogs with EPI caused by chronic pancreatitis may be more complicated. If the patient has episodes of acute pancreatitis (with digestive signs, anorexia, abdominal pain, etc.), measuring the minimum level of TLI one week after an episode – once the patient is stabilized – is recommended to diagnose EPI. Even so, for dogs with chronic pancreatitis and weight loss where there is no other valid explanation, especially if they have repeatedly *borderline* TLI values, a therapeutic trial with pancreatic enzymes is recommended.

Other laboratory tests are less useful for diagnosing EPI. PLI is decreased in almost all patients with EPI but there is an overlap of values between affected and

Box 2. Interpretation of serum cTLI (trypsine-like immunoreactivity) values.



Box 3. Vitamin B_{12} supplementation for dogs with hypocobalaminemia.

Subcutaneous administration option: 50 µg/kg (or dose according to table) weekly for six weeks then continue every 2-4 weeks							
Weight	< 5 kg	5-10 kg	10-20 kg	20-30 kg	30-40 kg	40-50 kg	> 50 kg
Dose (µg)	250	400	600	800	1000	1200	1500

Oral administration option: 50 µg/kg (or dose according to table) daily for at least 12 weeks then adjust according to need			
Weight	1-10 kg	10-20 kg	> 20 kg
Dose	¼ x 1 mg tablet	½ x 1 mg tablet	1 x 1 mg tablet

healthy patients; however, a specific canine pancreatic lipase test (cPLI) may be helpful in the case of isolated pancreatic lipase deficiency (14). Tests to assess fecal proteolytic activity are not recommended, due to their low sensitivity and specificity. The pancreatic elastase test is widely used in humans to evaluate exocrine pancreatic function, but in dogs it is very non-specific; high values rule out EPI, but low values do not confirm it (1,13).

Serum cobalamin should be measured in all dogs with EPI and is usually decreased in most patients. It is an important prognostic factor (15) and it impacts treatment, as dogs with low levels must receive cobalamin supplementation.

Treatment

Therapy for patients with EPI should primarily include administration of pancreatic enzymes, dietary recommendations, and vitamin B_{12} or cyanocobalamin supplements.

Pancreatic enzyme supplementation

These can be administered as powder or granules, capsules or coated tablets (to protect the enzymes from gastric acid); some clinicians will also suggest feeding raw pancreas, but this raises the possibility of infectious disease transmission. Some reports have indicated greater efficacy with the use of uncoated forms of supplement, but recent studies have demonstrated the efficacy of coated supplements (9,16). Pancreatic enzymes should be administered along with food (and if using granules, by mixing them with the food just before eating). Pre-incubation of enzymes before administration does not increase the efficacy of the product (13). The dose should be adjusted according to the patient's needs (*i.e.*, depending on the clinical signs), although digestive capacity generally does not fully recover, even for correctly supplemented patients (1). The side effects of pancreatic enzymes are minimal, although oral bleeding has been described in dogs given high doses; this was controlled by reducing the dose (1).

Diet

The absorption of fat does not completely normalize with pancreatic enzyme supplementation. However, even though low-fat diets were once the norm for dogs with EPI, this can be counterproductive for very thin dogs because the calorie content is quite restricted and this does not help them gain weight. Diets high in fiber should also be avoided, as this alters the activity of pancreatic enzymes and may decrease the assimilation of other nutrients (17). In general, highly digestible, moderate-fat, low-fiber diets are recommended. Some dogs respond well to maintenance diets. However, several studies have not shown clear benefits when comparing specific diets, and individual animals will respond differently to different types of diets. On a practical level, dietary trials should be carried out on each dog to see which is the most effective (17,18).

Cobalamin supplementation

Hypocobalaminemia is very common in animals with EPI and can develop even in dogs already on treatment with pancreatic enzyme supplements. It is therefore essential to monitor cobalamin levels; several studies indicate the negative prognostic factor of hypocobalaminemia in patients with EPI, with a major impact on long-term survival (5,15). All patients with low levels should be supplemented with cobalamin. Historically, this has been by subcutaneous injection, but recent studies indicate that it is probably effective to use a daily oral supplement **(Box 3)** (19).

Antibiotics

There is no good evidence that dogs with EPI improve with antibiotics. They often have bacterial overgrowth or dysbiosis of the intestinal flora, but this tends to be subclinical. However, if there is an incomplete response to enzyme supplementation and dietary modification, antibiotics such as ampicillin, metronidazole, or tylosin may be prescribed (17). Since dogs with EPI may have dysbiosis, probiotics could also be considered. Several studies indicate that probiotics may have a potential role in reducing intestinal inflammation and regulating intestinal dysbiosis, and encourage the use of therapies with a good risk/benefit profile (especially taking into account the emergence of bacterial resistance from antibiotic use) (20). However, further study is needed to confirm the efficacy and indications for probiotics in patients with EPI. In addition, it should be remembered that there may be a concurrent enteropathy, so if there is no adequate response to enzyme

supplementation and supportive treatment, it would be appropriate to continue with a diagnostic protocol for chronic enteropathies **(Box 1)**.

Antacids

In theory, antacids can be used to decrease gastric hydrolysis of supplemented pancreatic enzymes, but their efficacy has not been proven and it is probably better to increase the dose of the enzyme supplement if necessary. It has been shown that antacids reduce the destruction of lipase, although this does not translate into a clinical benefit (17).

