CHAPTER 115
HEPATITIS AND CHOLANGIOHEPATITIS

Mark P. Rondeau, DVM, DACVIM (Internal Medicine)

KEY POINTS

- Hepatitis is defined as any inflammatory cell infiltrate within the hepatic parenchyma; the term *cholangiohepatitis* describes the extension of that inflammation to include the intrahepatic bile ducts.
- Although many causes of hepatitis and cholangiohepatitis have been described in dogs and cats, the cause in many cases remains unknown.
- A suspicion of hepatitis or cholangiohepatitis may be based on supportive historical, physical examination, and clinicopathologic findings that are similar for most causes of hepatic disease. A diagnosis of hepatitis or cholangiohepatitis is made ultimately via histopathologic evaluation of hepatic tissue.
- The mechanisms of hepatocellular injury in animals with hepatitis and cholangiohepatitis are poorly understood. Elucidation of these mechanisms may provide the basis for future therapeutic options.
- Successful treatment of the patient with hepatitis or cholangiohepatitis involves addressing the underlying disease or inciting cause and providing aggressive symptomatic therapy and supportive care.

Hepatitis is defined as any inflammatory cell infiltrate within the hepatic parenchyma, and the term *cholangiohepatitis* describes extension of that inflammation to include the intrahepatic bile ducts.[1] A diagnosis of these conditions is based on histopathologic examination of hepatic biopsy specimens. The histopathologic appearance gives clues regarding the duration of the inflammation. Acute hepatitis is characterized by a combination of inflammation, hepatocellular apoptosis, necrosis, and possibly regeneration, but a lack of fibrosis. The relationship between the development of hepatitis and necrosis is complex, and it can be difficult to determine which abnormality was the initial lesion.[1] Chronic hepatitis, on the other hand, is identified by the presence of fibrosis, proliferation of ductular structures, and regenerative nodules in addition to an inflammatory infiltrate, apoptosis, and/or necrosis.[2] The type of inflammatory cellular infiltrate may give the clinician some clues regarding the cause. Occasionally, causative agents are identified within biopsy specimens. However, the cause remains unknown for many cases of hepatitis and cholangiohepatitis in dogs and cats. This chapter discusses the clinical presentation of animals with hepatitis and cholangiohepatitis and outlines the most commonly recognized clinical syndromes with respect to diagnosis and treatment of the specific disease. Effective treatment of patients with hepatitis or cholangiohepatitis includes specific therapy of any identified inciting cause and aggressive symptomatic and supportive therapy. A discussion of symptomatic treatment and supportive therapy for the sequelae of hepatitis and cholangiohepatitis can be found in Chapter 116.

HISTORICAL FINDINGS

In general, the historical findings associated with hepatitis are nonspecific, as with most types of liver disease. Exposure to certain etiologic agents or toxins may be ascertained from the client history and thus raise the suspicion for hepatic involvement. Because of the large reserve capacity of the liver, a short duration of clinical signs does not necessarily indicate acute disease. Animals with cholangiohepatitis (CH) may not show outward clinical signs until a significant portion of hepatic function is affected. Presenting owner complaints for animals with hepatitis may include vomiting, diarrhea, anorexia, lethargy, polyuria, polydipsia, abdominal distention, dysuria, neurologic abnormalities associated with hepatic encephalopathy or vascular accidents, and icterus.

PHYSICAL EXAMINATION FINDINGS

Similar to historical findings, the physical examination findings in animals with hepatitis are often nonspecific. Icterus, when present in the absence of hemolytic anemia, suggests disease of the hepatic parenchyma or extrahepatic biliary system. Animals with acute hepatitis are more likely to have fever and abdominal pain, and those with CH are more likely to have ascites. Hepatomegaly may be present in some patients, especially those with acute hepatitis. Many animals with hepatitis do not have any of these physical abnormalities present on the initial examination, and serum biochemical changes in those cases are likely to direct the clinician toward the liver as the site of disease.

