Chapter 9

Liver disorders

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INTRODUCTION

Hepatology (the study of the liver and the diseases that affect it) remains a particularly frustrating area in small animal internal medicine because the liver is involved in hundreds of metabolic processes and can be involved with a variety of pathologic and pathophysiologic changes. Fortunately, the liver has a remarkable functional reserve; in some cases as much as 70–80% of the functional liver mass must be impaired before signs of dysfunction become apparent and, under the right circumstances, the liver is capable of regenerating significant functional capacity over relatively short periods of time.

Alterations in the normal metabolic processes result in many of the clinical findings in animals with liver disease. Some of these important metabolic processes include: normal metabolism of lipids, protein, carbohydrate, vitamins, and minerals; bile acid synthesis and excretion; protein production; detoxification and excretion of many endogenous and exogenous substances; production of urea from ammonia; drug metabolism and excretion; managing translocated bacteria and bacterial products, coagulation, and reticuloendothelial function. Abnormalities of normal protein production and bilirubin metabolism can be especially significant determinants of clinical signs. Impaired albumin synthesis may result in decreased plasma oncotic pressure, therefore edema or ascites and impaired synthesis of procoagulant clotting proteins and anticoagulants may result in bleeding or thrombosis. Cholestasis may result in jaundice.

Despite the importance of the liver in normal metabolism, early diagnosis of liver disease is often impaired by the nonspecific nature of the typical clinical signs and by a paucity of findings at physical examination. Typically, animals with liver disease present with lethargy, anorexia, weight loss, and other nonspecific clinical signs. Signs referable to the gastrointestinal (GI) tract such as vomiting and diarrhea are also common. Vomiting is an important yet nonspecific finding, especially in cats. Either large or small bowel diarrhea may be noted, especially in dogs or in cats with concurrent intestinal or pancreatic disease. Diarrhea is a less common finding than vomiting. Abdominal pain may be noted in animals with acute liver diseases or in patients with concurrent or associated pancreatitis or peritonitis.

Neurologic manifestations of liver disease are common in animals with either congenital or acquired portosystemic shunts (PSSs) or acute fulminating hepatic failure. The signs associated with hepatoencephalopathy are generally those of central nervous system (CNS) depression or overt signs of cerebral and diencephalic dysfunction (**Figure 9.1**). Depression, behavioral changes, ataxia, central blindness, circling, head pressing, pacing, panting, stupor, coma, and seizures may be noted. Seizures are most common in animals with PSSs, especially following attempted surgical correction. Cats with

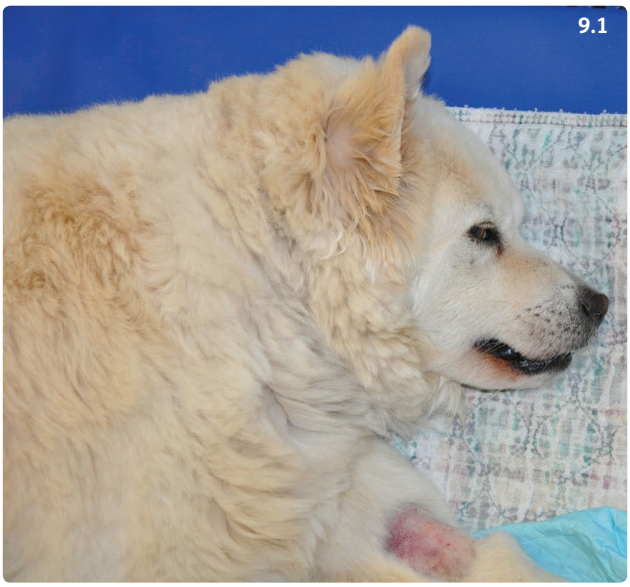


Figure 9.1 A terminally ill dog in an hepatic coma caused by fulminating hepatic lipidosis. Gross pathology and histopathology of this dog's liver showed marked hepatic lipidosis.

hepatoencephalopathy tend to have signs that are more difficult to ascribe to the CNS. Anorexia, CNS depression, and ptyalism are often noted in cats with liver disease and may not be attributed to the influence of hepatotoxins on the CNS, thus leading to underutilization of appropriate medical therapy for hepatoencephalopathy in this species.

Cholestasis resulting in icterus is common in animals with liver disease, but it may not be severe enough to be noted at physical examination early in the disease process. Posthepatic biliary disease, pancreatitis, and hemolytic anemia are also important causes of icterus. Animals with severe liver disease may not produce or normally activate procoagulant clotting factors, resulting in overt bleeding tendencies. GI bleeding is common. Nonspecific signs of anemia may be noted if bleeding is low grade and chronic, or melena may be obvious if bleeding is severe. Ecchymotic hemorrhage may be apparent. Platelet membrane abnormalities associated with changes in lipoprotein metabolism may result in thrombopathia or decrease platelet half-life and thus cause thrombocytopenia with resultant petechia. Changes in anticoagulant protein production may result in thrombosis or thromboembolism. The disrupted balance between bleeding and thrombosis in liver disease can be clinically very confusing.

Unless the patient is jaundiced or exhibits overt signs of encephalopathy or ascites, clinicopathologic abnormalities are frequently the first indicator of liver disease. Increased transaminase activities or increased activities of enzymes indicative of cholestasis are the earliest indicators of liver disease in most cases. Alanine aminotransferase (ALT) and aspartate transaminase (AST) activities are sensitive indicators of liver insult in both dogs and cats, while increased alkaline phosphatase (ALP) and gamma-glutamyltransferase (GGT) activities are indicative of cholestasis. Hypoalbuminemia may indicate decreased hepatic function, as can decreased blood urea nitrogen (BUN) and hypoglycemia. These biochemical indicators are not specific for decreased hepatic function, so more specific tests such as fasting and postprandial bile acids or plasma ammonia concentrations are often evaluated when hepatic dysfunction is suspected. Unfortunately, biochemical recognition of primary hepatic disease is complicated by the fact that disorders that involve the liver secondarily (reactive hepatopathies), as well as certain drugs, can cause abnormal liver test results. In addition to liver tests, radiology, ultrasonography, cross-sectional imaging, and cytologic and histologic examination of liver tissue are employed in the evaluation of the hepatobiliary system.

FELINE HEPATIC LIPIDOSIS

Definition/overview

Feline hepatic lipidosis is a syndrome that can be either a primary idiopathic condition or secondary to a variety of common diseases of cats. Hepatic lipidosis is the most common liver disease of the cat, accounting for approximately 50% of diagnoses. The disorder accounts for approximately 10% of liver related deaths. Other names include feline fatty liver syndrome, steatosis, and fatty liver.

Etiology

A variety of factors have been proposed as potential etiologies, none of which has been confirmed. A multifactoral pathogenesis leading to malnutrition is likely. The major risk factor is obesity and a prolonged reduction of food intake, but obesity is not universally present in affected cats. Anorexia may be caused by concurrent disease, dietary change, or decreased food intake. Environmental stress is potentially an additional important risk factor. Changes in the intestinal microbiome may play an important role.

Pathophysiology

The exact pathogenesis remains to be defined. Decreased caloric intake causes a negative nitrogen balance. Fatty acids are mobilized from tissue stores and transported to the liver. Decreased protein metabolism and amino acid availability means that there is insufficient apoprotein to facilitate removal of fatty acids and fat accumulates in the hepatocytes. Histologically, >80% of hepatocytes will be heavily vacuolated with triglyceride. This decreases the ability of the cell to function and liver function slowly decreases.

Clinical presentation

Most affected animals are 2 years old or older. Cats with secondary hepatic lipidosis tend to be older than cats with idiopathic hepatic lipidosis. There is no apparent breed or gender predisposition, but older females seem to be more at risk. Affected cats are commonly obese and/or have experienced a stressful event of some type (e.g. a change in environment or concurrent disease). This is followed by anorexia and rapid weight loss or muscle wasting. Anorexia persists and the cat is presented for veterinary evaluation usually between 1 and 3 weeks after onset. Jaundice develops in most cats and is usually evident on presentation to a veterinarian.

At examination cats are depressed, dehydrated, and icteric (**Figure 9.2**) and show varying degrees of muscle

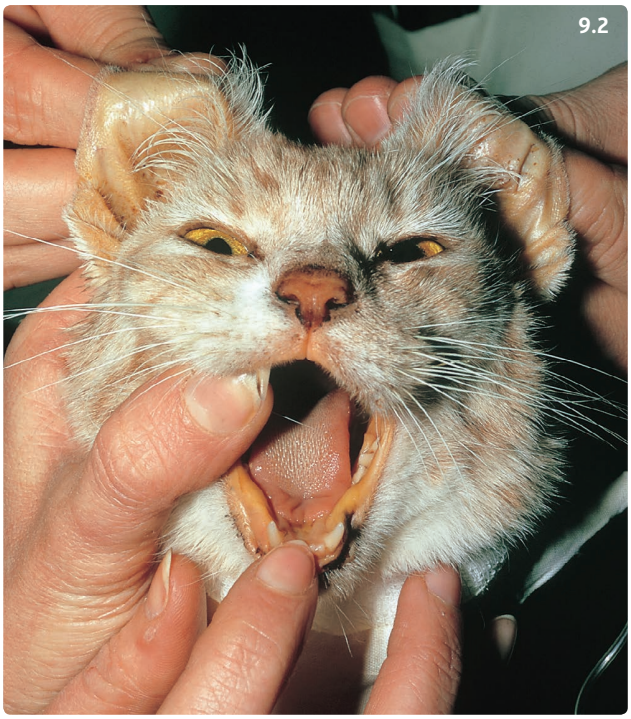


Figure 9.2 Jaundice in a cat with hepatic lipidosis. (Courtesy M. Schaer)

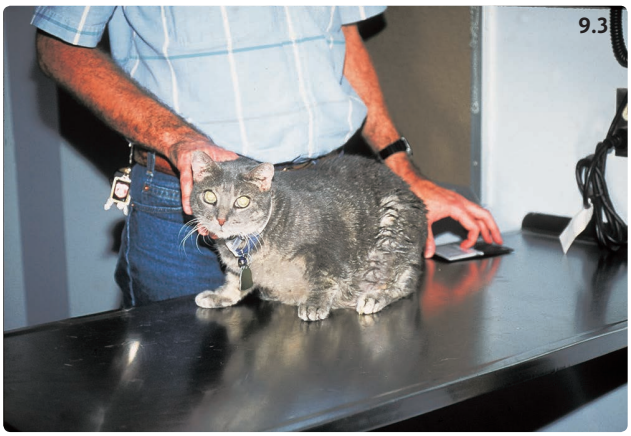


Figure 9.3 Marked subcutaneous fat pads in a cat with hepatic lipidosis. (Courtesy M. Schaer)

wasting. However, fat pads remain intact, reflecting the cat's inability to mobilize fat in this disease and the marked muscle breakdown for gluconeogenesis (**Figures 9.3**, **9.4**). Hepatic encephalopathy (**Figure 9.5**) may be related to severe hepatocellular dysfunction or to a relative deficiency of arginine, to which the anorexic cat is predisposed (cats cannot synthesize arginine and must rely on dietary sources). Abdominal palpation may reveal hepatomegaly that is smooth surfaced.

Figure 9.4 Marked muscle wasting along the back of a cat with hepatic lipidosis.

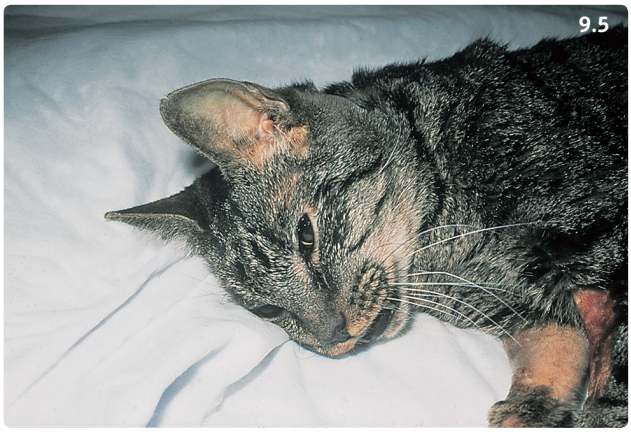


Figure 9.5 A Domestic Shorthair cat with hepatic encephalopathy associated with hepatic lipidosis. (Courtesy M. Schaer)

Differential diagnosis

Idiopathic hepatic lipidosis, secondary hepatic lipidosis, pancreatitis, inflammatory bowel disease (IBD), feline infectious peritonitis (FIP), hepatic lymphoma, cholangitis, liver flukes, biliary neoplasia.

Diagnosis

Diagnosis is based on hepatic cytology or histologic examination of a liver biopsy specimen. Typical laboratory findings are those of cholestasis; total bilirubin values range from normal (5 µmol/l [0.3 mg/dl]) to 256.5 µmol/l (15 mg/dl) or higher. There is usually a mild nonregenerative anemia.

Poikilocytosis is common and target cells may be noted. Liver enzyme activities are increased; ALT is normal or moderately increased (50–450 IU/l), AST is normal or moderately increased (50–450 IU/l), and ALP is occasionally normal but usually moderately to markedly increased (75–1,200 IU/l). Albumin and globulin concentrations are

usually normal. Fasting serum bile acid concentrations are above normal (0.75–5.6 µmol/l [0.3–2.3 µg/ml]) in most cats, but it should be noted that measurement of serum bile acids is considered redundant if hyperbilirubinemia is present, as it is in most affected cats. Glucose may be increased due to stress. Hypokalemia is often present. Greater than 50% of cats will have prolongation of PIVKA (proteins induced by vitamin K antagonism or absence), prothrombin time (PT), or partial thromboplastin time (PTT), but overt bleeding tendencies are rare. Of the commonly used coagulation screening tests, PIVKA is the one most likely to detect an abnormality. Coagulopathies associated with hepatic lipidosis are often responsive to vitamin K1.

Abdominal radiographs may reveal hepatomegaly. Ultrasonographic examination of the liver and surrounding structures allows other diseases in the differential diagnosis, such as cholangitis and extrahepatic bile duct obstruction, to be ruled out. The principal ultrasonographic feature of hepatic lipidosis is hyperechogenicity.

Tissue diagnosis can be made by aspiration cytology in some patients, but in others it is achieved by fine needle percutaneous biopsy (**Figure 9.6**), laparoscopy (**Figure 9.7**), or by exploratory laparotomy. Specimens are placed in buffered 10% formalin, in which they usually float.