Glucocorticoids

The use of glucocorticoids may be justified in patients with a concurrent chronic enteropathy (*e.g.*, inflammatory bowel disease) or in cases of chronic pancreatitis in breeds such as the English Cocker Spaniel, where there is evidence of an immune-mediated etiology (21). As noted above, further diagnostic tests may be needed for some patients to detect other concomitant problems that may require different treatment, and administration of glucocorticoids may be appropriate in certain cases. Any efficacy and benefit of using immunosuppressants such as azathioprine in the subclinical phase of EPI has not been proven, and is not recommended.

Prognosis

Several studies indicate that ~60% of EPI patients respond well to treatment, 17% have a partial response, and 23% have a poor response, leading to euthanasia in some cases (5). In general, a positive initial response is related to longer-term survival (5). For cases with an underlying chronic pancreatitis, it is important to monitor for other possible concomitant problems such as the presence of diabetes mellitus. Hypocobalaminemia at diagnosis, especially if not accompanied by high levels of folate, is a poor prognostic sign (15).

In all events, pancreatic acinar atrophy is an irreversible process requiring lifelong treatment. Appropriate communication with owners is important; if they are willing to accept the necessary financial implications and be involved in the management and treatment of the disease, the prognosis is generally good, with improvement in the clinical picture at a minimum for most patients.

CONCLUSION

EPI is a debilitating disease that results from pancreatic acinar tissue atrophy or destruction following chronic pancreatitis. EPI should be ruled out in all patients with suspected chronic enteropathy and suggestive clinical signs (such as weight loss, polyphagia, and diarrhea) and in dogs with chronic pancreatitis and unexplained weight loss for other reasons. The supplementation of pancreatic enzymes and cobalamin, along with the administration of a suitable diet, are fundamental pillars in treating affected dogs.

REFERENCES

1. Westermarck E, Wiberg M. Exocrine pancreatic insufficiency in the dog: historical background, diagnosis and treatment. *Top Companion Anim Med* 2012;27:96-103.
2. Clark LA, Cox ML. Current status of genetic studies of exocrine pancreatic insufficiency in dogs. *Top Companion Anim Med* 2012;27:109-112.
3. Alvarez MS, Herrería-Bustillo V, Utset AF, *et al*. Juvenile diabetes mellitus and concurrent exocrine pancreatic insufficiency in a Labrador retriever; long-term management. *J Am Anim Hosp Assoc* 2015;51(6):419-423.
4. Batchelor DJ, Noble PJ, Cripps PJ, *et al*. Breed associations for canine exocrine pancreatic insufficiency. *J Vet Intern Med* 2007;21(2):207-214.
5. Batchelor DJ, Noble PJ, Taylor RH, *et al*. Prognostic factors in canine exocrine pancreatic insufficiency: prolonged survival is likely if clinical remission is achieved. *J Vet Intern Med* 2007;21:54-60.
6. Volkman M, Steiner JM, Fosgate GT, *et al*. Chronic diarrhea in dogs – retrospective study in 136 cases. *J Vet Intern Med* 2017;31:1043-1055.
7. Stockham SL, Scott MA. Exocrine pancreas and intestine. In: *Fundamentals of Veterinary Clinical Pathology* 2nd ed. Ames IA, Blackwell Publishing, 2008;739-762.
8. Villaverde C, Manzanilla EG, Molina J, *et al*. Effect of enzyme supplements on macronutrient digestibility by healthy adult dogs. *J Nutr Sci* 2017;6:e12.
9. Parambeth JC, Fosgate GT, Suchodolski JS, *et al*. Randomized placebo controlled clinical trial of an enteric coated micro-pelleted formulation of a pancreatic enzyme supplement in dogs with exocrine pancreatic insufficiency. *J Vet Intern Med* 2018; 32(5):1-9.
10. Steiner JM. Review of commonly used clinical pathology parameters for general gastrointestinal disease with emphasis on small animals. *Toxic Pathol* 2014; 42:189-194.
11. Swift NC, Marks SL, MacLachlan NJ, *et al*. Evaluation of serum feline trypsin-like immunoreactivity for the diagnosis of pancreatitis in cats. *J Am Vet Med Assoc* 2000; 217:37-42.
12. Simpson KW, Fyfe J, Cornetta A, *et al*. Subnormal concentrations of serum cobalamin (vitamin B_{12}) in cats with gastrointestinal disease. *J Vet Intern Med* 2001;15;26-32.
13. Steiner JM. Exocrine pancreatic insufficiency. In; *Textbook of Veterinary Internal Medicine* 8th ed. Ettinger SJ, Feldman EC, Coté E (eds). St Louis, MO; Elsevier, 2017;1694-1697.
14. Xenoulis P, Fradkin J, Rapp S, *et al*. Suspected isolated pancreatic lipase deficiency in a dog. *J Vet Intern Med* 2007;21:1113-1116.
15. Soetart N, Rochel D, Drut A, *et al*. Serum cobalamin and folate as prognostic factors in canine exocrine pancreatic insufficiency: an observational cohort study of 299 dogs. *Vet J* 2019:243;15-20.
16. Mas A, Noble PJ, Cripps PJ, *et al*. A blinded randomized controlled trial to determine the effect of enteric coating on enzyme treatment for canine exocrine pancreatic efficiency. *BMC Vet Res* 2012;8:127.
17. German A. Exocrine pancreatic insufficiency in the dog: breed associations, nutritional considerations, and long-term outcome. *Top Companion Anim Med* 2012;27 (2);104-108.
18. Biourge VC, Fontaine J. Pancreatic insufficiency and adverse reaction to food in dogs: a positive response to a high-fat, soy isolate hydrolysate–based diet. *J Nutr* 2004;134;2166S–2168S.
19. Toresson L. Oral cobalamin supplementation in dogs with exocrine pancreatic insufficiency. *J Vet Intern Med* 2017;31(4):1283.
20. Makielski K, Cullen J, O'Connor A, *et al*. Narrative review of therapies for chronic enteropathies in dogs and cats. *J Vet Intern Med* 2019;33:11-22.
21. Coddou MF, Constantino-Casas F, Blacklaws B, *et al*. Identification of IgG4-related disease in the English Cocker Spaniel and dogs of other breeds. *J Vet Intern Med* 2018; 32(1);538.