MECHANISMS OF HEPATOCELLULAR INJURY

The pathogenesis by which hepatitis and cholangiohepatitis lead to hepatocellular necrosis and apoptosis is not understood completely. Experimental studies have suggested many mechanisms of hepatocellular injury, but their specific evaluation in dogs and cats with hepatitis is lacking. Mechanisms of hepatocellular injury that are not specific to hepatitis include tissue hypoxia, lipid peroxidation, intracellular cofactor depletion, intracellular toxin production, cholestatic injury, endotoxic insults, and hepatocyte plasma membrane injury.[3]

Hepatocytes are especially susceptible to anoxia because the liver receives a mixture of venous and arterial blood. Hypoxic damage quickly leads to plasma membrane and cytosolic organelle injury secondary to adenosine triphosphate (ATP) depletion. Free radicals may cause oxidative cellular injury that can result in lipid peroxidation and subsequent plasma membrane damage.

Cellular toxins may bind to nucleic acids and inhibit protein synthesis. Cholestasis causes retention of bile acids that directly damage cellular organelles. Endotoxins work via various mechanisms, most of which involve stimulation of inflammatory cells to produce inflammatory mediators (cytokines such as prostaglandins and leukotrienes) that perpetuate inflammation within the liver parenchyma. Experimental work in mouse models suggests an important role for tumor necrosis factor-α (TNF-α) in the initiation and perpetuation of hepatitis. TNF-α, produced secondary to the interaction of the costimulatory molecules CD154 on T cells and

CD40 on hepatocytes and Kupffer cells, stimulates hepatocyte apoptosis through the Fas-Fas ligand pathway.[4] A better understanding of the complex mechanisms of hepatocellular injury in animals with hepatitis may encourage the development of novel therapeutic modalities for affected patients.

CAUSES OF HEPATITIS AND CHOLANGIOHEPATITIS IN DOGS AND CATS

Box 115-1 lists the reported causes of hepatitis and cholangiohepatitis in dogs and cats. A complete discussion of all disease entities is beyond the scope of this chapter. A discussion of the most common clinical syndromes follows.

Idiopathic Causes
Feline cholangitis complex

The feline cholangitis complex is one of the most common hepatobiliary disorders in cats.[5] This syndrome has been reported in dogs[6] but is primarily a feline disease. Several classification schemes have been proposed to define the various elements of this syndrome. The World Small Animal Veterinary Association (WSAVA) Liver Standardization Group has proposed a classification system that divides

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BOX 115-1 *Causes of Hepatitis and Cholangiohepatitis in Dogs and Cats*

Idiopathic

Canine chronic hepatitis
Feline cholangitis complex
Nonspecific reactive hepatitis
Lobular dissecting hepatitis

Viral

Infectious canine hepatitis
 (adenovirus type I)
Acidophil cell hepatitis
Herpesvirus (neonates)
Feline infectious peritonitis

Bacterial

Feline cholangitis complex
Leptospirosis
Bartonellosis
Tyzzer's disease (*Clostridium piliforme*)
Salmonellosis
Listeriosis
Tularemia
Brucellosis
Yersiniosis
Helicobacter spp.
Mycobacteria
Septicemia

Rickettsial

Ehrlichiosis
Rocky Mountain spotted fever

Protozoal

Toxoplasmosis
Neosporosis
Leishmaniasis
Cytauxzoonosis
Hepatozoonosis
Coccidiosis

Parasitic

Visceral larval migrans
Dirofilariasis (caudal vena caval syndrome)
Liver fluke migration
Schistosomiasis
Echinococcus cysts

Fungal

Histoplasmosis
Blastomycosis
Coccidioidomycosis
Aspergillosis (disseminated)
Phycomycosis

Algal

Prototheosis

Hepatotoxins

Acetaminophen
Aflatoxin
Amiodarone
Aspirin
Azathioprine
Azole antifungals
Carprofen
Cycads (e.g., Sago palm)
Diazepam (oral)
Halothane
Lomustine
Methimazole
Phenobarbital
Phenytoin
Primidone
Tetracyclines
Trimethoprim/sulfadiazine or sulfamethoxazole
Xylitol
Zonisamide

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feline cholangitis into two main categories: neutrophilic cholangitis and lymphocytic cholangitis.[7]