Management

The mainstay of therapy is complete nutritional support and treatment of known concurrent illness. Protein should not be restricted unless severe signs of hepatoencephalopathy are present and cannot be controlled by other means. Adequate caloric support (80–100 kcal/kg/day) is critical and can rarely be accomplished without enteral support. Food is best administered through an esophagostomy or gastrostomy tube. Nasoesophageal feeding can be used, but the long-term nature of the enteral nutritional support needed makes this a less than ideal delivery method. Feeding tubes should be left in place until the cat is eating on its own. This may take months in some cats. Parenteral treatment with vitamin K1 (0.5–1.5 mg/kg IM) should be administered approximately 12 hours prior to biopsy. Fluids with potassium supplementation are important until an enteral feeding method is established. Serum phosphorus should be monitored closely during the initial 48 hours after starting enteral feeding. Re-feeding-induced hypophosphatemia is common and, if severe, may result in hemolysis or signs of CNS dysfunction that might be confused with hepatoencephalopathy. Careful administration of parenteral phosphate supplementation may be necessary during this period. B vitamins have been recommended in the management of cats with hepatic lipidosis. Soluble multi-B vitamin supplements have been recommended as additives to fluids used in the initial management of cats with hepatic lipidosis. Thiamine and cobalamin have both been implicated in the potential pathogenesis. Serum cobalamin has been noted to be low in cats with hepatic lipidosis, especially those with concurrent pancreatitis or IBD, and supplementation (1 mg IM q1–4weeks) is recommended. Other supplements that have been recommended include L-carnitine (250 mg/day PO), vitamin E (10 mg/kg/day PO), and SAMe

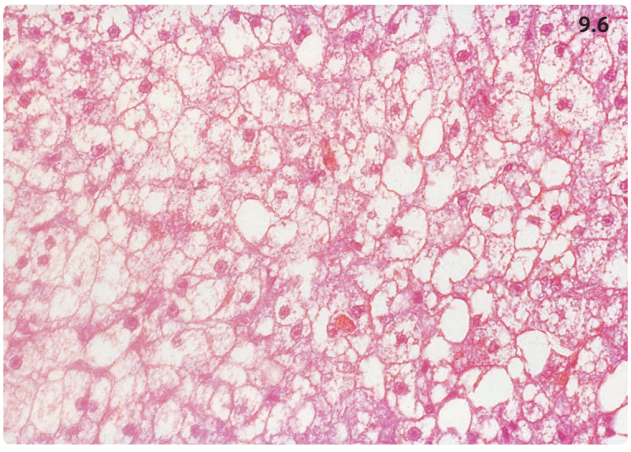


Figure 9.6 Histologic appearance of the liver in feline hepatic lipidosis. Note the empty hepatocytes, which contained fat removed during the fixing process.

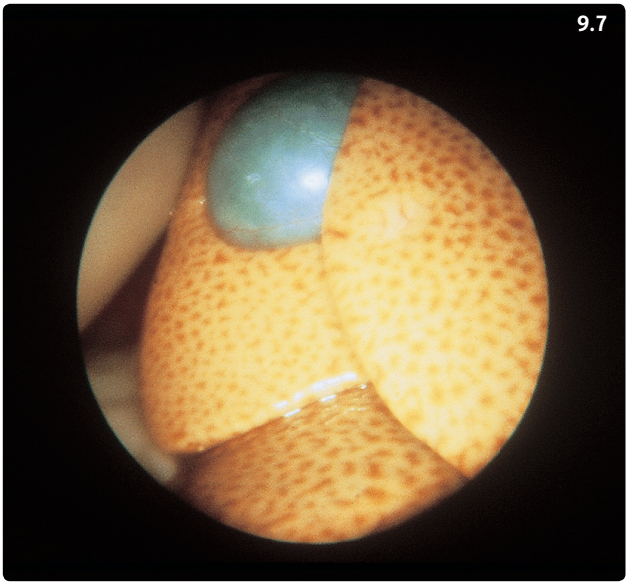


Figure 9.7 Laparoscopic view of the liver of a cat with hepatic lipidosis. Note the fatty liver and distended gallbladder.

(20 mg/kg PO q12h). Efforts should be made to correct any sources of psychological stress that may have triggered the initial anorexia.

The prognosis for cats with idiopathic hepatic lipidosis treated with adequate nutritional support is good. From 75% to >90% of cats will respond completely to therapy. Relapse is rare. If secondary hepatic lipidosis is present, the prognosis is dependent on the underlying disease. Less than 10% of cats with hepatic lipidosis will recover if adequate nutritional support is not maintained.

FELINE INFLAMMATORY LIVER DISEASE

Definition/overview

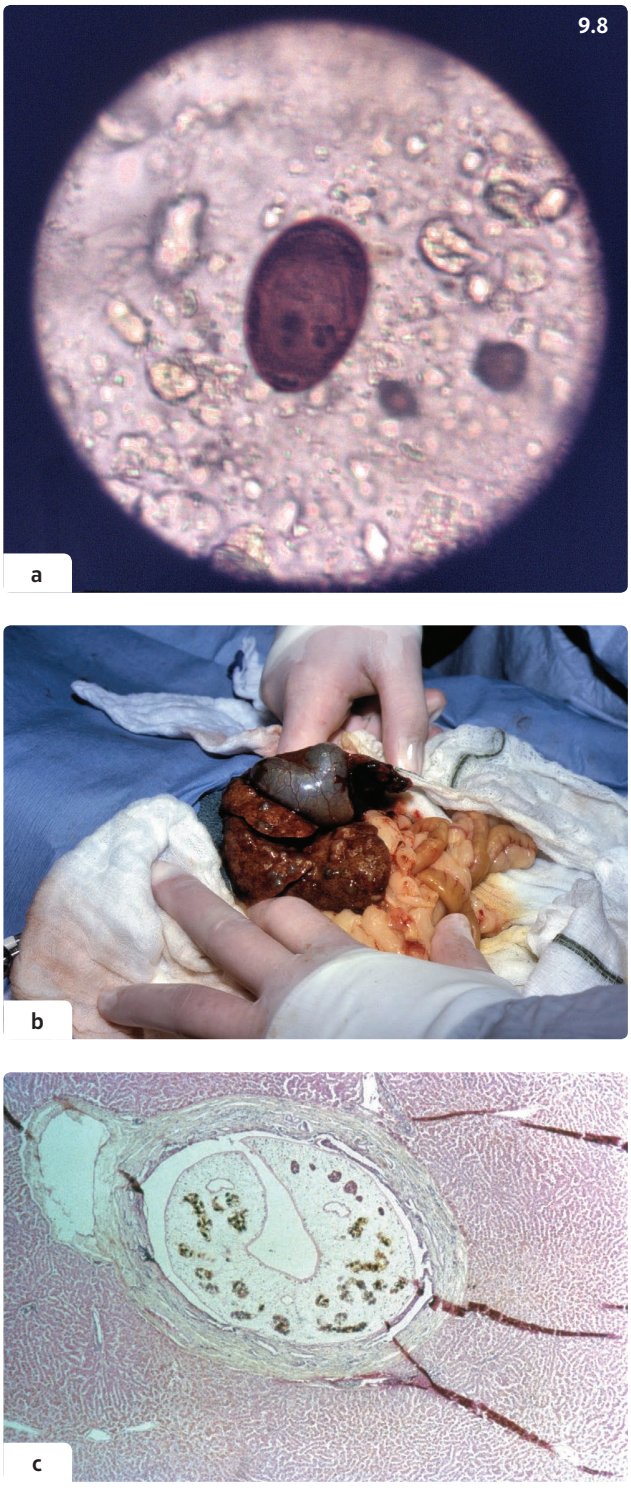
Chlolangitis is a complex of related inflammatory hepatobiliary disorders that accounts for approximately 25% of the liver diseases in cats. The WSAVA Liver Standardization Group has proposed a nomenclature system that recognizes three distinct forms of cholangitis in cats: neutrophilic, lymphocytic, and cholangitis associated with liver flukes (**Figures 9.8a–c**). The neutrophilic form is subdivided into an acute (neutrophilic infiltrate) and a chronic (mixed infiltrate) form. The term cholangitis has been recommended in preference to cholangiohepatitis.

Etiology

Inflammatory liver diseases are characterized by the predominant inflammatory cell infiltrate seen histopathologically. The inflammation is usually seen in the portal areas and can be characterized as suppurative (neutrophilic) (**Figure 9.9**), nonsuppurative (lymphocytic–plasmacytic) (**Figures 9.10–9.12**), or biliary cirrhosis (fibrosis). Cholangitis is the primary finding, with extension of the inflammation across the limiting plate into the surrounding hepatic parenchyma and periportal necrosis being common. Whether these classifications represent different stages in the progression of one disease, or are separate etiologic entities, is not known, nor is the underlying etiology of inflammatory liver disease in cats.

Pathophysiology

Bacterial, allergic, and immune mechanisms have all been speculated to be involved in the pathogenesis of inflammatory liver disease in cats. Bacterial cholangitis from ascending infection from the duodenum may either initiate the inflammatory process or perpetuate it early in the disease course. Immune mechanisms probably also play a role, especially in lymphocytic cholangitis and chronic mixed cholangitis. Cats with cholangitis, especially those with suppurative disease, may also have



Figures 9.8a–c Liver fluke. (a) Microscopic view of a liver fluke (*Platynosum concinum*) ovum from a cat living in South Florida. (b) Surgical view of liver fluke-induced chronic cholangitis in a cat living in North Central Florida. (c) Histopathology section of liver fluke residing in a bile duct causing inflammation and fibrosis. Taken from the cat in 9.8b. (Courtesy M. Schaer)

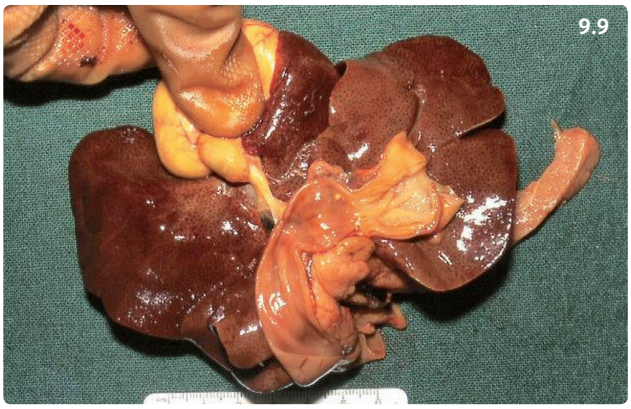


Figure 9.9 Postmortem view of the liver of a cat with suppurative cholangitis and cholecystitis. The cystic duct was obstructed by inspissated bile. (Courtesy M. Schaer)

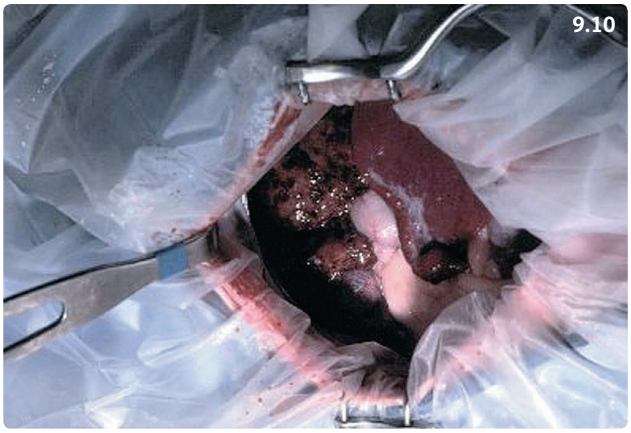


Figure 9.10 Surgical exploratory on a cat with chronic lymphocytic–plasmacytic hepatitis with telangiectasia. (Courtesy M. Schaer)

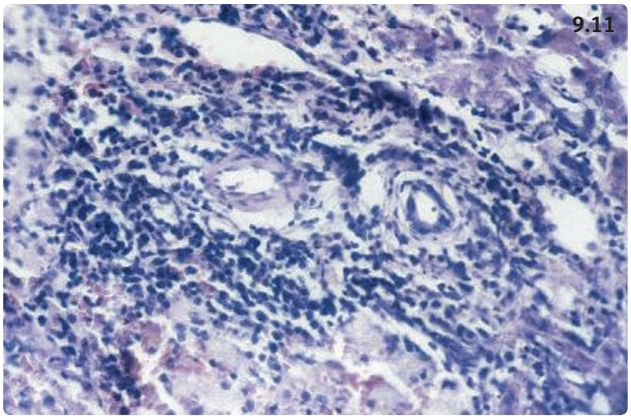


Figure 9.11 Photomicrograph of the specimen in Figure 9.10 showing marked periportal lymphocytic–plasmacytic infiltrates. (Courtesy M. Schaer)

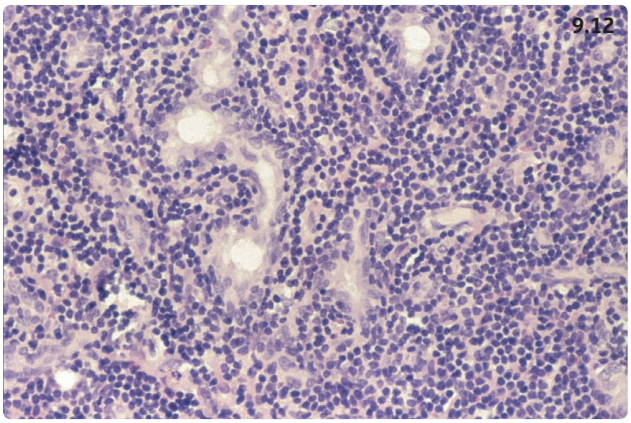


Figure 9.12 High-power photomicrograph of lymphocytic–plasmacytic cholangitis in a cat. (Courtesy M. Schaer)

concurrent cholecystitis, pancreatitis, and IBD. The relationship between these three inflammatory conditions is not well characterized, but it has been speculated that the underlying initiator of the inflammatory process may affect the liver, the pancreas, and the small intestine concurrently. The term 'triaditis' has been coined to describe those situations in which inflammation of the liver, pancreas, and small intestine are seen to occur concurrently.

Clinical presentation

The clinical findings seen in cats with inflammatory liver disease are similar to those seen with hepatic lipidosis and other liver diseases. Vomiting, anorexia, lethargy, and weight loss are typical. Fever is occasionally seen. Diarrhea, while not usual, is more common than in cats with hepatic lipidosis and may represent that subset of cats with concurrent IBD. Affected cats are rarely obese. A mild ascites may be present (**Figure 9.13**). Cats with suppurative cholangitis are more likely to be severely systemically ill when compared with cats with lymphocytic cholangitis. Cats of all ages can be affected. Males predominate in populations of cats with suppurative cholangitis compared with those with lymphocytic cholangitis. Suppurative cholangitis often has an acute course, while disease characterized by lymphocytic–plasmacytic inflammation may be more chronic. In evaluating liver enzymes, ALP tends not to be as elevated as in cats with hepatic lipidosis, while ASDT, ALP, and GGT activities tend to be higher. About 50% of cats will have high serum bilirubin concentrations. Neutrophil counts, transaminase activities, and total bilirubin concentrations tend to be higher in cats with suppurative cholangitis when compared with cats with lymphocytic cholangitis.

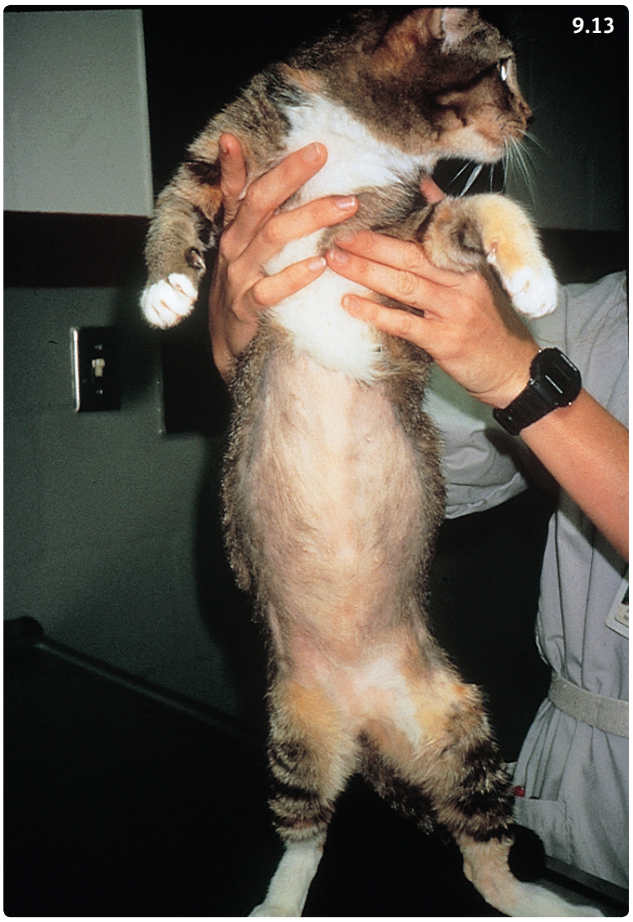


Figure 9.13 Mild abdominal distension caused by a sterile inflammatory exudate in a cat with cholangitis.