NUTRITION FOR THE DIABETIC CAT

Diabetes mellitus can have far-reaching effects on the body's metabolism; Dr. Vandendriessche offers a common-sense approach to the patient and reviews how careful dietary choice, along with lifestyle changes, can help achieve optimal control of the problem.

KEY POINTS

- Feline type 2 diabetes is a very common illness, but successful treatment requires a holistic approach which includes both insulin therapy and attention to diet.
- The diet for a diabetic cat should be designed to allow gradual weight loss whilst ensuring satiety and good glycemic control.

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Introduction

Diabetes mellitus is probably the most common feline endocrinopathy, with type 2 diabetes being much more frequently encountered than type 1, being diagnosed in up to 95% of diabetic cats. Each new feline patient that presents with diabetes is a challenge for both the veterinarian and the nutritionist, because it requires us to take into account many different factors with the ultimate goal of achieving euglycemia and improving both the patient's quality of life and life expectancy.

Not only does the correct medical treatment – with a long-acting insulin – need to be initiated, the nutrition and the overall management of the feline patient must be adjusted in order to both reduce (and, ideally, eventually eliminate the need for) insulin dosage and enable the cat to reach its ideal body weight. All these changes have to be implemented in agreement with the owner's abilities and the cat's preferences; otherwise compliance with the proposed alterations is unlikely to be successful. As both a practicing veterinarian and a board-certified nutritionist, I hope to supply you with hints, gained from my experiences throughout the years dealing with such patients, in a way that will help you to tackle such cases with more confidence in the future.

Obesity and diet

Many cats with type 2 diabetes have a mild to severe form of obesity **(Figure 1)**. It is therefore necessary to change their diet to a food which is specifically designed to make them lose weight; however, it is essential that weight loss is achieved in a controlled manner, so that the cat remains healthy, yet the diet chosen must limit the glycemic load. Such a diet is typically low in energy,

Figure 1. Most cats with type 2 diabetes are at least mildly obese, and it is essential to ensure that they are offered a diet which is specifically designed to help them lose weight.

high in fiber and protein, and low in soluble carbohydrate; it should also be enriched with anti-oxidants and L-carnitine. A diet that is low in energy will allow the owner to feed a larger volume of food, which will help to maintain satiety between meals; this is aided by the increased amount of insoluble fiber in the diet. The soluble fiber fraction in the food will slow the uptake of nutrients, thus helping to control the glycemic load. The high-protein content is necessary to avoid muscle breakdown due to the caloric restriction in the food; this has a synergistic effect with increased activity levels (see below) which together helps improve lean body mass development. Anti-oxidants will counteract the negative effects of obesity-related chronic inflammation, and L-carnitine will facilitate the use of fat – rather than glucose – as an energy source by the cells.

The choice between a dry and a wet diet should be made in consultation with the owner, and should take into account the cat's preferences and habits prior to the diagnosis. In general, wet diets are often better at achieving satiety; so moisturizing kibble may be a good option if a cat does not like pouches or pates. Another advantage of moisturizing kibble or using wet food is that urinary health may improve, as recurrent cystitis is a common comorbidity in diabetic and/or obese cats. However the most important thing is to ensure that the cat has a consistent, predictable food intake (which for some cats might only be achievable with a dry diet).

The amount to be fed should be calculated using an estimation of the cat's ideal bodyweight, and as a starting point the aim should be to supply 293kJ per kg bodyweight: ideally the cat should lose between 0.5 and 2% of its body weight each week once on the new diet. Weight assessment should therefore be done during each follow-up consultation **(Figure 2)** and adjustments to the ration made in accordance with the weight loss.

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Figure 2. All diabetic cats should be subject to regular weight checks, and the diet adjusted if necessary.

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Figure 3. An automatic feeder allows a cat to be fed multiple small meals throughout the day, which will mimic its natural feeding behavior.

Feeding regime

Meal supervision is also a crucial factor in managing these patients, and feeding should be tailored around the insulin injections. In practice this means that two larger meals (2x 30% of daily amount) should be fed at 12-hour intervals, offered before the insulin injections, with the remainder of the feed given between times in smaller portions.