Neutrophilic Cholangitis

Histologically, neutrophilic cholangitis (NC) is characterized by infiltration of neutrophils within the wall or lumen of intrahepatic bile ducts. This disease can be seen in acute and chronic stages. In acute neutrophilic cholangitis (ANC), edema and neutrophilic inflammation may extend into the portal areas. In chronic neutrophilic cholangitis (CNC), a mixed inflammatory infiltrate may be noted in portal areas, along with varying degrees of fibrosis and bile duct hyperplasia.[7] This syndrome was referred to previously as *acute cholangiohepatitis* or *suppurative cholangitis-cholangiohepatitis*.[8,9] NC can occur in cats of any age, breed, or sex. Clinical signs are nonspecific and include anorexia, lethargy, vomiting, and weight loss. The duration of these clinical signs ranges from a few days to a few months and may be shorter in cats with ANC than in those with CNC,[8] but this is not a consistent finding.[10,11] Physical examination findings commonly include dehydration and icterus. Fever is present in 19% to 37.5% of cases.[10,12] Some reports suggest that fever is associated more commonly with ANC than CNC,[12] whereas others recognize no difference.[10,11] Hepatomegaly is seen in fewer than half of the cases and abdominal pain is noted occasionally.[8,10,11] Biochemical analysis commonly reveals increased activity of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and γ-glutamyltransferase (GGT) ranging in severity from mild to severe. However, increased liver enzyme activity may be absent in some cases.[13] Cholangitis in cats has been associated with inflammatory bowel disease (IBD) and pancreatitis,[12] and many investigators believe that NC is the result of an ascending bacterial infection from the gastrointestinal (GI) tract. However, rates of bacterial isolation using traditional methods have varied greatly, from less than 20% to more than 60% in affected cats.[8,10] When isolated, common bacterial species include *Escherichia coli, Enterococcus* spp., *Clostridium* spp., and *Staphylococcus* spp. Samples for aerobic and anaerobic bacterial cultures should be obtained in any cat suspected of having cholangitis; gallbladder bile is preferred to liver tissue as the culture source.[14] Treatment with a broad-spectrum antimicrobial therapy, focusing on enteric flora, is recommended pending results of culture and susceptibility testing. Prognosis for cats with NC is typically good with aggressive treatment, although sequelae may include bile duct obstruction, acute necrotizing pancreatitis, sepsis, and multiple organ dysfunction.

Lymphocytic Cholangitis

Lymphocytic cholangitis (LC) is a chronic form of disease that is characterized histologically by a mixed inflammatory infiltrate (typically small lymphocytes, or lymphocytes and plasma cells) within portal areas and is associated with varying degrees of fibrosis and bile duct hyperplasia.[7] Inflammation within the walls or lumens of intrahepatic bile ducts may be present but is not a specific hallmark of the disease. LC likely includes a wide spectrum of clinical diseases with varying severity and clinical significance.[14] LC likely includes syndromes that have been referred to previously as *chronic cholangiohepatitis, nonsuppurative cholangitis-cholangiohepatitis,* and *lymphocytic portal hepatitis*.[5,8,9,12] The clinical picture of cats with LC varies widely and has significant overlap with other forms of hepatobiliary disease in cats, including NC.[10,11] Nonspecific clinical signs, including anorexia, lethargy, vomiting, and weight loss, may be chronic and intermittent.[8] Physical examination findings may include icterus, hepatomegaly, or ascites, but none are consistent findings. Signs of hepatic encephalopathy (dullness, ptyalism, seizures) may develop in severely affected cats. Definitive diagnosis is made by liver biopsy. As discussed for NC, ancillary diagnostics

provide information to support hepatobiliary disease but are not specific for LC. Activity of serum liver enzymes is increased in many but not all cases and varies in severity. Abdominal radiographic and ultrasonographic findings are nonspecific but may aid in the recognition of concurrent disease. The cause of LC is unknown, although a chronic response to an ascending bacterial infection from GI flora and an association with IBD and pancreatitis (as seen with NC) has been suggested.[8,9] Immunohistochemical analysis of hepatic biopsy specimens from cats with LC has shown a predominance of CD3+ T cells infiltrating the bile duct epithelium and periportal areas, a smaller proportion of B cells forming discrete aggregates in the portal regions, and expression of major histocompatibility complex class II on the biliary epithelium.[15,16] These findings, combined with anecdotal response to glucocorticoid therapy and the fact that active infection has been documented rarely in cats with LC, have led to the suspicion that LC is an immune-mediated disease. Treatment typically involves immunosuppressive glucocorticoid therapy in animals with no evidence of infection. Treatment with ursodeoxycholic acid (10 to 15 mg/kg PO q24h) has anecdotal and theoretic benefits, although no clinical studies examining its efficacy in cats have been published. Prognosis is typically good with appropriate management, although concurrent disease is common and may affect prognosis.