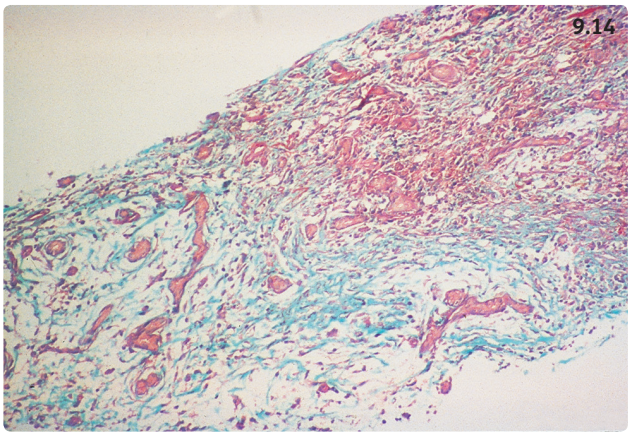


Figure 9.14 Low-power view of a trichrome-stained needle biopsy specimen from the cat in Figure 9.13. There is marked hepatic fibrosis (blue staining) in addition to inflammatory cells.

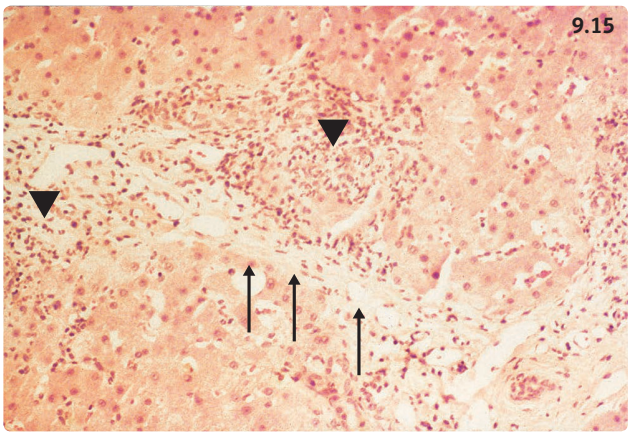


Figure 9.15 Histologic appearance of the liver in a 4-year-old Persian cat with cholangitis. There is marked fibrosis (arrows) and an infiltrate of plasma cells and lymphocytes (arrowheads).

However, all liver enzymes may be normal early in the course of disease.

Differential diagnosis

As for hepatic lipidosis.

Diagnosis

Diagnosis is usually dependent on histopathology, as cytology is often normal or reveals nonspecific changes. Biopsy for both histopathology and culture should be performed if inflammatory liver disease is suspected. The advent of readily available ultrasonography has resulted in needle biopsy becoming the most popular method of obtaining tissue for histopathology (**Figures 9.14**, **9.15**). Ultrasonography can also provide important information pertaining to co-existing cholecystitis. However, the diagnostic accuracy of needle obtained biopsies has been questioned. Laparoscopically or surgically obtained 'wedge' samples should be considered for histopathology and bacterial culture and sensitivity when feasible; the larger samples give the pathologist more tissue to assess (**Figure 9.16**, biopsy comparison). Prior to biopsy, coagulation parameters should be evaluated. As in cats with hepatic lipidosis, PIVKA may be the most sensitive indicator of potential bleeding tendencies. Vitamin K1 (0.5–1.5 mg/kg SC) given 12–24 hours prior to biopsy may decrease the risk of bleeding. Culture of aspirated bile may be a more sensitive indicator of bacterial infection than culture of biopsy specimens.

Management

In addition to the supportive care and nutritional support important in the management of cats with hepatic lipidosis, antibiotics effective against gram-negative and/or anaerobic bacteria should be used when treating cats with inflammatory liver disease. This is probably most important when treating suppurative cholangitis.

Metronidazole is effective against anaerobes and some gram-negative aerobes and it has immune modulating effects. Ampicillin, amoxicillin, amoxicillin–clavulanate, and enrofloxacin are excreted in the bile and are also good choices.

Immunosuppressive agents should be added to the treatment regimen in cats with lymphocytic or mixed inflammatory disease and in cats with suppurative disease that fail to respond to antibiotics alone. Prednisolone (2–4 mg/kg/day initially then slowly tapered to 1 mg/kg every other day) is used most commonly. Other immunosuppressives that may be used in cats responding poorly to glucocorticoids include chlorambucil (approximately 1 mg for cats <3.2 kg, 2 mg for cats >3.2 kg, PO q48h) and oral cyclosporine. Ursodeoxycholic acid (10–15 mg/kg PO q24h) is a safe treatment alternative that can be used in cats with suppurative or nonsuppurative disease. The drug appears to have multiple actions including shifting the bile acid pool to a less toxic hydrophilic population, a choleretic effect, reducing expression of class 2 major histocompatibility complex, and an anti-inflammatory effect. Bile duct patency is required before using ursodeoxycholic acid. Since the drug is commercially available in a 300 mg capsule size in the USA, accurate dosing of ursodeoxycholic acid for a cat can be prepared by a compounding pharmacist.

Antioxidants are important in the management of liver diseases as oxidative damage appears to be an important factor in perpetuation of inflammation and initiation of fibrosis. Vitamin E (aqueous alpha tocopherol, 10–100 IU/kg/day) has been advocated for its antioxidant effects. SAMe (90–180 mg PO q24h) is a precursor of glutathione. Glutathione is an important antioxidant that has been shown to be reduced in dogs and cats with liver disease. The nutraceutical SAMe may help replace glutathione. It also may have hepatoprotective effects in preventing programed cell death (apoptosis), which occurs during inflammatory liver disease. Milk thistle extract (silymarin) is a nutraceutical that is widely used for its hepatoprotective effects. It may be of benefit as an antioxidant, as an antifibrotic agent, or as an aid in hepatic regeneration. The recommended dose is 50–200 mg/kg PO q24h. Two products containing silybin and vitamin E are marketed: Marin®, which is a combination of silybin and vitamin E plus zinc, and Marin® Plus, which contains silybin, vitamin E, zinc, medium chain triglyceride oil, and curcumin. Silybin is one of the active ingredients in milk thistle. Additionally, there is a product (Denamarin®) that contains both silybin and SAMe.

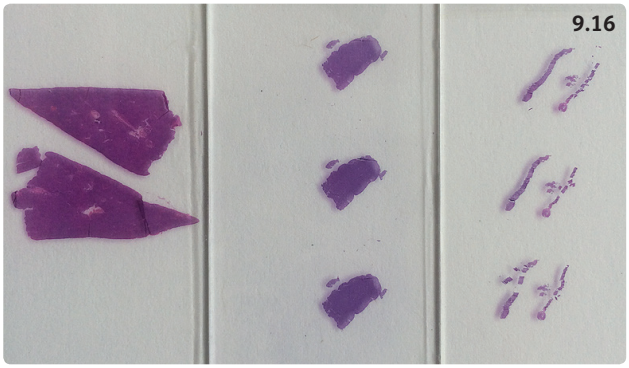


Figure 9.16 Sub-gross views of liver biopsy slides. Laparotomy liver wedge biopsy (left); laparoscopic liver wedge biopsy (middle); ultrasound guided Tru-cut liver biopsy (right). All stained with H&E stain (Courtesy J. Greene and I. Langohr)

CHRONIC INFLAMMATORY LIVER DISEASE IN DOGS

Definition/overview

The dog suffers from a variety of chronic inflammatory liver diseases (e.g. administration of primidone, phenytoin, and phenobarbital; abnormal copper metabolism in the Bedlington Terrier, West Highland White Terrier, Skye Terrier, Dalmatian, and Labrador Retriever; spontaneous and experimentally induced infectious canine hepatitis), often resulting in subsequent cirrhosis (**Table 9.1**). All have similar clinical signs. In the dog, chronic hepatitis (CH) (formerly chronic active hepatitis) has been associated with leptospirosis. A syndrome of CH has also been recognized in the Dobermann, Dalmatian, and American Cocker Spaniel. CH resulting in subsequent cirrhosis is rare in cats.

Etiology

Chronic inflammatory liver diseases have overlapping histologic appearances and are mostly of unknown etiology. Once started, the immune system, oxidative stress, and stellate cell activation with subsequent fibrosis play

Table 9.1 Inflammatory disorders of the canine liver.

- Chronic hepatitis: breed related (e.g. Dobermann, Cocker Spaniel, Labrador Retriever)
- Copper storage hepatopathy: Bedlington Terrier, West Highland White Terrier
- Chronic nonsuppurative hepatitis
- Chronic portal triaditis
- Chronic drug-induced hepatitis
- Chronic cholangiohepatitis
- Chronic cholangitis
- Chronic lobular hepatitis
- Lobular dissecting hepatitis
- Chronic major bile duct obstruction
- Idiopathic hepatic fibrosis

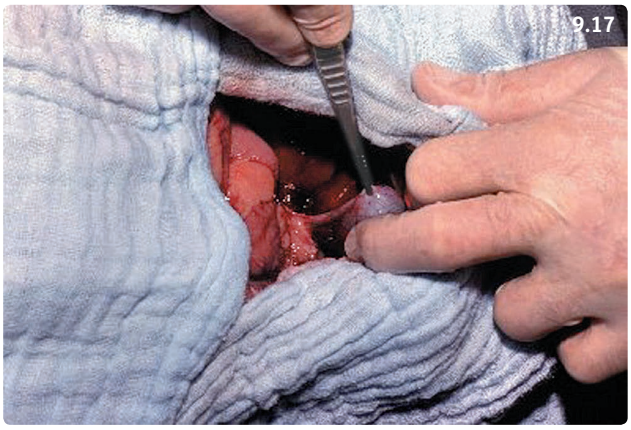


Figure 9.17 Surgical exploratory in a dog showing the gallbladder and parenchymal liver disease that turned out to be chronic lymphocytic–plasmacytic hepatitis on biopsy. (Courtesy M. Schaer)

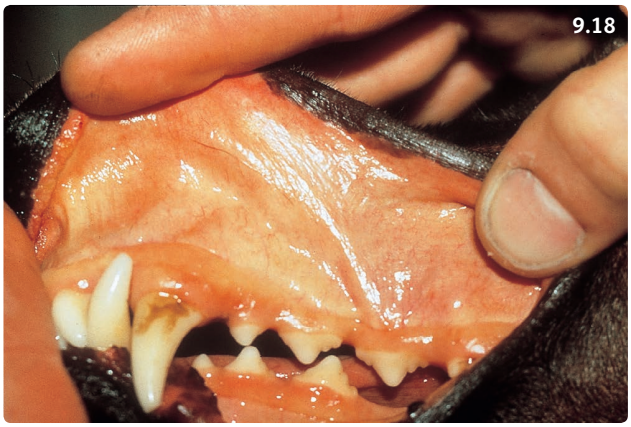


Figure 9.18 Icteric mucous membranes in a 5-year-old female spayed Dobermann with chronic hepatitis.

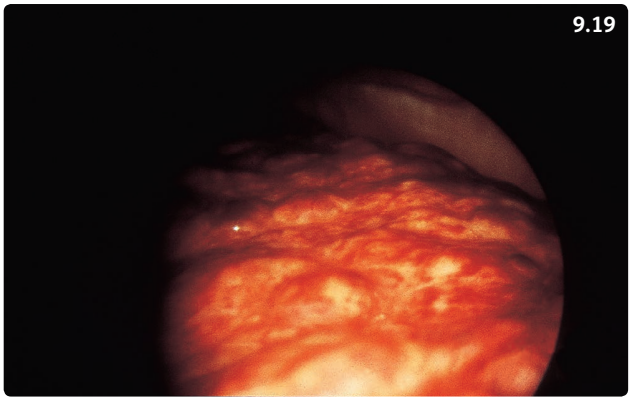


Figure 9.19 Laparoscopic view of regenerative nodules on the liver in a dog with chronic hepatitis.

an important role in perpetuation of hepatocellular injury.

Pathophysiology

CH has many potential initiating insults but is often idiopathic. Unless the initiating insult is copper or bacterial infection, the histopathologic description will usually be that of chronic and active inflammation without an obvious etiology. CH (**Figure 9.17**) is characterized by continuing hepatic inflammation, necrosis, apoptosis, fibrosis, and regeneration. The immune system and oxidative injury play an important role in perpetuation of disease.

Clinical presentation

Clinical signs are nonspecific. Inappetence and lethargy are common complaints. Occasional vomiting, diarrhea, and pica may also be reported. Behavioral changes and other signs consistent with hepatoencephalopathy, ascites, and icterus may develop later in the course of disease (**Figure 9.18**). Signs may be chronic or appear acute with the disease often advanced before a diagnosis is made.

Differential diagnosis

Infections; vascular hepatopathy; drug-induced, familial, or lobular dissecting hepatitis.

Diagnosis

Chronic inflammatory liver disease is characterized histologically by hepatocellular apoptosis and necrosis, a variable mononuclear or mixed inflammatory cell infiltrate, regeneration, and fibrosis. More ominous histologic features suggestive of progression are implied when confluent areas of necrosis are identified that form zones of parenchymal collapse that bridge between portal triads and central veins or span lobules between portal triads. Chronic inflammatory liver disease should be suspected when recurrent slight to moderate increases of serum ALT, AST, and ALP activities are observed. Persistence of the chronic inflammatory process for months to years disrupts normal liver architecture (**Figure 9.19**) and the earlier biochemical pattern of 'low-grade' hepatocellular necrosis progresses to one of hepatic insufficiency. The waxing and waning nature of the changes in enzyme activities, as well as the potential for relatively insignificant increases late in the disease course, make chronic inflammatory liver disease sometimes difficult to detect biochemically. However, as the disease progresses, indicators of liver dysfunction, such as hypoalbuminemia, decreased BUN, and prolonged PT, are suggestive of advanced liver disease. Earlier indicators of liver insufficiency are hyperbilirubinemia, hyperammonemia, and increased serum bile acids. Disruption of clotting factor synthesis may result in bleeding, which

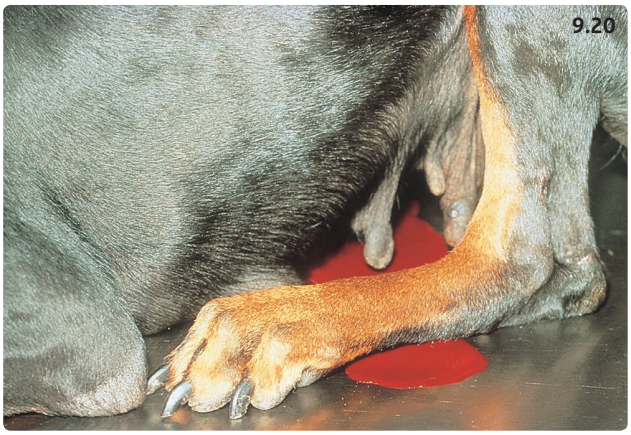


Figure 9.20 Bleeding from the skin after percutaneous liver biopsy in a Dobermann with advanced chronic hepatitis. Prebiopsy clotting studies had been normal.

is most often characterized by GI bleeding, resulting in melena or low-grade anemia (**Figure 9.20**). A hypercoagulable state may also be present, resulting in thrombosis of the portal vasculature. Histologic examination of a liver biopsy sample confirms the diagnosis (**Figures 9.21–9.23**).