When the patient will only eat wet diets, the owner's time schedule will dictate feeding times, as the food should be given fresh, but if the cat will eat kibble, investing in one (or more) automatic feeders is a must. These will enable the cat to be fed multiple small meals throughout the day, thus mimicking its natural behavior **(Figure 3)**. The advantage of having more than one automatic feeder is that the cat has to exercise more – *i.e.*, it has to move between the feeding stations. Importantly, however, it is essential to alter the schedule each day, so that the cat does not know which feeder will open at which time. Failure to do so means that the cat will simply wait in front of the feeder it knows will open next.

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Figure 4. Owner should provide the food on a raised area so that the cat has to jump to feed. This will help the cat expend more energy getting to its food.

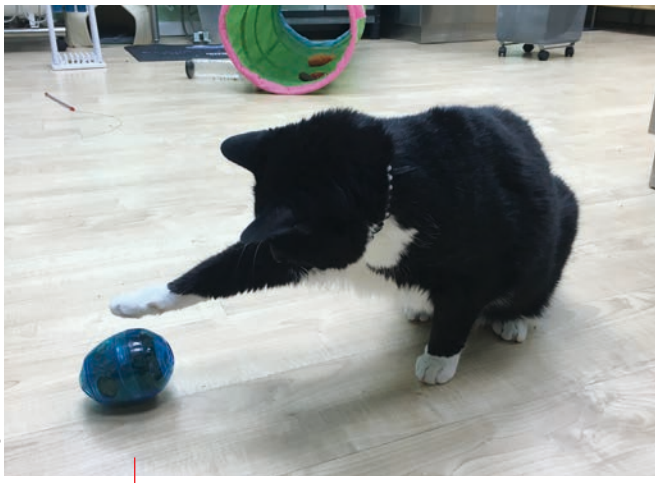

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Figure 5. Feeding toys not only ensure that a cat expends energy in obtaining its food, they also provide mental stimulation.

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Figure 6. Diabetic cats should be encouraged to maintain their activity levels; both physical activity and loss of body fat can contribute to remission of the diabetic state. By enriching a cat's environment with things such as boxes, tunnels and climbing frames, the cat will be encouraged to explore its surroundings.

Activity stimulation

As mentioned before, it is necessary to stimulate physical activity in these patients, and in many cases a cat's activity levels can be increased by simply altering the way in which it is fed. Some of the options available include:

- Advising the owner not to feed their pet on the floor but rather to provide the food on a raised area, so that the cat has to jump up to feed **(Figure 4)**. This should however take into account the cat's abilities to jump; this should be discussed with the owner and, if necessary, the place chosen to feed the cat may need to be altered as the cat loses weight. The more weight the patient loses, the harder it should be made for the cat to reach its food.
- Encourage the owner to distribute the food throughout the cat's living area, rather than just supplying it in a single bowl. This can easily be done with both kibble and wet diets.
- Suggest that the owner uses feeding toys so that the cat has to expend more energy getting to its food **(Figure 5)**.
- Enrich the cat's living environment in any way possible; this will encourage the cat to explore its surroundings and will provide both mental and physical stimulation. **(Figure 6)**.

CONCLUSION

In summary, each cat with type 2 diabetes should have its feeding regime reviewed and, if necessary, be prescribed a diet which is specifically designed to achieve healthy weight loss, facilitate glycemic control and reduce the time required to reach euglycemia. Along with simple alterations to the cat's lifestyle and environment, this will improve the cat's quality of life and aid in delivering the desired weight loss.

"The choice between a dry or a wet diet should be made in consultation with the owner, and should take into account the cat's preferences and habits prior to the diagnosis of diabetes."

Veerle Vandendriessche

FURTHER READING

- Gottlieb S, Rand JS, Marshall R, *et al*. Glycemic Status and Predictors of Relapse for Diabetic Cats in Remission. *J Vet Intern Med* 2015;29:184-192.
- de Godoy MRC, Shoveller AK. Overweight adult cats have significantly lower voluntary physical activity than adult lean cats. *J Feline Med Surg* 2017;19(12):1267-1273.
- Gottlieb S, Rand JS. Managing feline diabetes: current perspectives. *Vet Med Res Reports* 2018;9:33-42.
- Larsen JA. Risk of obesity in the neutered cat. *J Feline Med Surg* 2017;19(8):779-783.
- Roomp K, Rand JS. Management of Diabetic Cats with Long-acting Insulin. *Vet Clin North Am Small Anim Pract* 2013;43:251-266.
- Zoran DL, Rand JS. The Role of Diet in the Prevention and Management of Feline Diabetes. *Vet Clin North Am Small Anim Pract* 2013;43:233-243.

DIAGNOSIS OF CANINE PANCREATITIS

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Professor Burgener received his veterinary degree from the University of Bern, Switzerland in 1996. His career since then included various academic posts at the universities of Baton Rouge (USA), Bern, Leipzig and Utrecht before he moved to his current position as Professor and Chair of Small Animal Internal Medicine at Vienna, where he is also Head of the Small Animal Clinic. His research interests center around gastroenterology topics, and he has published over 60 articles in peer-reviewed publications, as well as being an *ad hoc* reviewer for more than 30 different scientific journals.

KEY POINTS

- Canine pancreatitis is a commonly encountered disease, but the pathophysiology is poorly understood, and the etiology remains unknown in most cases.
- Diagnosing pancreatitis remains a challenge for the clinician, due to a variety of factors; histology is still considered the gold standard, but is rarely used.

Despite the fact that pancreatitis is a disease commonly encountered in first opinion practice, diagnosis can be far from straightforward, as Iwan Burgener describes in a paper that focuses on the pros and cons of the diagnostic options available.

Introduction

The synthesis and storage of digestive enzymes in the pancreas carries the risk of self-digestion and subsequent inflammation, *i.e.*, pancreatitis. Strictly speaking, the term *pancreatitis* refers to inflammation (*i.e.*, infiltration with inflammatory cells) of the exocrine pancreas, but it is also commonly expanded to include diseases of the exocrine pancreas characterized mainly by necrosis (necrotizing pancreatitis) or irreversible structural changes such as fibrosis (chronic pancreatitis), sometimes with only a minimal inflammatory component (1).

The exocrine pancreas has several mechanisms to prevent self-digestion (*e.g.*, enzyme precursors, storage of enzymes in granules separated from lysosomes, localized high pH levels, good blood supply, etc.). Only if all these protective mechanisms are breached at the same time will pancreatitis develop. The disease itself proceeds in two stages. In the first stage, trypsin (activated from trypsinogen) is released, which in turn activates other digestive enzymes, leading to local changes such as edema, hemorrhage, infiltration with inflammatory cells, and necrosis of acinar cells and peripancreatic fat. In the second stage, the actual inflammatory process advances with recruitment of inflammatory cells and release of cytokines, which can lead to systemic organ disorders and ultimately death.

Pancreatitis is classified into acute (AP) and chronic forms (CP), depending on whether permanent histopathologic changes are absent (AP) or present (CP). Histologically, AP consists of neutrophilic inflammation associated with interstitial edema and necrosis of mesenteric fat **(Figure 1)**. In CP, fibrosis is more prominent than inflammatory changes, with cystic degeneration of the tissue gradually increasing as the fibrosis increases.

Etiology

Pancreatitis is the most common disorder of the exocrine pancreas in dogs. Despite this, the pathophysiology is poorly understood, and its etiology remains unknown in most cases. Miniature Schnauzers are more likely to be presented with pancreatitis than other breeds (2), and this is probably due to mutations in the *SPINK* gene, which determines the pancreatic secretory trypsin inhibitor. Other breeds with a potentially increased

risk of pancreatitis include the Cavalier King Charles Spaniel, Cocker Spaniel, Boxer, Border Collie and Yorkshire Terrier (3). Risk factors for pancreatitis include ingestion of fatty meals, trauma, local ischemia, endocrine disorders (hyperadrenocorticism, diabetes mellitus, and hypothyroidism) and the use of various drugs. Calcium, glucocorticoids, L-asparaginase, azathioprine, potassium bromide, zinc and glucantime have been identified as risk factors in the dog, but the causal relationship is not really proven for all of these drugs. Drawing comparisons from the human literature, it is also prudent to consider non-steroidal anti-inflammatory drugs (NSAIDs), thiazide diuretics, furosemide, vinca alkaloids, cholinesterase inhibitors, estrogens and salicylates as potential inducers of pancreatitis. Hyperlipidemia, and especially hypertriglyceridemia, have also been shown to cause pancreatitis in the dog. On the other hand, bacterial and fungal infections are rarely found as triggers, although *Babesia canis* is known to be a causative agent (4).

Diagnosis

Diagnosing pancreatitis antemortem remains a challenge for the clinician. This is for various reasons, including the undefined etiology, the often mild and nonspecific clinical signs, the poor sensitivity and specificity of most of the clinicopathological and imaging findings, the fact that concomitant disorders frequently occur, and the difficulty in obtaining or interpreting biopsy samples. Histology is still considered the gold standard of pancreatitis diagnostics, even though it is rarely used.

Clinical signs

Pancreatitis presents clinically pronounced differences, ranging from subclinical to multiple organ failure. The clinical picture usually corresponds to the picture of an acute abdomen, with anorexia, vomiting, abdominal pain, and dehydration, with or without diarrhea, commonly noted. Major systemic complications may be seen with severe pancreatitis (*e.g.*, disseminated intravascular coagulation (DIC), pulmonary thromboembolism, cardiovascular shock, and multi-organ failure). Chronic pancreatitis (where the clinical signs are even more non-specific than with the acute version) is less common in dogs than in cats.

Imaging

Abdominal radiographs may reveal a loss of detail in the cranial abdomen and/or a mass effect. However, radiography is both insensitive and non-specific for the diagnosis of pancreatitis, and is mainly recommended to rule out concomitant diseases such as intestinal obstruction and foreign bodies. Abdominal ultrasound is usually considered the imaging method of choice for the diagnosis of pancreatitis, and is also helpful for the diagnosis or exclusion of other diseases that cause similar