Management

Specific treatment is unavailable in most cases and usually depends on the inciting cause. Supportive therapy includes vitamin E, ursodeoxycholic acid, SAMe, and silymarin. Anti-inflammatory or immunosuppressive therapy using prednisolone, cyclosporine, penicillamine, azathioprine, and/or colchicine may be useful.

HEPATIC ABSCESS

Definition/overview

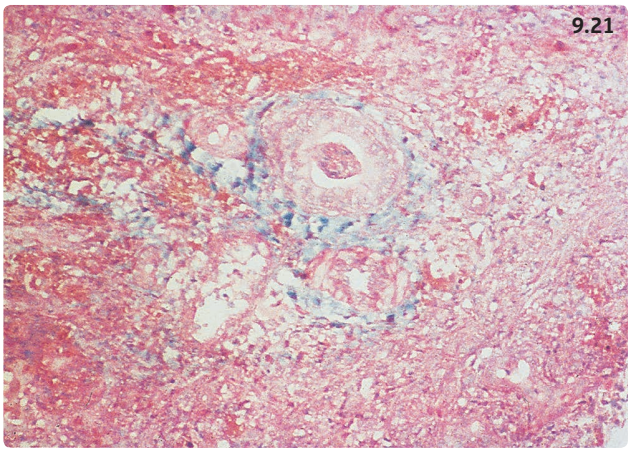
Hepatic abscesses following bacterial infection of the liver occur uncommonly in dogs and cats (**Figures 9.24a–c**).

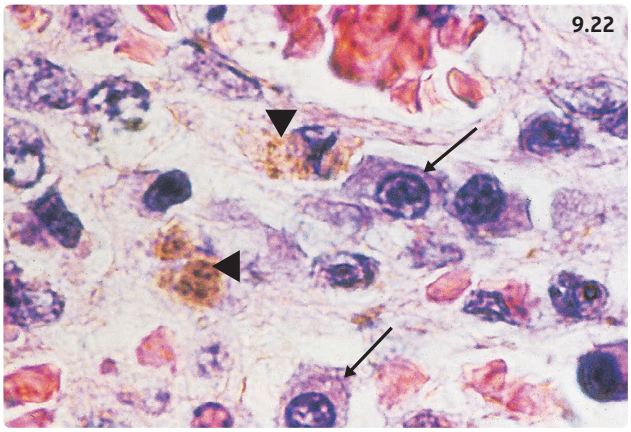
Etiology

Hematogenous or ascending biliary infection may result in hepatic abscess formation. Gram-negative enteric organisms or gram-positive and gram-negative anaerobic organisms (especially clostridial organisms) may be noted. It may be part of systemic infection. *Bartonella* can cause diffuse hepatic infection and microabscessation.

Pathophysiology

Hepatic abscesses are usually associated with systemic infection or hepatic damage. Bacteria arrive in the liver hematogenously via a systemic arterial or portal venous route (translocation) or via the biliary tree.





Figures 9.21, 9.22 (9.21) Histologic appearance of the liver in chronic hepatitis. There is widespread hepatocellular degeneration, portal fibrosis (blue staining), and bile stasis. (9.22) Higher-power view in the same patient shows periportal round cells (arrows) and bile stasis (arrowheads).

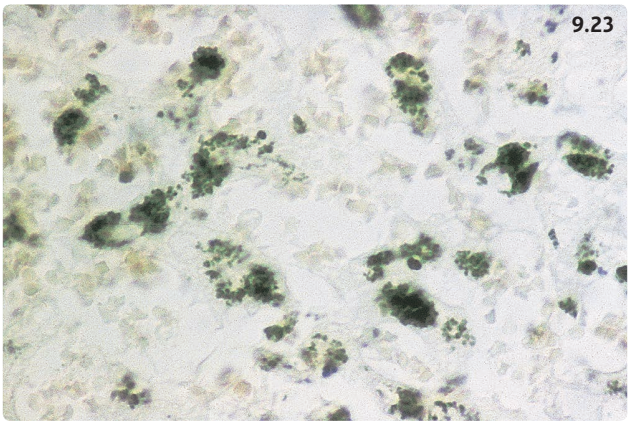
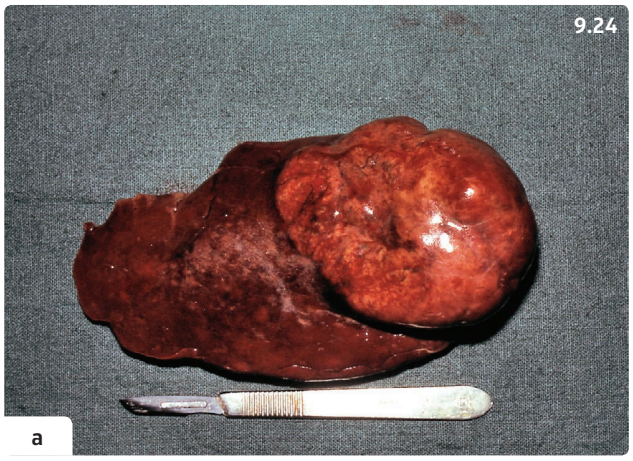
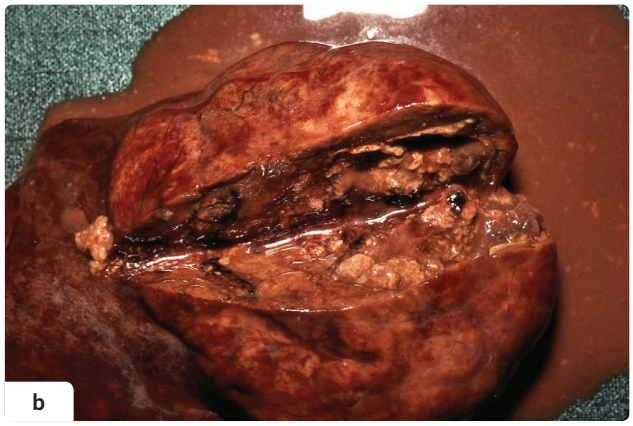
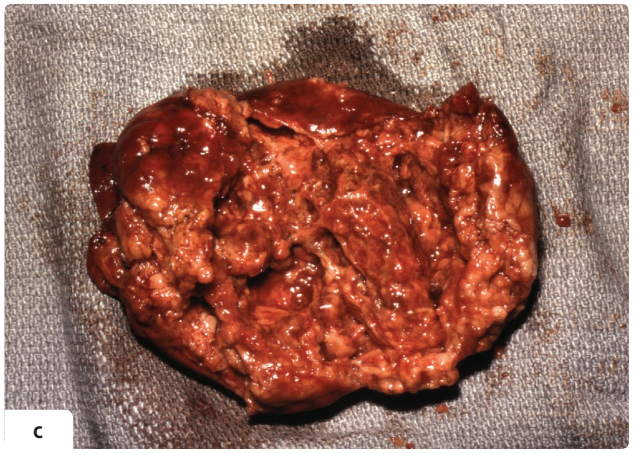


Figure 9.23 Copper stain of the liver in a Dobermann with chronic hepatitis.

Immunosuppression or damaged hepatic parenchyma results in infection and subsequent abscess formation.







Figures 9.24 a–c Surgical specimen of an abscessed liver lobe showing the intact and necrotic tissue. (Courtesy M. Schaer)

Cats tend to have multiple small abscesses while dogs more often have one or a few larger abscesses.

Clinical presentation

Usually older dogs or cats with nonspecific GI signs or signs of sepsis. Fever may be noted but hypothermia is more likely in cats. Abdominal pain may be noted, especially if rupture of an abscess has occurred resulting in septic peritonitis.

Differential diagnosis

Inflammatory liver diseases, pancreatitis, septic or bile peritonitis, hepatic neoplasia.

Diagnosis

Complete blood count (CBC) findings are consistent with inflammation; septic changes may be noted. ALT and AST activities may be increased but cats may have normal liver enzyme activities. Hypoalbuminemia, hyperglobulinemia, and mild hyperbilirubinemia are common. Hypoglycemia associated with sepsis or decreased hepatic function may be seen. Abdominal ultrasound usually reveals hypo- to anechoic structures with a hyperechoic rim within hepatic parenchyma. Fine needle aspiration for cytology and culture reveals evidence of bacterial infection. Culture and sensitivity are important in directing definitive treatment.

Management

Focal abscesses should be treated with surgical excision or drainage. Percutaneous drainage may be carried out. Antibiotics based on Gram staining and culture and sensitivity should accompany appropriate surgical management. Broad-spectrum coverage with fluoroquinolone and clavulanate-potentiated amoxicillin or sulbactam-potentiated ampicillin, with or without metronidazole for added anaerobic coverage, is appropriate for treatment while waiting for culture results. Definitive antibiotic treatment should be for a minimum of 6–8 weeks with follow-up ultrasound and blood work evaluation. Mortality rates may exceed 50%.

ACUTE HEPATITIS AND ACUTE HEPATOCELLULAR DEGENERATION AND NECROSIS

Definition/overview

Acute hepatitis and acute hepatocellular degeneration are characterized by focal or diffuse damage to the hepatocytes. Hepatocytes may be killed by a spectrum of insults, but death occurs through apoptosis or necrosis. Mild insults may cause apoptosis, while stronger insults will cause necrosis.

Etiology

The causes of hepatocellular disruption are many and varied and are often undetermined. Recognized hepatotoxins include: chemical solvents such as carbon tetrachloride; mycotoxins such as aflatoxin; Cyanophyceae algae; cycasin from cycad plants; drugs such as acetaminophen, azole antifungals, methimazole, and diazepam in the cat; drugs such as mebendazole, oxybendazole, trimethoprim–sulfa antibiotics, immunosuppressives such as cyclosporine, azathioprine, and chlorambucil, nonsteroidal anti-inflammatory drugs (NSAIDs) such as carprofen, azole antifungals, and the artificial sweetener xylitol in some dogs; certain mushrooms (*Amantinum* spp.); viruses including canine adenovirus 1, herpesviruses, FIP virus; bacteria such as *Clostridium piliformis*, *Bartonella*, *Leptospira*, and possibly *Helicobacter*. Clinical signs, biochemical data, and histologic findings do not usually indicate a specific cause, resulting only in a histologic diagnosis of acute hepatic necrosis or 'toxic' hepatitis (**Figure 9.25**).

Pathophysiology

The predominant lesion of acute hepatitis is multifocal apoptosis and necrosis of individual hepatocytes associated with abnormal liver enzyme activity. The proportion of each cell type varies with time and the host response, as well as with the possible cause.

Clinical presentation

Clinical signs are variable and include inappetence, lethargy, and vomiting. Icterus develops if the hepatocellular insult is extensive. Neurologic signs caused by hepatoencephalopathy may be seen.

Differential diagnosis

Acute pancreatitis, infectious CH, acute gastroenteritis, and some toxicoses.

Diagnosis

The predominant biochemical abnormality is an increase in serum ALT and AST activities, the magnitude of which depends on the severity and extent of the hepatocellular damage. Serum ALP is usually normal or only slightly increased early in the disease process. An increase in serum bilirubin concentration may occur if a sufficient number of hepatocytes have been damaged or destroyed or if there has been sufficient damage to cause cholestasis. The patient will recover if enough functional liver remains to support regeneration.

A liver biopsy is often neither helpful nor essential in the diagnostic evaluation if the history strongly implicates the cause, and it may be contraindicated by liver-associated coagulopathies. Histologic examination can be useful for assessing the severity and extent of the disease process or determining if the acute onset of clinical disease is associated with chronic histologic changes. A liver biopsy is justified if recurrent abnormal ALT/AST values have been documented (see Chronic inflammatory liver disease).

Figure 9.25 Postmortem liver specimen from a dog with fatal peracute hepatic necrosis of unknown etiology. Note the loss of normal parenchymal architecture due to the dark red patches of necrosis. (Courtesy M. Schaer)

Management

Few hepatotoxins have specific antidotes but silymarin has been shown to be effective at blocking hepatocellular binding sites for some toxins. Successful recovery depends on aggressive supportive therapy and management of oxidative stress. The prognosis is usually good if the inciting cause is removed, permanent loss of functional mass is less than 50%, and the liver has retained the capacity to regenerate.

CIRRHOSIS

Definition/overview

Cirrhosis is the end stage of CH in the dog. It is a diffuse hepatic disease process characterized by fibrosis and by an alteration of normal hepatic architecture by structurally abnormal regenerative nodules. Portocentral vascular anastomoses and acquired PSSs may be present (**Figure 9.26**). The disease occurs in two morphological presentations: (1) micronodular cirrhosis, in which regenerative nodules are less than 3 mm in diameter, and (2) macronodular cirrhosis, in which the nodules are greater than 3 mm and usually up to several centimeters and of different sizes. Lobular dissecting hepatitis is a form of cirrhosis seen in adolescent and young adult dogs.

Etiology

The cause of cirrhosis is varied and is seldom determined.

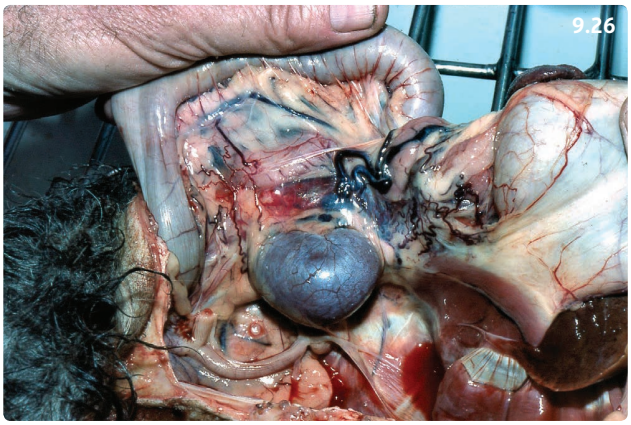


Figure 9.26 Postmortem view showing acquired extrahepatic shunt vessels (dark tortuous vessels) in a Schnauzer that had micronodular cirrhosis. (Courtesy M. Schaer)

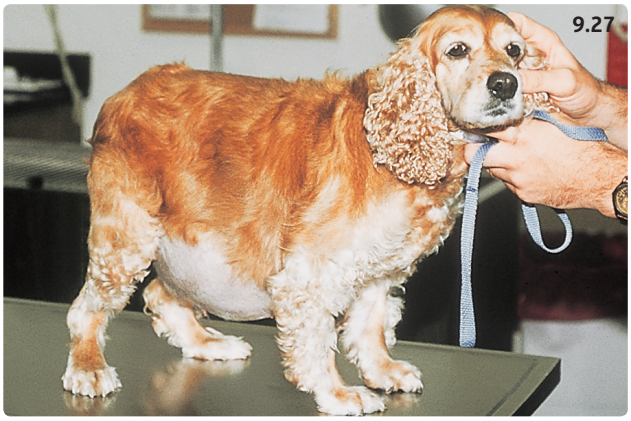


Figure 9.27 Ascites in a Cocker Spaniel secondary to hepatic fibrosis and cirrhosis.

Pathophysiology

Increased hepatic vascular resistance and portal hypertension resulting from the fibrosis and regenerative nodules eventually lead to icterus, ascites, multiple acquired PSSs, and associated hepatoencephalopathy.