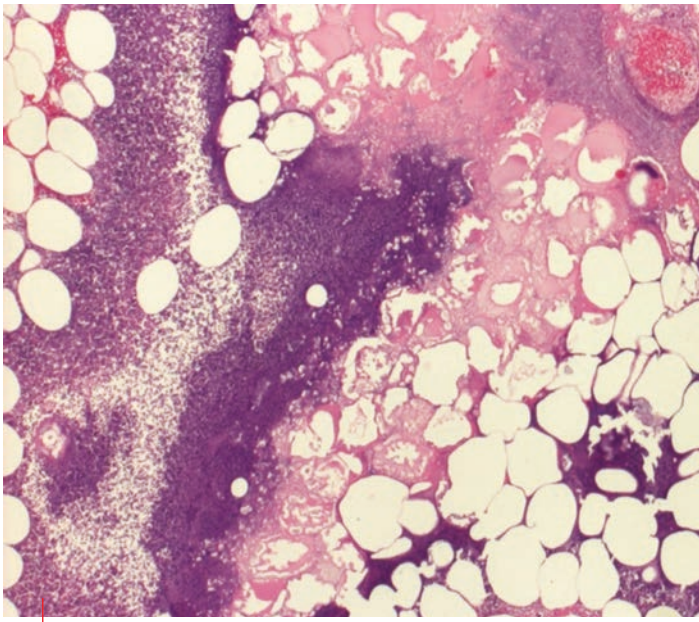

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Figure 1. A histopathology slide showing necrotizing steatitis of the surrounding fat tissue in acute pancreatitis.

clinical signs. There are only a limited number of studies that have systematically evaluated the performance of abdominal ultrasonography for the diagnosis of canine pancreatitis, revealing sensitivities of 69% at best, and most of these studies are more than a decade old (5). Since then, there have been significant advances in both the quality of the equipment and the expertise of the radiologists. It is of utmost significance to underline the fact that the performance of abdominal ultrasonography for the diagnosis of pancreatitis is highly dependent on the expertise

"Because biopsy is not practical in most cases, there is currently no real gold standard for the diagnosis of canine pancreatitis; a combined approach – involving obtaining a full history and physical examination, careful laboratory analysis and ultrasonographic examination – is the best method to achieve an accurate non-invasive verdict of pancreatitis."

Iwan Burgener

of the ultrasonographer and the quality of the equipment used. Ultrasonographic findings such as a hypoechoic pancreas, hyperechoic mesentery and abdominal effusion are relatively specific for pancreatitis, although other pancreatic lesions (*e.g.*, neoplasia, hyperplastic nodules) may share a similar appearance with pancreatitis. It is important to recognize that some changes detected during abdominal ultrasonography may be age-related, such as pancreatic duct dilation – a finding which was previously thought to be specific to pancreatitis.

Contrast-enhanced computed tomography (CT) is an extremely valuable tool for the evaluation of human patients with suspected pancreatitis. To date, few studies have evaluated the suitability of CT as a diagnostic tool for canine pancreatitis, but a recently published report confirmed that computed tomographic angiography was better than ultrasound at identifying dogs with severe acute pancreatitis and portal vein thrombosis (5). Magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP) are becoming the imaging modality of choice in humans for the pancreatic and biliary tract, but to date there is only limited experience of these techniques in dogs.

Routine blood work

Hematology and biochemistry tests are not specific for pancreatitis and do not appear to differ significantly between patients with AP and CP. The most common abnormal findings in serum chemistry are elevation of alkaline phosphatase and alanine aminotransferase, azotemia (mostly pre-renal), jaundice (mostly post-hepatic) and hypercholesterolemia; typically between 50-70% of these parameters will be outwith the normal reference range. Serum lipase and amylase activity are not specific to the pancreas and are not particularly sensitive for pancreatitis, but can potentially be used for diagnosis in an emergency if the clinical picture fits. Finally, an elevated serum trypsin-like immunoreactivity (TLI) concentration is quite specific for pancreatitis, but has only a sensitivity of about 30-50%.

DGGR-based lipase assays

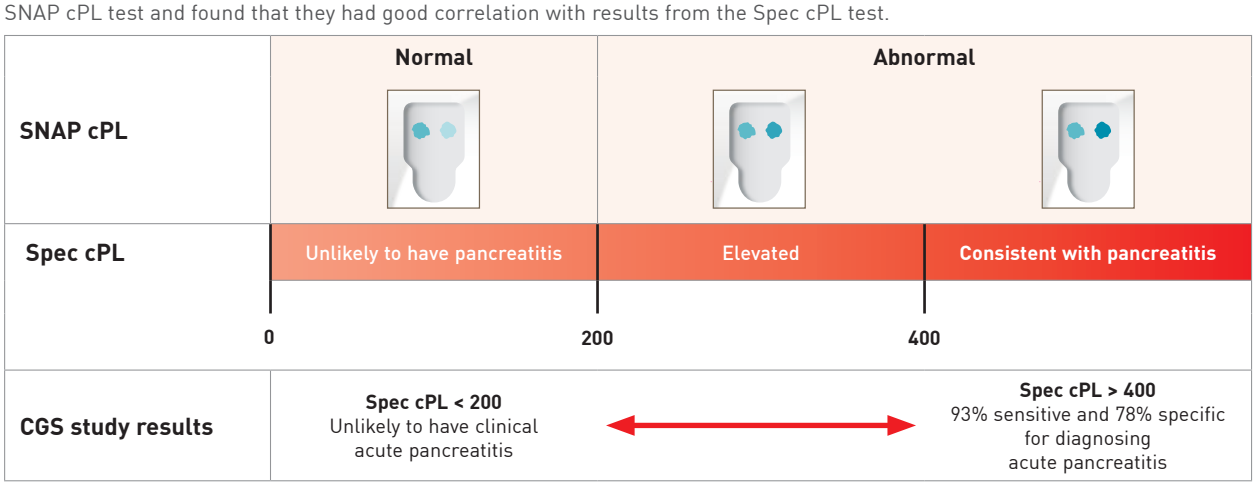
Lipase levels can be determined by enzymatic lipase activity or by immunologic assays. Enzymatic assays measure (as the name suggests) the activity of enzymes, whereas immunologic assays detect certain parts of the protein/isoenzyme via antibodies (6,7). Most enzymatic assays utilize a 1,2-diglyceride as a substrate, others triolein, and yet others DGGR (1,2-o-dilauryl-rac-glycero-3-glutaric acid-(6'-methylresorufin) ester).