Clinical presentation

Cirrhosis is a common presentation in dogs, but is uncommon in cats. Clinical signs most often include lethargy, inappetence, ascites (**Figure 9.27**), and mental depression that can progress to encephalopathy. GI signs such as vomiting and/or diarrhea are occasionally seen. Polyuria and polydipsia are inconsistent findings, but when present may be severe and clinically reminiscent of diabetes insipidus or psychogenic polydipsia. Bleeding, noted as petechiae or ecchymoses, may be seen in more severely affected dogs. GI bleeding is common and may manifest as obvious melena or may be more subtle and contribute to an iron deficiency anemia. Some patients are compensated and show few clinical signs, while others are icteric and show signs of liver failure.

Differential diagnosis

Metastatic disease, nodular regeneration, hepatocutaneous syndrome.

Diagnosis

Biochemical findings may indicate severe liver disease, but they are also often subtle. Serum ALT, AST, and ALP activities may be moderately increased, or they may be normal or only slightly increased because of the decreased hepatic cell mass. Other biochemical abnormalities are more consistent and reflect the reduced functional capacity of the liver and altered hepatic blood flow. Decreased BUN and a decreased serum albumin concentration may be noted. Increased serum bilirubin concentration is a late indicator of liver insufficiency. Persistent bilirubinuria will be detected before jaundice develops. Determination of total serum bile acids and plasma ammonia concentrations are the most reliable tests for detecting hepatic insufficiency. Serum bile acids are appropriately determined in the anicteric patient, but plasma ammonia is a better indicator of hepatic dysfunction in the dog with icterus. Reduced hepatocellular mass, altered portal blood flow, and cholestasis result in an increase in serum bile acid concentrations.

Jaundice may develop in the cirrhotic patient without prior clinical evidence of liver disease and may require differentiation from extrahepatic impairment of bile flow. While ultrasound evaluation of the biliary tree is the most effective means of noninvasively determining if extrahepatic bile flow is impaired, the increased total serum bilirubin concentration is often lower (usually <102.6 µmol/l [6 mg/dl]) in the cirrhotic patient than in the patient with extrahepatic biliary obstruction. The absence of a marked increase in serum ALP activity, a decrease in BUN, a decrease in serum albumin concentration, or an increased plasma ammonia concentration supports a diagnosis of cirrhosis.

Histologic confirmation of cirrhosis is important, since on gross visual inspection cirrhosis may resemble metastatic disease, nodular regeneration, or hepatocutaneous syndrome (**Figure 9.28, 9.29**).

Management

Supportive measures are aimed at controlling the complications of chronic liver failure (e.g. hepatic encephalopathy, coagulation abnormalities, and infection). Ascites should be managed by reducing the sodium content in the

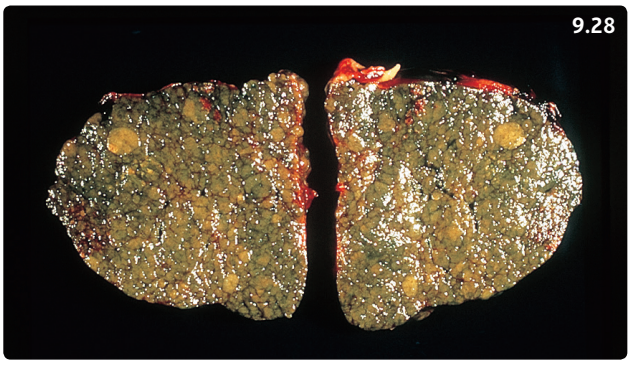


Figure 9.28 Cross-section of the liver of a 4-year-old Spitz with severe cirrhosis. Regenerative nodules are dispersed throughout the parenchyma.

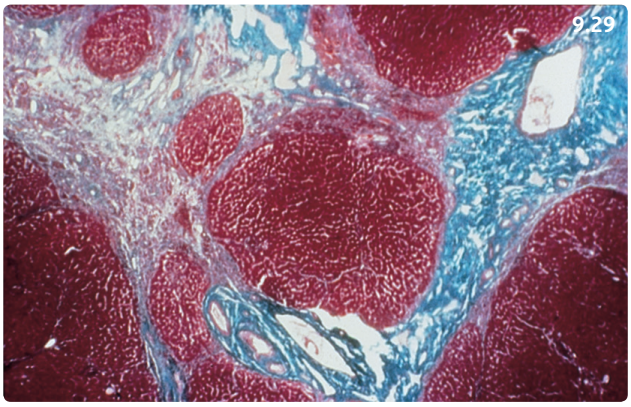


Figure 9.29 Trichrome stain of a section of cirrhotic liver showing fibrosis (blue) and nodules (red).

diet and the judicious use of diuretics. Potassium-sparing diuretics should initially be used as dogs with chronic fibrosis are prone to developing hypokalemia. Any suspected bleeding associated with gastroenteric ulcerations should be treated with anti-ulcer drugs such as sucralfate and proton pump inhibitors. The diet should ideally be one that contains adequate protein and calories to maintain weight. The protein content of the diet should not be reduced until necessitated by evidence of hepatoencephalopathy. When signs of hepatoencephalopathy become apparent it should be managed with lactulose and oral antibiotics such as neomycin or metronidazole. The protein content of the diet should be reduced only to the extent necessary to control the neurologic signs. Management of fibrosis is usually not helpful once a dog is showing signs of liver failure associated with cirrhosis, but prednisone, D-penicillamine, colchicine, and silymarin have all been advocated to reduce fibrosis. Antioxidants and anti-inflammatory drugs, as discussed under chronic inflammatory liver diseases, may also be indicated.

HEPATOCUTANEOUS SYNDROME

Definition/overview

Hepatocutaneous syndrome is a metabolic disease in which a vacuolar hepatopathy is associated with an ulcerative necrolytic dermatitis. Other terms used include superficial necrolytic dermatitis, necrolytic migratory erythema, diabetic dermatopathy, and metabolic epidermal necrosis.

The disease affects primarily middle aged to older dogs, with the average age being about 10 years. Males are more commonly affected than females. No definitive breed predilection has been noted; however, West Highland White Terriers, Shetland Sheepdogs, Cocker Spaniels, German Shepherd Dogs, Scottish Terriers, Lhasa Apsos, and Border Collies may be overrepresented.

Etiology

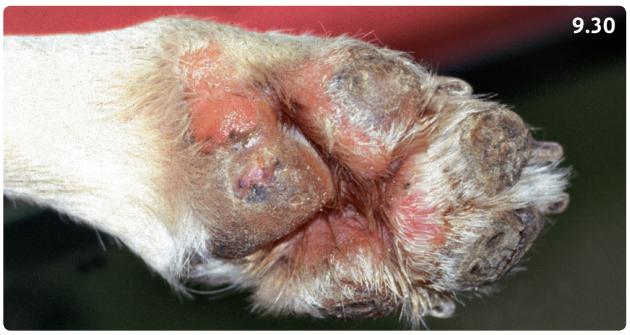
The cause of the syndrome is unknown. It is characterized by liver disease in which there is extensive hepatocyte vacuolization coupled with parenchymal collapse together with a characteristic superficial necrolytic dermatitis. Diabetes mellitus may also be noted.

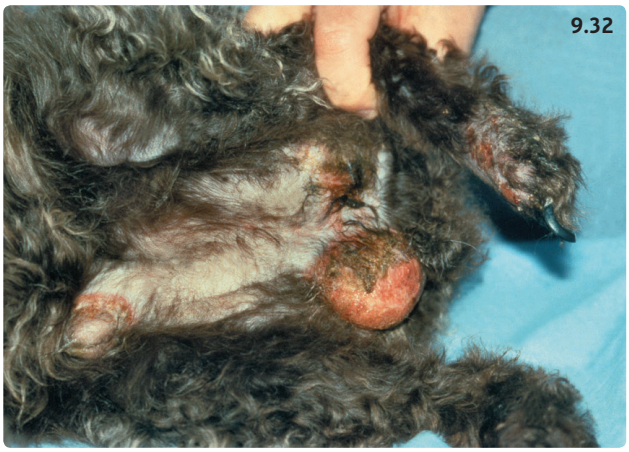
Pathophysiology

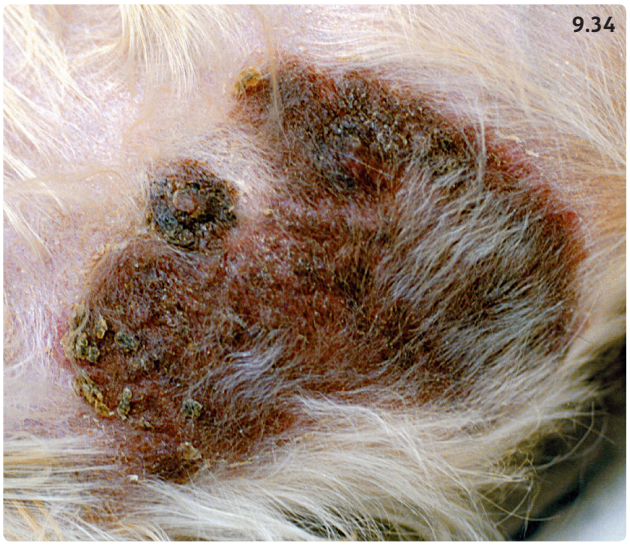
The consistent finding in dogs is liver disease and skin disease in a patient with severe hypoaminoacidemia. The cause of either set of lesions is not understood, but it is speculated that a metabolic derangement that results in increased catabolism or loss of amino acids is present, and this sets up an environment that has a detrimental effect on the skin, resulting in striking inter- and intracellular edema and marked parakeratosis, with resulting ulceration, exudation, and crusting. The footpads are often affected. Whether the changes in the liver are a cause or an effect of the hypoaminoacidemia is not known. In humans, this syndrome is most often seen as a paraneoplastic condition associated with glucagonomas. This has been documented in dogs, but in most cases a glucagonoma or evidence of a pancreatic mass is not seen. In addition to the characteristic vacuolar hepatopathy, this syndrome has been seen with phenobarbital and primidone-associated liver disease and intestinal malabsorption.

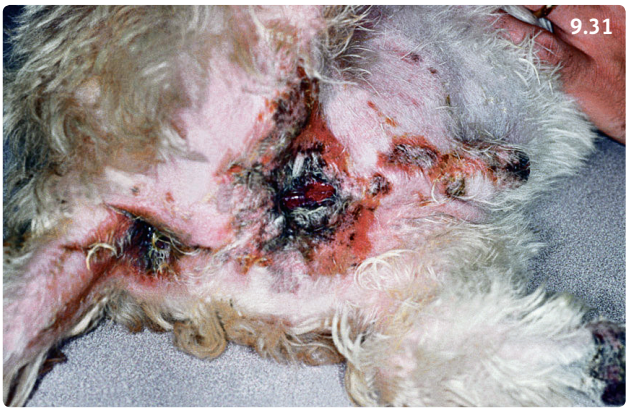
Clinical presentation

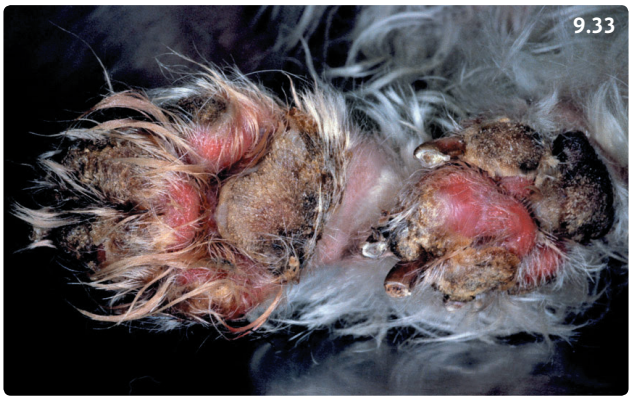
The most common presentation is the development of skin lesions that include erythema, crusting, exudation, ulceration, and alopecia involving the footpads, pressure points on the trunk and limbs, perineum, muzzle, and periocular areas **(Figures 9.30–9.34)**. Lameness due











Figures 9.30–9.34 These five images illustrate typical lesions associated with the hepatocutaneous syndrome in the dog, showing the erythema, crusting, ulceration, and hair loss involving the foot pads and ventral trunk including the perineum. (Courtesy R. Marsella)

to footpad ulceration is often an initial presenting complaint. Some dogs may present only for liver disease and typically show lethargy and anorexia. Most of these dogs either will have subtle skin lesions at the initial presentation or will develop the skin lesions within weeks of the initial presentation.

Differential diagnosis
Macronodular cirrhosis, metastatic neoplasia, glucagonoma.

Diagnosis
Serologic abnormalities seen in affected dogs include: increased ALT, AST, and ALP activities; variable glucagon concentrations (increased in only some patients with glucagonoma, diabetes mellitus, pancreatitis, and chronic hepatic insufficiency); fluctuating hyperglycemia without ketoacidosis; nonregenerative to mildly regenerative anemia; abnormalities in red cell morphology (polychromasia, anisocytosis, poikilocytosis, target cells); hypoalbuminemia; and severe hypoaminoacidemia. Liver function test results can range from normal to severely abnormal. Results of liver cytology are consistent with severe, vacuolar degeneration of hepatocytes.

Ultrasonographic imaging of the liver in dogs with hepatocutaneous syndrome can be very striking. A unique 'honeycomb' pattern is found and this has been reported as being pathognomonic. This pattern consists of variably sized hypoechoic regions measuring 0.5–1.5 cm in diameter surrounded by highly echogenic borders.

Skin biopsy is the most consistent means of definitively diagnosing hepatocutaneous syndrome. Skin biopsy specimens should be taken from multiple sites; include the footpad when lesions are present. The dermatohistopathology of the disease is unique and striking, with changes consisting of marked inter- and intracellular edema, which is localized to the upper half of the epidermis. Severe edema produces loss of cellular structure and resultant intraepidermal clefts and vesicles. Basal cell hyperplasia is also seen. Irregular epidermal hyperplasia is overlaid by marked diffuse parakeratotic hyperkeratosis.

The liver lesions reflect chronic hepatocellular degeneration with severe intracellular fat accumulation. Severe lobular collapse and nodular regeneration are residual evidence of ongoing hepatocellular regeneration and degeneration, with resultant parenchymal loss.

Management
Amino acid supplementation has been the primary approach to treatment either by increasing protein in the diet or by parenteral administration of amino acid mixtures. Amino acid solution (Aminosyn™ 10%; a crystalline amino acid solution) can be administered at a dose of 24 ml/kg slowly over about 8–12 hours into a large central vein (jugular), initially weekly, then less often as the lesions improve. Oral protein supplements used by body builders can supplement the IV administration of amino acids. Consideration should be given to measuring blood ammonia concentrations before initiating this treatment because it is possible to worsen hepatoencephalopathy with the therapy; however, hepatoencephalopathy is rarely seen in patients with hepatocutaneous syndrome. Measuring blood ammonia concentrations can be done daily or weekly until improvement is noted. Some dogs may require monthly IV amino acid infusions, but many dogs can go several months between infusions. The prognosis is guarded, but some dogs will respond well, with long-term survival possible.

FAMILIAL COPPER TOXICITY

Definition/overview
A hereditary metabolic disturbance resulting in excessive hepatic copper accumulation is seen in breeds such as the Bedlington Terrier, Labrador Retriever, Skye Terrier, West Highland White Terrier, and Dalmatian. The defect is best characterized in Bedlington Terriers where there is an autosomal recessive pattern of inheritance and is similar to hepatolenticular degeneration in humans (Wilson's disease). The disease is one form of chronic liver disease that progresses to cirrhosis.

Etiology
In the Bedlington Terrier, the disease is caused by an inherited metabolic defect caused by a deletion in the COMMD1 gene leading to an abnormal metallothionein copper-binding protein. The abnormal protein, or other derangements in copper metabolism in other breeds, leads to a defect in copper transport, which causes an accumulation of copper in hepatocytes resulting in inflammation or necrosis.