Recently, some reports have suggested that DGGR-based assays are more specific for the measurement of pancreatic lipase in canine serum than other total lipase activity assays (8,9). However, another study reported that the specificity of a DGGR-based assay for the measurement of serum lipase activity in dogs was lower than that for the more traditional 1,2-diglyceride-based assays (10). If DGGR were a specific substrate for pancreatic lipase, dogs with exocrine pancreatic insufficiency (EPI) should have negligible serum lipase activity when measured with a DGGR-based assay. Indeed, serum lipase activity has been shown to be significantly lower in dogs with EPI than in healthy control dogs (11). However, 33 out of 48 (69%) EPI dogs in this study had serum lipase activities within the reference interval, suggesting that DGGR is not exclusively hydrolyzed by pancreatic lipase, and DGGR-based assays are thus not specific for this enzyme. This would suggest that DGGR also acts as a substrate for non-pancreatic lipases, but which other lipases are detected by the DGGR-based assay remains to be determined.

Given the above, only the use of DGGR as a substrate will most likely not lead to similar results in different DGGR-based assays. However, moderate-to-good sensitivity and specificity of two DGGR-based lipase assays have been reported. A DGGR-based lipase assay[1] has been shown to have high agreement with the best-established test for pancreatic lipase immunoreactivity (Spec cPL®, Idexx, USA) in dogs with suspected pancreatitis (8), but agreement between ultrasonography and

[1] Lipase colorimetric for Roche Cobas Integra 800, Roche Diagnostics, Rotkreuz, Switzerland.

Figure 2. A recent independent study by the Comparative Gastroenterology Society (CGS) compared results obtained with the SNAP cPL test and found that they had good correlation with results from the Spec cPL test.



both lipase assays results was only fair. Another DGGR-based lipase assay[2] has demonstrated excellent precision, reproducibility and linearity and substantial agreement between DGGR lipase and the Spec cPL, with similar sensitivity and specificity for the diagnosis of acute and chronic pancreatitis, even though the study population was very small (9).

Pancreatic lipase immunoreactivity (PLI)

In contrast to lipase activity in serum, PLI only measures lipases synthesized by acinar cells of the exocrine pancreas. The antibodies used in the Spec cPL test[2] are specific and do not show cross-reactivity with other lipases (6,7,12). Serum PLI is highly specific for exocrine pancreatic function and shows a high sensitivity for moderate-to-severe pancreatitis (13). Furthermore, the Spec cPL test has demonstrated the best overall performance characteristics (sensitivity and specificity) compared to amylase, lipase, and cTLI for diagnosing histopathologic lesions of pancreatitis in dogs (13).

In recent years, a test for cage-side use on the patient has also become available (SNAP cPL, Idexx, USA). This test is semi-quantitative and should be used to exclude pancreatitis with a negative result. A positive cage-side result should be followed by a determination of PLI concentration for confirmation of the diagnosis and subsequent follow-up measurement. The SNAP cPL test result appears to have good correlation with the Spec cPL test – both tests were developed by the same laboratory and employ the same diagnostic antibodies (14)

[2] DiaSys Lipase DC FS, Holzheim, Germany.

CONCLUSION

As there is currently no real gold standard for antemortem diagnosis of pancreatitis in dogs, the combination of a complete history and physical examination, measurement of pancreatic lipase immunoreactivity, and ultrasonographic examination of the pancreas is the best approach for an accurate non-invasive diagnosis of pancreatitis. The diagnosis should ideally be confirmed by pancreatic cytology and/or pancreatic histopathology (ultrasound-guided, laparoscopy or laparotomy), but this is rarely done. Abdominal ultrasound is useful but requires experience, and normal findings do not exclude pancreatitis.

(Figure 2). Another study has also shown a high correlation between the two tests, suggesting that the cage-side test is the most sensitive single test that can be done in-house (15).

Looking ahead, new commercial immunologic lipase assays are becoming available, but some of them are not yet validated in the literature. For example, in a recent study, a newly released assay for the measurement of canine pancreatic lipase showed significant bias and poor concordance with partially different clinical interpretations when compared with the validated assay (16). Further research is therefore needed before newly released assays can be recommended for clinical use.