Pathophysiology
Accumulation of copper leads to major hepatic injury as the hepatic mitochondria become damaged by oxidants. Acute release of copper from the necrotic hepatocytes may cause hemolytic anemia. With progressive disease, the liver diminishes in size and a mixture of micro- and macronodular cirrhosis develops.

Clinical presentation
Young adults may present for signs of acute hepatic failure or the clinical signs and biochemical findings may be similar to those described for CH.

Differential diagnosis
Infections; drug-induced, familial, or lobular dissecting hepatitis; idiopathic CH.

Diagnosis
Diagnosis is suggested by increased ALT/AST activities and confirmed by measurement of the copper concentration of fresh liver tissue. Hepatic copper concentrations tend to increase slowly until middle age, but the concentration is often high enough at 1 year of age to suggest the presence of a defect.

Management
Dogs are best treated before clinical signs become severe. Asymptomatic animals may be helped by treating with zinc supplements and restriction of dietary copper. Treatment with D-penicillamine (10–15 mg/kg PO q12h) or another chelator such as trientine hydrochloride (10–15 mg/kg PO q12h) prevents progression of the disease in many dogs and will slowly result in decreased hepatic copper concentrations. Affected dogs and carriers of the gene should be identified and removed from breeding programs.

DRUG-INDUCED LIVER DISEASE

Definition/overview
Drugs can cause liver injury ranging from a transient asymptomatic increase in serum transaminase activity to clinically overt acute or chronic liver disease.

Etiology
Drugs can induce liver injury either by a direct toxic action, the formation of toxic metabolites, or indirectly via a hypersensitivity reaction.

Pathophysiology
Direct-acting hepatotoxins usually cause acute necrosis when the drug or a metabolite interacts chemically with an essential structural component or metabolic enzyme system of the hepatocyte (e.g. acetaminophen). A drug or its metabolite may induce liver injury either by altering the regulatory system of the immune response so that reactions to self-antigens are no longer suppressed, or by altering hepatocyte antigens so that they are no longer recognized as self-components.

Clinical presentation
Animals may present with several signs depending on the inciting cause and include depression, ataxia, weight loss, anorexia, vomiting, behavioral changes, coagulopathy, jaundice, and ascites.

Differential diagnosis
Infections; familial, lobular, or dissecting hepatitis; idiopathic CH.

Diagnosis
A hypersensitivity response is very difficult to prove, since challenge exposes the patient to unnecessary risk. Sulfa-containing drugs, anticonvulsants, anthelmintics, NSAIDs, halothane, azole antifungals, xylitol artificial sweeteners, cyclophosphamide, methimazole, and others have been implicated in veterinary medicine (**Figures 9.35, 9.36**).

Management
It is prudent to discontinue the inciting drug. If the drug is essential, then the dose should be modified as much as possible. Fasting and postprandial bile acid concentrations (assuming there is no increase in serum bilirubin) should be determined, as major hepatic damage is less likely if the concentrations are normal.

9.36

HEMATOLOGY	
PCV	0.35 l/l (35%)
Total WBCs	7.68 × 109/l (7.68 × 103/µl)
Platelets	Normal
URINALYSIS	
SG	1.025
pH	6.5
Bilirubin	>68 µmol/l (>4 mg/dl)
CHEMISTRIES	
AP	424 U/l
AST	320 U/l
ALT	835 U/l
Total bilirubin	195 µmol/1 (11.4 mg/dl)
Total protein	86 g/l (8.6 g/dl)
Creatinine	212 µmol/l (2.4 mg/dl)
BUN	4.6 mmol/l (28 mg/dl)

Figures 9.35, 9.36 This 11-year-old hyperthyroid male Siamese cat had methimazole hepatotoxicosis. He had icterus (9.35) and elevated liver enzyme levels (9.36). (Courtesy M. Schaer)

EXTRAHEPATOBILIARY OBSTRUCTION (EXTRAHEPATIC IMPAIRMENT OF BILE FLOW)

Definition/overview

Extrahepatic biliary obstruction refers to the impairment of bile flow in the biliary system between the liver and the duodenum. Acute, total extrahepatic impairment of bile flow is rare.

Etiology

Neoplasia (**Figure 9.37**), infection, and trauma should be considered. Chronic pancreatitis and tumors of the pancreas and the bile duct epithelia are the most common causes, although cholelithiasis and choledocholithiasis have been reported in both the cat and the dog. Inspissated bile (most often associated with an underlying liver disorder), liver flukes, duodenal or pyloric neoplasia, diaphragmatic hernia, congenital abnormalities, and mucinous cystic hyperplasia are additional causes.

Pathophysiology

Neoplasia or pancreatitis in the dog and cat may result in a mass effect or sufficient inflammation/fibrosis/fat necrosis to cause an extraluminal anatomic obstruction involving the common bile duct (**Figure 9.38**). Scars usually form around or within the bile ducts. No matter the cause, obstruction causes leakage of bile from the ducts into the connective tissue of portal areas. This causes inflammation and fibrosis of the portal areas, with bile duct proliferation and an inflammatory infiltrate of pigment-laden macrophages, lymphocytes, neutrophils, and plasma cells.

Clinical presentation

Signs include inappetence, icterus, and repeated vomiting (especially if the pancreas is involved). Both cats and dogs may be presented with a chronic history of anorexia, lethargy, and jaundice. Physical findings are usually unremarkable except for icterus. If a patient with suspected pancreatic pathology (see Chapter 10: Pancreatic disorders) remains icteric beyond 10–14 days of symptomatic medical management, an extrahepatic component should be suspected and managed accordingly.

Differential diagnosis

Liver flukes, neoplasia, cholelithiasis, traumatic gallbladder or bile duct lesion.

Diagnosis

Extrahepatic cholestasis causes a marked increase in the hepatic expression of ALP, resulting in a concomitant increase in serum activity. Increased serum cholesterol concentrations can also occur. Retained bile acids also cause hepatocellular damage, with an associated mild to moderate increase in ALT activity. Severe cholestasis results in decreased bile acid excretion into the small intestine with subsequent fat, and therefore fat soluble vitamin, malabsorption. Clotting studies reveal increased PT and PTT, which should revert to normal with parenteral vitamin K1 therapy. Bilirubinuria will be noted on urine dipsticks as strongly positive. Ultrasonography is a valuable, noninvasive diagnostic tool since it allows visualization of a dilated extrahepatic bile duct and may reveal the cause of obstruction (**Figure 9.39**).

Acute pancreatitis occasionally causes a mild to moderate increase in ALT activity, a marked increase in ALP activity, and increased total serum bilirubin

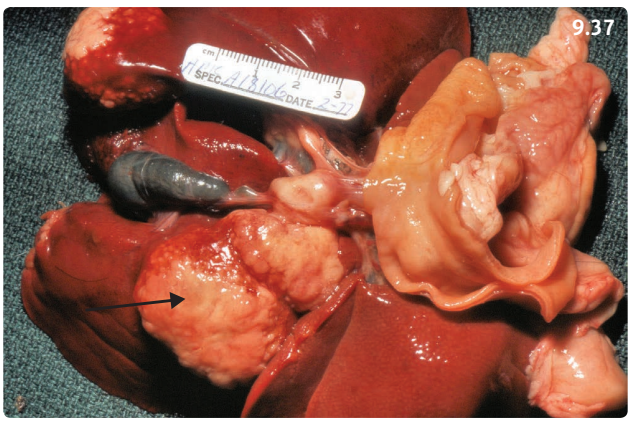


Figure 9.37 Postmortem image of a cat that had a cystadenocarcinoma (arrow) of the common bile duct. (Courtesy M. Schaer)

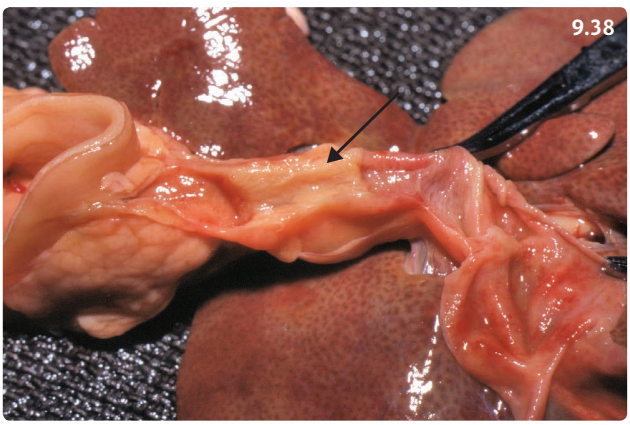


Figure 9.38 Postmortem image of a cat that had a common bile duct occlusion (arrow) caused by metastatic pancreatic adenocarcinoma. (Courtesy M. Schaer)

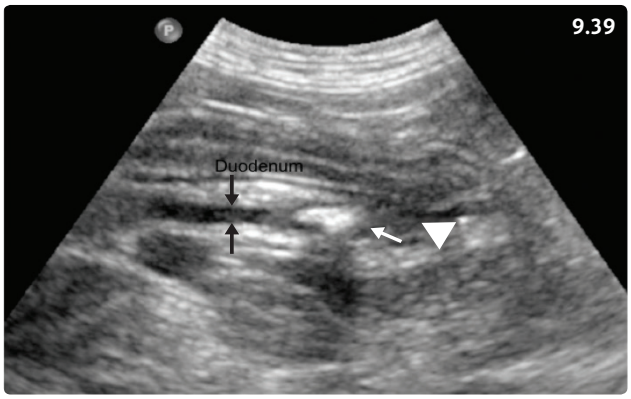


Figure 9.39 Ultrasound image of a cat with a cholelith located in the distal portion of the common bile duct (white arrow). The common bile duct is dilated above the obstruction (black arrows). The duodenal papilla is visible (white arrowhead). (Courtesy L. Gaschen)

concentration. The biochemical pattern may appear similar to that of extrahepatic biliary obstruction or CH with intrahepatic cholestasis. An acute onset of repeated vomiting preceding the development of jaundice suggests acute pancreatitis. Marked increases in serum pancreatic lipase immunoreactivity (cPLI, fPLI) may be noted. Suggested causes for the transient increase in the liver enzymes and bilirubin associated with acute pancreatitis include inflammation of the peripancreatic tissue, which compresses the bile duct, the release of proteases into the portal blood, which damage hepatobiliary tissue, and oxidative stress, which damages hepatocellular membranes and results in proinflammatory cytokine release.

Management

Surgical correction is the treatment of choice. If no obstruction is found at laparotomy, the liver should be biopsied and the patient managed accordingly. Treatment with ursodeoxycholic acid and antioxidants such as acetylcysteine, SAMe/silybin combinations, or vitamin E is also helpful.

CHOLETHIASIS (GALLSTONES)

Definition/overview

Cholelithiasis occasionally occurs in dogs and cats. Most are incidental findings on abdominal radiographs or at necropsy (**Figure 9.40**). On rare occasions, choleliths can cause obstruction of the common bile duct, but simply finding them on radiographs in patients with evidence of liver disease is not justification for removal.

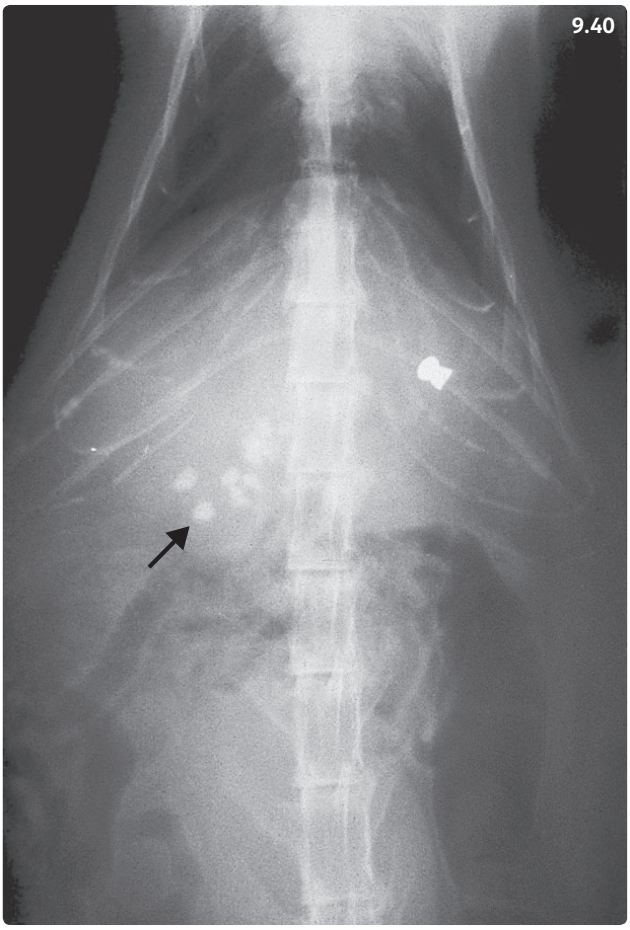


Figure 9.40 Survey abdominal radiograph in a cat showing a collection of gallstones (arrow). This was an incidental finding (as was the airgun pellet). (Courtesy B. Jones)

Etiology

Dogs and cats typically develop mixed choleliths composed of calcium salts, bilirubin, and occasionally cholesterol. This is different from humans where choleliths are typically dietary-induced cholesterol-containing stones.

Pathophysiology

Gallstones in dogs usually contain mucin, calcium, and bilirubin. In cats they are more often calcium carbonate and mixed choleliths composed of calcium carbonate, calcium bilirubinate, and cholesterol.

Clinical presentation

Dogs and cats with cholelithiasis are often asymptomatic. If signs are apparent, they may include vomiting, icterus (the stones move into the common bile duct and cause obstruction), anorexia, fever, and abdominal pain. Middle aged small breed dogs and cats are predisposed.

Occasionally, perforation of the gallbladder or common bile duct is seen.

Differential diagnosis
Parasitism, neoplasia, nonbiliary tract disorders, gallbladder mucocele.

Diagnosis
While seldom radiopaque, choleliths are typically easily diagnosed by abdominal ultrasonography (**Figures 9.41, 9.42**). They appear as hyperechoic foci with acoustic shadowing originating from the gallbladder or common bile duct. Dilation of the common bile ducts and/or intrahepatic ducts may be noted.

Management
In cases with evidence of bile flow obstruction, exploratory laparotomy for surgical removal of stones should be performed and the patency of the common bile duct assessed. Follow-up therapy with ursodeoxycholic acid, antioxidants, and antimicrobials is recommended.

BILE DUCT RUPTURE

Definition/overview
Obstruction or trauma may result in perforation or rupture of the structures of the biliary tract. The common bile duct, distal to the opening of the last hepatic duct, seems to be the most common site of ductal rupture.

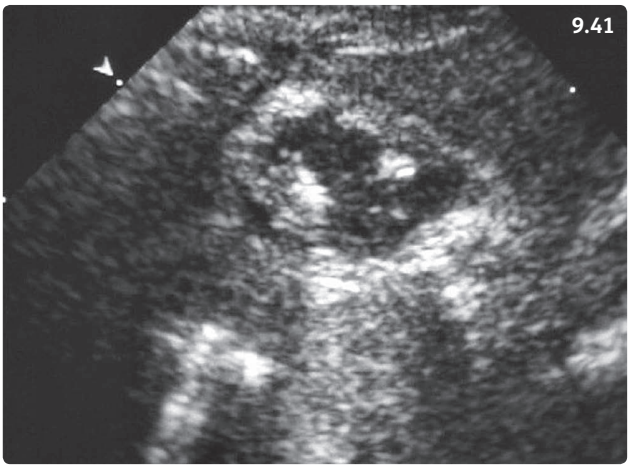
Etiology
Blunt trauma, penetrating wounds, pathology associated with a tumor or infection, and liver biopsies have been associated with rupture of the biliary system.