REFERENCES

1. Xenoulis PG. Diagnosis of pancreatitis in dogs and cats. *J Small Anim Pract* 2015;56(1);13-26.
2. Bishop MA, Xenoulis PG, Levinski MD, *et al*. Identification of variants of the *SPINK1* gene and their association with pancreatitis in Miniature Schnauzers. *Am J Vet Res* 2010; 71(5):527-533.
3. Watson PJ, Roulois AJ, Scase T, *et al*. Prevalence and breed distribution of chronic pancreatitis at post-mortem examination in first-opinion dogs. *J Small Anim Pract* 2007;48(11):609-618.
4. Möhr AJ, Lobetti RG, Van der Lugt JJ. Acute pancreatitis: a newly recognised potential complication of canine babesiosis. *J S African Vet Assoc* 2000;71:232-239.
5. French JM, Twedt DC, Rao S, *et al*. Computed tomographic angiography and ultrasonography in the diagnosis and evaluation of acute pancreatitis in dogs. *J Vet Intern Med* 2019;33(1):79-88. doi: 10.1111/jvim.15364. Epub 2018 Dec 11.
6. Steiner JM, Teague SR, Williams, DA. Development and analytic validation of an enzyme-linked immunosorbent assay for the measurement of canine pancreatic lipase immunoreactivity in serum. *Can J Vet Res* 2003;67;175-182.
7. Steiner JM, Williams DA. Development and validation of radio-immunoassay for the measurement of canine pancreatic lipase immunoreactivity in serum of dogs. *Am J Vet Res* 2003;64;1237-1241.
8. Kook PH, Kohler N, Hartnack S, *et al*. Agreement of serum Spec cPL with the 1,2-o-dilauryl-rac-glycero glutaric acid-(6′-methylresorufin) ester (DGGR) lipase assay and with pancreatic ultrasonography in dogs with suspected pancreatitis. *J Vet Intern Med* 2014;5;28(3);863-870.
9. Goodband EL, Serrano G, Constantino-Casas F, *et al*. Validation of a commercial 1,2-o-dilauryl-rac-glycero glutaric acid-(6′-methylresorufin) ester lipase assay for diagnosis of canine pancreatitis. *Vet Rec Open* 2018;26;5(1);e000270.
10. Graca R, Messick J, McCullough S, *et al*. Validation and diagnostic efficacy of a lipase assay using the substrate 1,2-0-dilauryl-rac-glycero glutaric acid-(6′ methyl resorufin)-ester for the diagnosis of acute pancreatitis in dogs. *Vet Clin Pathol* 2005;34;39-43.
11. Steiner JM, Suchodolski JS, Gomez R. DGGR is not a specific substrate for pancreatic lipase. In: *Proceedings*, WSAVA-FASA-VA Congress 2015, Bangkok, Thailand.
12. Neilson-Carley SC, Robertson JE, Newman SJ, *et al*. Specificity of a canine pancreas-specific lipase assay for diagnosing pancreatitis in dogs without clinical or histologic evidence of the disease. *Am J Vet Res* 2011;72(3);302-307.
13. Trivedi S, Marks SL, Kass PH, *et al*. Sensitivity and specificity of canine pancreas-specific lipase (cPL) and other markers for pancreatitis in 70 dogs with and without histopathologic evidence of pancreatitis. *J Vet Intern Med* 2011;25;1241-1247.
14. McCord K, Morley PS, Armstrong J, *et al*. A multi-institutional study evaluating the diagnostic utility of the SPEC cPL(™) and SNAP® cPL(™) in clinical acute pancreatitis in 84 dogs. *J Vet Intern Med* 2012;26;888-896.
15. Kalenyak K, Schadow A, Burgener IA. Diagnosis of canine pancreatitis dependent on SNAP cPL™ and Spec cPL™. In: *Proceedings*, 22nd ECVIM-CA/ESVIM Congress 2012, Maastricht, The Netherlands.
16. Hofel E, Rieker T, Suchodolski JS, *et al*. Measurement of canine and feline pancreatic lipase immunoreactivity – analytical comparison of new commercial assays with established assays. *Tierarztl Prax Ausg K Kleintiere Heimtiere* 2015;43(6):399-408.

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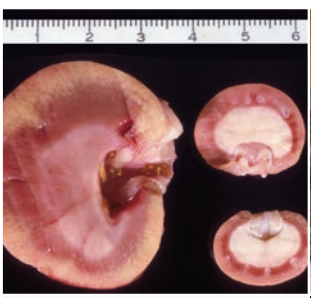

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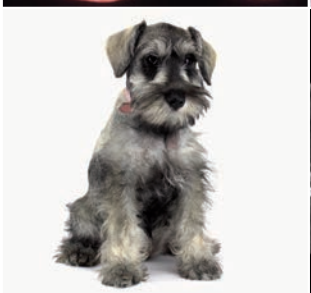

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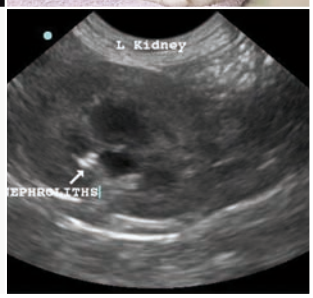

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COMING UP...

In our next issue, we will look at various aspects of renal disease.

- Early detection of renal disease
  Hannah Joy Sargent and Jonathan Elliott, UK
- Feline renal transplant
  Lillian Aronson, USA
- Dietary protein levels in cats with CKD
  Meredith Wall, Australia
- Management of ureteral obstruction in dogs and cats
  Lillian Aronson, USA
- Ultrasound imaging of feline kidney disease
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- Hyperlipidemia and proteinuria in Miniature Schnauzers
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