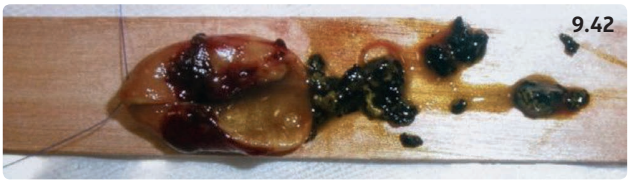
Pathophysiology
Extravasation of bile elicits a strong inflammatory response and causes transudation of lymph from serosal surfaces (**Figure 9.43**).

Clinical presentation
The clinical course is usually protracted. There is acute abdominal pain for the first 48 hours followed by anorexia, depression, fever, slow abdominal distension, and icterus. Hepatobiliary sepsis is life-threatening.

Differential diagnosis
Hepatic tumors, acute pancreatitis, FIP.

Diagnosis
An exudative, yellow–green-colored abdominal effusion is found at abdominocentesis. Macrophages containing bile pigment may be noted in a smear of the fluid (**Figure 9.44**).





Figures 9.41, 9.42 Dog with cholecystitis and bilirubin gallstones. (9.41) Ultrasound image. (9.42) The surgically removed gallbladder, which was diagnosed as cholecystitis. Gallstones are also present. (Courtesy M. Schaer)

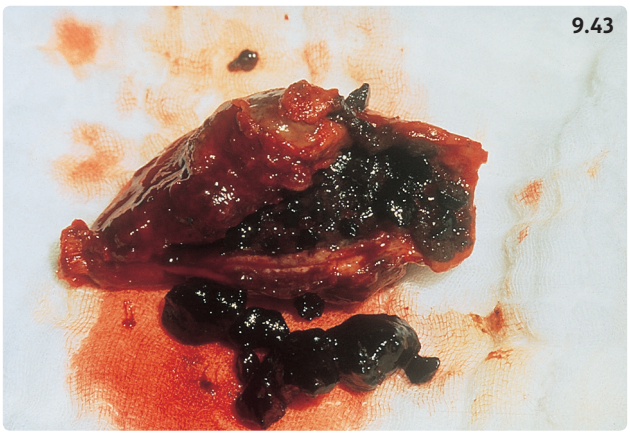


Figure 9.43 Cholecystitis in a 4-year-old German Shepherd Dog. The inflamed gallbladder had ruptured, causing a bile peritonitis. Note the inspissated bile in the gallbladder. A pure culture of *E. coli* was grown from the purulent abdominal fluid.

Management
Exploratory surgery is always indicated.

GALLBLADDER MUCOCELES

Definition/overview
Gallbladder mucoceles are an increasingly common finding in dogs; they appear as dilation or distension of the gallbladder with accumulated mucus. Marked distension

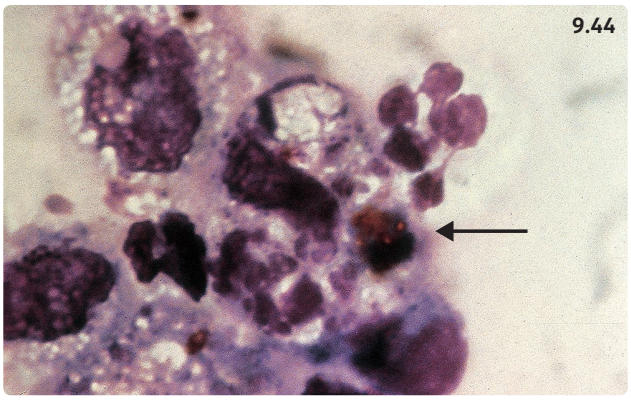


Figure 9.44 Cellular appearance of the fluid in bile peritonitis. Note the neutrophils and macrophages containing bile (arrow). (Courtesy D. Meyer)

may eventually result in rupture of the gallbladder and subsequent peritonitis.

Etiology
The cause is not known, but it is suspected that gallbladder mucoceles result from dysfunction of mucus-secreting cells within the gallbladder mucosa and altered wall contractility.

Pathophysiology
Mucus hypersecretion and formation of a biliary sludge result in the formation of a semi-solid mass of gallbladder contents that cannot pass from the gallbladder to the common bile duct. Over time the gallbladder distends and secondary cholecystitis may result. Rupture of the gallbladder and resultant peritonitis is possible, but is not seen in all cases. An association with hyperadrenocorticism and hypothyroidism has been postulated.

Clinical presentation
Nonspecific clinical signs such as vomiting, anorexia, and lethargy are usually the presenting complaint, but the finding of a gallbladder mucocele can be an incidental finding on ultrasound examination of the abdomen for another reason (**Figure 9.45**). Physical examination findings can include abdominal pain, jaundice, and fever if there is inflammation of the hepatobiliary tree.

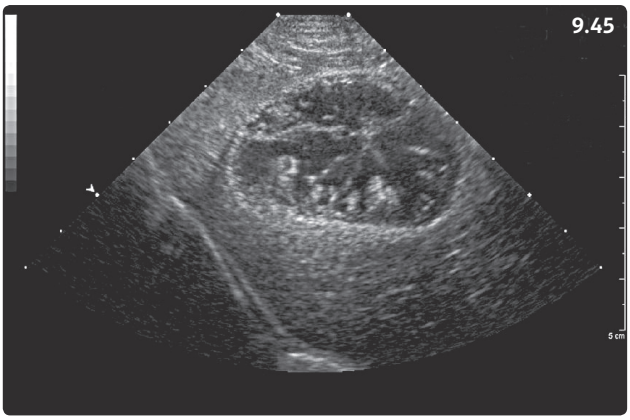
Differential diagnosis
Pancreatitis, bile duct obstruction.

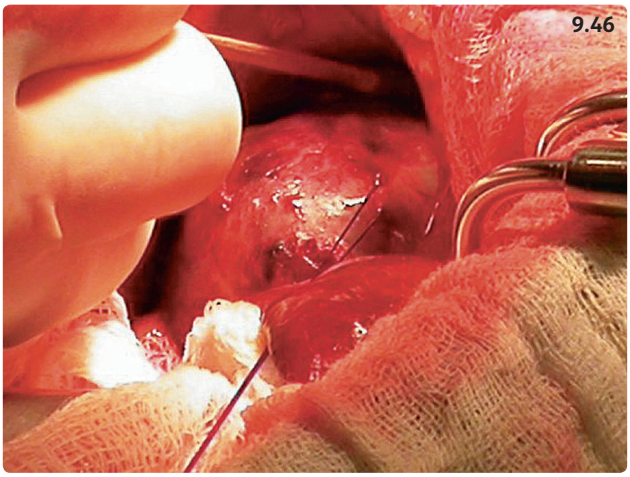
Diagnosis
Ultrasonography is a highly reliable means of identifying gallbladder mucocele and gallbladder rupture. The gallbladder may have a 'kiwi fruit' appearance.

Management
The management of dogs that are not showing clinical signs is controversial, as it is unknown what percentage of dogs with gallbladder mucoceles will progress to a gallbladder rupture. Asymptomatic dogs should be treated with ursodeoxycholic acid, antioxidants, and antimicrobials and monitored via abdominal ultrasound. Dogs showing clinical signs should have a cholecystectomy (**Figure 9.46**).

LIVER TUMORS

Definition/overview
Primary and metastatic tumors occur in the liver. Metastatic tumors are reportedly twice as frequent as primary tumors. Primary tumors include bile duct





Figures 9.45, 9.46 Dog with a mucocele. (9.45) Ultrasound image. (9.46) Different dog at surgery, showing a severely inflamed gallbladder with several foci of necrosis. These would have perforated if surgery had not been done immediately. (Courtesy M. Schaer)

carcinoma, hepatocellular adenoma and carcinoma (hepatoma), and lymphoma. Hepatocellular carcinomas have been associated with a paraneoplastic hypoglycemia in the dog. Lymphosarcoma is the most common liver tumor, especially in cats.

Etiology

The cause of primary tumors is not usually determined. Metastatic tumors in the dog often arise from the pancreas, mammary glands, adrenals, bone, lungs, thyroid, GI tract, and spleen, whereas in the cat they usually arise from the kidney, pancreas, and GI tract. Malignant transformation of cystadenomas is possible.

Pathophysiology

Biliary and hepatocellular cancer occur as multifocal nodular or diffuse infiltrations of large areas of liver or as solitary masses.

Clinical presentation

Clinical signs are vague and nonspecific in most patients. They include inappetence progressing to anorexia, weight loss, vomiting, abdominal distension, and terminal jaundice in some patients (**Figure 9.47**).

Differential diagnosis

Parasitism, hepatobiliary cysts, cirrhosis.

Diagnosis

Those tumors that do not cause extrahepatic biliary obstruction may cause increases in serum AST, ALT, and ALP activities and total serum bilirubin concentration that may appear similar to the pattern associated with CH.

Abdominal radiographs are often read as normal, but they may reveal hepatomegaly (**Figure 9.48**). Hepatocellular carcinomas may be very large and noted on palpation or abdominal radiographs. Ultrasound-guided biopsy or laparotomy and biopsy are essential for diagnosis of neoplastic disease. The gross appearance of neoplastic lesions may appear similar to nodules associated with cirrhosis (**Figure 9.49**). Histologic evaluation can differentiate between the two lesions. Microscopic examination of a hepatic aspirate can help diagnose hepatic lymphoma (**Figure 9.50**).

Figure 9.47 Abdominal distension and loss of muscle mass in a Bull Terrier suffering from advanced hepatocellular carcinoma.

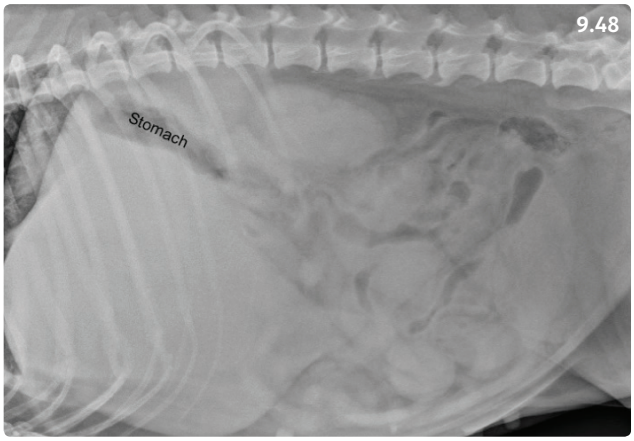


Figure 9.48 Lateral abdominal radiograph showing marked hepatomegaly and dorsal displacement of the stomach in an older dog with hepatic carcinoma. (Courtesy L. Gaschen)

Figure 9.49 Postmortem specimen from a dog with macronodular cirrhosis. (Courtesy M. Schaer)

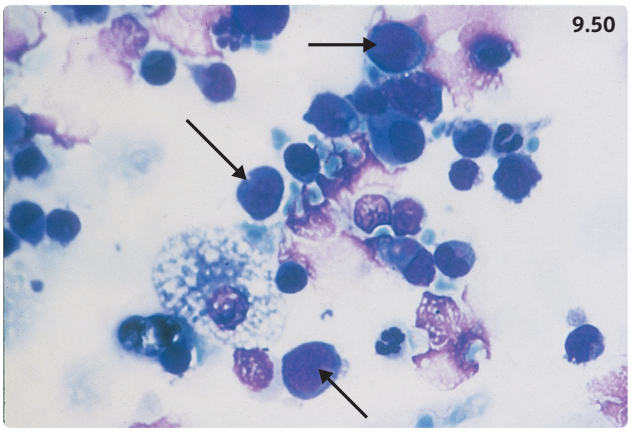


Figure 9.50 Microscopic examination of an hepatic aspirate can help differentiate between hepatic lymphoma and lipidosis in cats with jaundice and hepatomegaly. This aspirate from the liver of a 13-year-old Siamese confirmed a diagnosis of lymphoma (arrows).

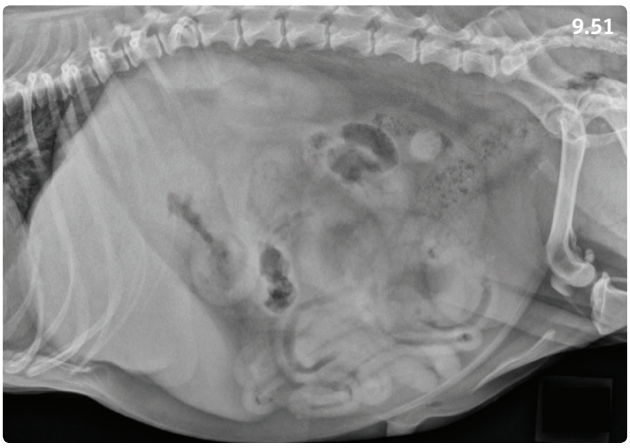


Figure 9.51 Lateral abdominal radiograph showing the typical cushingoid pendulous abdomen with liver enlargement. (Courtesy L. Gaschen)

Management
Primary tumors confined to a single lobe may be resected surgically. The abdominal cavity should be evaluated for metastatic spread and biopsy specimens of hepatic lymph nodes should be obtained. Chemotherapy may be appropriate in selected patients.

VACUOLAR AND STEROID HEPATOPATHY

Definition/overview
This is a unique and idiosyncratic response of the canine liver to either exogenous administration or endogenous overproduction of corticosteroids and perhaps adrenal sex hormones. The disorder is characterized by hepatocellular glycogen accumulation, with associated hepatomegaly and a variety of clinical and laboratory signs, most often associated with the steroids themselves. Scottish Terriers are reported to have a breed-specific syndrome associated with a vacuolar hepatopathy and elevated serum ALP.

Etiology
Exogenous administration of glucocorticoids and naturally occurring hyperadrenocorticism can induce morphologic changes in hepatocytes and abnormal clinicopathologic test results in the dog. Other steroid hormones and adrenal sex hormones may cause similar changes. Some dogs can acquire vacuolated hepatopathy without any specific etiology. Steroid hepatopathy is not typically seen in cats.

Pathophysiology
While most dogs receiving glucocorticoids accumulate hepatocellular glycogen, not all develop the same degree of change. Some dogs develop focal necrosis and severe hepatomegaly, whereas others exhibit almost no response. The reason for this individual variation is unknown. Scottish Terriers with vacuolar hepatopathy typically do not have clinical signs. Increased ALP activity is often dramatic. Adrenal steroids are thought to play a role in the development of the vacuolar hepatopathy in most cases. Progression to inflammation and fibrosis is more likely in Scottish Terriers than other dogs with steroid hepatopathy.

Clinical presentation
Dogs present with clinical signs associated with corticosteroid use – a history of polydipsia/polyuria, polyphagia, nocturnal restlessness, panting, and weight gain. Later there may be a history of ventral and lateral abdominal hairlessness, thin skin, pendulous abdomen (**Figure 9.51**), and muscle wasting. There may be palpable hepatomegaly. Icterus is absent. There may be a history of oral, otic, or ophthalmic administration of corticosteroids. Failing this, endogenous overproduction of glucocorticoids should be suspected.

Differential diagnosis
Includes all causes of hepatomegaly including hepatic neoplasia, other causes of vacuolar hepatopathy, and hepatic amyloidosis.

Diagnosis

Increased ALP activity is the most consistent finding. The increased ALP activity is predominantly due to an isoenzyme of ALP produced by the canine liver in response to glucocorticoids. ALP activity may be dramatically increased, similar to the increases associated with extrahepatic biliary obstruction and cholangitis. In contrast, serum bilirubin concentration remains normal in most dogs with steroid hepatopathy. Also, while ALT may show a mild to moderate increase, the AST usually remains close to normal (**Figure 9.52**). The serum bile acid concentration may be mildly increased (usually <25 µmol/l in the fasted state [10.25 µg/ml]).

Microscopic examination of a hepatic aspirate or biopsy specimen reveals a characteristic vacuolar degeneration as glycogen is lost during tissue fixation and staining (**Figure 9.53**).

Management

Withdrawal of steroid therapy or treatment of endogenous adrenal production is usually all that is required. Treatment with ursodeoxycholic acid and SAMe may hasten recovery.

CANINE HEPATIC LIPIDOSIS

Definition/overview

Accumulation of small (microvesicular) lipid-containing vacuoles within the cytoplasm of hepatocytes is seen rarely in dogs. Accompanying hepatic failure may be noted (**Figures 9.54a, b**).

9.52

Glucose	5.2 mmol/l (93 mg/dl)
BUN	6.1 mmol/l (17 mg/dl)
Creatinine	61.9 µmol/l (0.7 mg/dl)
Cholesterol	**15.6 mmol/l (607 mg/dl)**
Total bilirubin	5.1 µmol/l (0.3 mg/dl)
Total protein	65 g/l (6.5 g/dl)
Albumin	34 g/l (3.4 g/dl)
AP	**2,519 U/l**
Calcium	2.5 mmol/l (10.1 mg/dl)
Phosphorus	0.6 mmol/l (2.0 mg/dl)
AST	88 U/l
ALT	**239 U/l**
Globulin	31 g/l (3.1 g/dl)
Chloride	107 mmol/l (107 mEq/l)
Sodium	146 mmol/l (146 mEq/l)
Potassium	3.9 mmol/l (3.9 mEq/l)
Total CO_2	22 mmol/l (22 mEq/l)

Figure 9.52 Serum chemistry profile showing some of the commonly elevated parameters (in bold) caused by glucocorticoid hepatopathy in the dog.

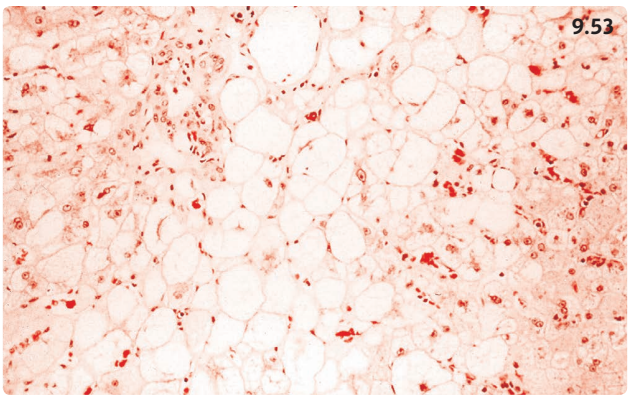
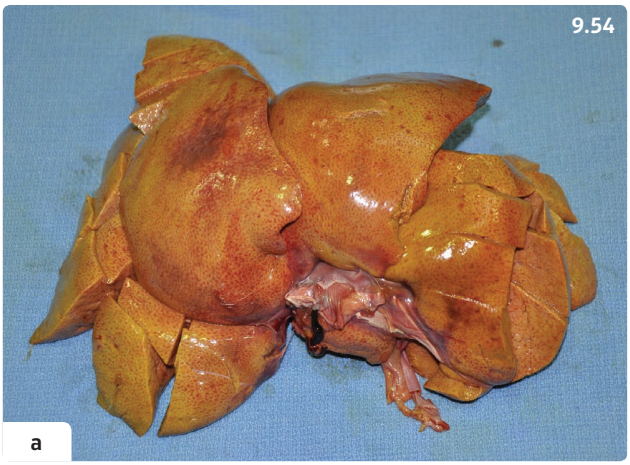
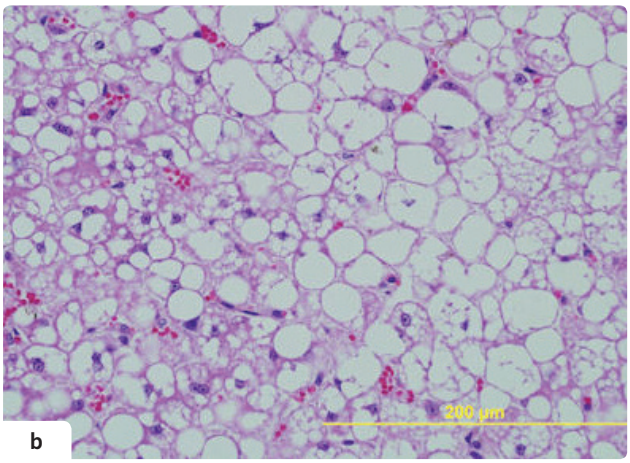


Figure 9.53 Histologic appearance of canine glucocorticoid hepatopathy. Note the vacuolated cells that contained glycogen prior to fixation.





Figures 9.54a, b Postmortem specimen and histopathology from a diabetic ketoacidotic dog dying from fuminating hepatic lipidosis. (Courtesy M. Schaer)

Etiology
Hepatic lipidosis in dogs is usually associated with ketoacidotic diabetes mellitus or juvenile hypoglycemia of small breed dogs.

Pathophysiology
Excessive transport of fatty acids into the liver from mobilization of fat stores associated with insulin resistance, decreased hepatocyte and mitochondrial oxidation of fatty acids, and decreased transport of lipoproteins from the liver. Severe lipid accumulation may result in severe hepatic failure.

Clinical presentation
Clinical signs are usually due to ketoacidotic diabetes mellitus or associated with starvation and hypoglycemia in toy breed neonates.

Diagnosis
Hepatic cytology or biopsy.

Management
Glucose supplementation, nutritional support, and treatment of any underlying disease should be attempted in neonatal toy breed puppies with hepatic lipidosis. Dogs with diabetes mellitus should be treated for ketoacidosis. Because liver failure and hepatoencephalopathy may be contributing to clinical signs, appropriate treatment of fulminant hepatic failure and hepatoencephalopathy is important.

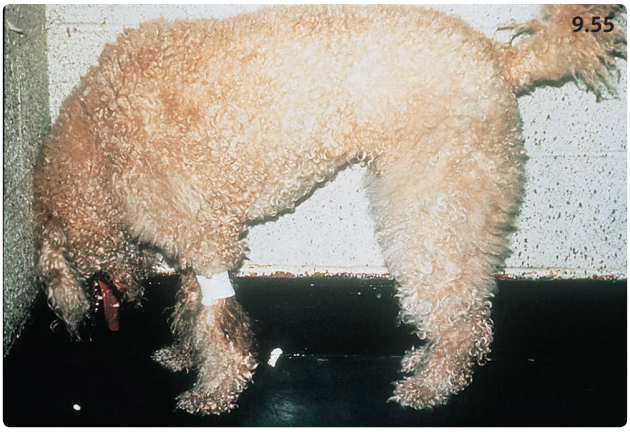
CONGENITAL PORTOSYSTEMIC VASCULAR ANOMALIES (PORTOSYSTEMIC SHUNTS)

Definition/overview
Congenital anomalies of the portal vascular system (PSSs) occur commonly in the dog and are being recognized with increasing frequency in the cat. The anomalous vascular development can involve one or more vessels of the hepatic portal circulation. Single intrahepatic shunts are more common in large breed dogs and single extrahepatic shunts are more common in cats and small breed dogs. Other intrahepatic vascular anomalies are being identified.

Etiology
The reason, or reasons, congenital PSSs develop is not known, but there appears to be a genetic basis in certain lines of Miniature Schnauzers, Irish Wolfhounds, Old English Sheepdogs, and Cairn Terriers. A proposed microvascular dysplasia within the liver has been reported for the latter breed as well as in other small breeds and in cats. Yorkshire Terriers and Miniature Schnauzers are breeds that appear to be at increased risk. Mixed breed cats are most commonly affected and of the purebreds, Himalayans and Persians appear to be at increased risk. Affected male dogs and cats are often cryptorchid. Most animals develop signs by 10 months of age, but they may be subtle and adequately compensated (or accepted by the owner) until they become more prominent later in life (up to 10 years of age).

Pathophysiology
Pathologic changes are secondary to decreased portal venous blood flow with subsequent increased hepatic arteriolar flow. Portal blood shunts past sinusoidal flow and hepatocellular contact, resulting in systemic delivery of materials absorbed from the GI tract including products of the intestinal microbiome. The liver appears grossly small and often mottled, and there is typically atrophy of the hepatocytes, with arteriolar hyperplasia and small or absent portal veins. Other features include sinusoidal congestion, biliary hyperplasia, lipogranulomas, increased periportal connective tissue, and periportal vacuolization.

Clinical presentation
The signalment and history provide important clues to the diagnosis. Affected animals may be normal in stature or may be small for their age, less active than their littermates, and may be labeled 'poor-doers'. Neurologic signs are common in the dog and include seizures and personality changes (**Figures 9.55**, **9.56**). Intermittent depression, disorientation, aggression, head pressing, blindness, mydriasis, and seizures have also been observed. Cats often show depression and anorexia. Polydipsia/polyuria, ptyalism (**Figure 9.57**), and recurrent formation of



Figures 9.55 A Poodle with hepatic encephalopathy demonstrating behavioral changes such as head pressing and 'getting lost' in corners.

Figure 9.56 An abrasion on the head of a Pug as a result of head pressing. The animal was diagnosed with a portosystemic shunt and the signs disappeared after corrective surgery.

Figure 9.57 Ptyalism in a Himalayan kitten with hepatic encephalopathy as a result of a portosystemic shunt.

urinary calculi are also common findings. Renal, cystic, and urethral calculi may be the first clinical indication of an underlying congenital PSS in some dogs. Urate urolithiasis develops commonly. Signs may or may not be associated with eating. Unexpected prolonged recovery from general anesthesia or an exaggerated response to tranquilizers has been noted.

Findings on physical examination are often unremarkable. Occasionally, an inappropriately small body stature is present (**Figure 9.58**). Slightly enlarged kidneys have been palpated in some cats or small dogs, but this is more often detected radiographically.

Differential diagnosis

Portal vein hypoplasia, congenital enzyme deficiency of the urea cycle, infectious diseases (canine distemper, FIP, diseases related to feline leukemia virus and feline immunodeficiency virus, toxoplasmosis), idiopathic epilepsy, metabolic disorders (e.g. hypoglycemia, thiamine deficiency), hydrocephalus, toxicity.

Figure 9.58 Dobermann littermates. The smaller dog has a portosystemic shunt with associated stunted growth.

Diagnosis

ALT and ALP activities may be normal or only slightly increased. Serum albumin and BUN concentrations are decreased in many patients with a PSS. Decreased concentrations occur because of hepatic atrophy and insufficient portal blood flow. These two parameters are valuable indicators of liver insufficiency on the biochemical profile.

A mild hypoglycemia may also be detected. The combination of a compatible history and biochemical abnormalities indicates the need for a function test such as serum bile acids or blood ammonia. Ammonium biurate crystals may be observed in the urine sediment (**Figure 9.59**) and evaluation of the hemogram may reveal a slightly decreased MCV. Serum iron is decreased in over 50% of dogs with confirmed PPS.

Imaging may reveal microhepatica in some patients (**Figure 9.60**). Visual confirmation of the portal vascular anomaly requires ultrasonography, CT angiography, scintigraphy, a cranial mesenteric angiogram, splenoportography, or jejunal vein portography (**Figure 9.61**).

Histologically, the liver may appear normal architecturally or there may be subtle changes of hepatic cord atrophy, small or absent portal veins, and an increase in arteriolar structures. Other nonspecific findings that may be reported include periportal or midzonal vacuolization, mild to moderate biliary hyperplasia, mild periportal fibrosis, and foci of iron-rich fatty macrophages (lipogranulomas). The latter finding is rare in normal dogs under the age of 6 years and should raise the suspicion of an underlying congenital portosystemic shunt.

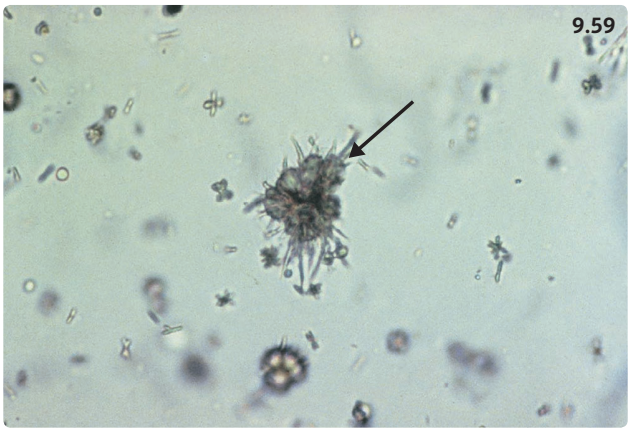


Figure 9.59 Ammonium biurate crystal (arrow) in the urine sediment in a dog with a portacaval shunt.

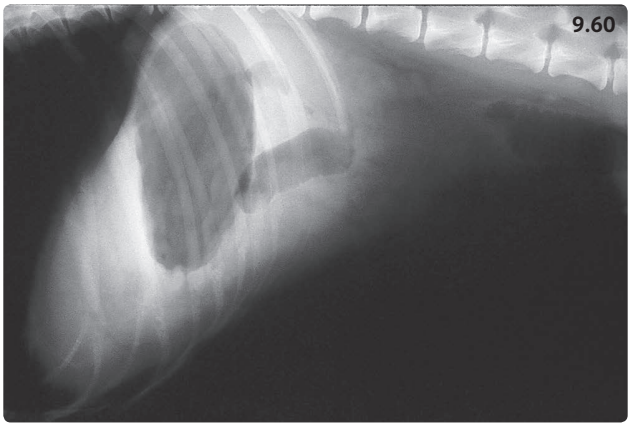


Figure 9.60 Lateral radiograph showing microhepatica, as evidenced by the vertical gastric axis, in a Dalmatian with a portosystemic shunt.

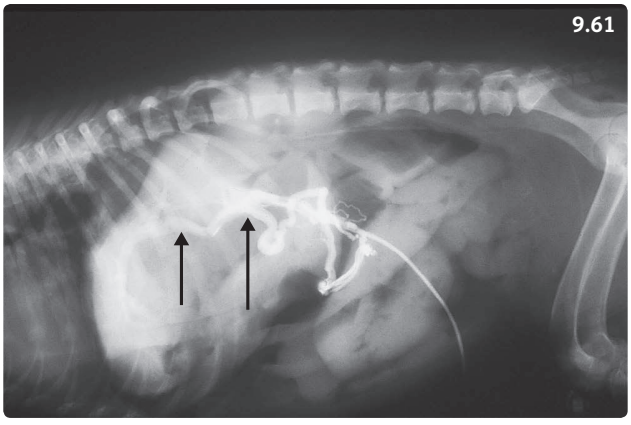


Figure 9.61 Mesenteric venous portography confirmed a shunt (arrows) in this 2-year-old Lhasa Apso.

Management

Surgical ligation or compression of the anomalous vessel is the treatment of choice in the dog and cat, but some shunts are now being treated by the implantation of coils under fluoroscopic guidance. If surgery is not an option, medical management with a low-quantity/high-quality protein diet, plus lactulose and neomycin or metronidazole to ameliorate signs of encephalopathy, may provide satisfactory results for months to several years depending on the severity of the vascular insufficiency.

FURTHER READING

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