Canine chronic hepatitis

Although many causes of chronic hepatic inflammation in dogs have been identified, the term *canine chronic hepatitis* (CCH) describes an idiopathic, progressive necroinflammatory disease of unknown cause that is common in the canine population.[1] Evidence supports an immune-mediated process as the perpetuating factor,[1,17,18] although it is unclear whether the disease is a primary or secondary immune response. Because of the chronic nature of the disease and the large reserve capacity of the liver, many affected animals are not identified until the onset of fulminant hepatic failure. However, increasing numbers of cases are now being identified at an earlier asymptomatic stage as a result of increased hepatic enzyme activity that is noted on routine serum biochemical screening.

Animals of any age and sex are affected, although middle-age female dogs may be overrepresented. CCH is seen with increased frequency in certain breeds (Box 115-2), suggesting a familial predisposition. No specific diagnostic findings separate CCH from other causes of hepatitis. Ultimately, the diagnosis is based on histopathologic examination of liver tissue revealing inflammation (usually lymphocytic and plasmacytic, occasionally neutrophilic), necrosis and/or apoptosis, evidence of regeneration, fibrosis and/or

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BOX 115-2   *Breeds Predisposed to Chronic Hepatitis*

American Cocker Spaniel
Bedlington Terrier*
Dalmatian*
Doberman Pinscher*
English Cocker Spaniel
English Springer Spaniel
Labrador Retriever*
Skye Terrier*
Standard Poodle
West Highland White Terrier*

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*Proven or suspected copper-associated hepatopathy.

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hyperplasia of ductular structures and the absence of an identifiable underlying cause.[1] The optimal treatment protocol for animals with CCH has not been well studied, but immunosuppressive therapy is the mainstay of treatment. Corticosteroids are the only class of drug shown potentially to provide benefit[19] and their use is indicated in patients with signs of hepatic failure. Other immunomodulatory drugs that may be used include ursodeoxycholic acid, metronidazole, azathioprine, and cyclosporine. Colchicine may delay progression of hepatic fibrosis. Copper chelation may be beneficial when copper retention is a significant contributing factor. The overall prognosis is difficult to ascertain because asymptomatic animals may have a slowly progressive course and excellent prognosis. However, once hepatic failure and/or cirrhosis develops, the prognosis is poor.

Role of Copper

The role of copper in the pathogenesis of CCH is unclear. Elevated hepatic copper levels have been identified in many dogs with CCH, but because biliary excretion is the major mechanism of maintaining copper homeostasis, any cause of cholestasis would be expected to increase hepatic copper levels.[18] However, it has been shown in the Bedlington Terrier that elevated copper levels (caused by an inherited defect in excretion) lead to chronic hepatitis and cirrhosis.[1] However, it may be difficult to determine which came first, the copper accumulation or the hepatitis. A propensity for increased hepatic copper levels in association with CCH has been described for many breeds in addition to the Bedlington Terrier, and these are listed in Box 115-2.

A suspected primary hepatic copper storage disorder also has been reported in one cat.[20] Whether the copper accumulation is a primary or secondary event, the excessive copper is damaging to hepatocytes. Copper chelation treatment has improved or resolved the hepatic pathologic findings in a group of Doberman Pinschers with elevated hepatic copper levels and subclinical CCH.[21] Hepatic tissue should be harbored for copper quantification in any dog undergoing liver biopsy. If elevated levels are identified, a reduction of dietary copper and chelation with d-penicillamine (10 to 15 mg/kg q12h, given 1 to 2 hours before feeding) or trientine (10 to 15 mg/kg q12h, given 1 to 2 hours before feeding) are likely to be beneficial.

Nonspecific reactive hepatitis

Nonspecific reactive hepatitis is a histologic diagnosis that describes the liver's response to a variety of extrahepatic disease processes. The lesion is characterized by widespread inflammatory infiltrates (usually lymphocytes and plasma cells) in the portal areas and parenchyma in the absence of hepatocellular necrosis.[2] Identification of this lesion should alert the clinician that a liver-specific problem is unlikely and that further investigation into the underlying disease process is necessary.

Viral Causes

Viral hepatitis is uncommon in dogs and cats. Most viral infections carry a poor prognosis. Specific therapy is not available or has not been evaluated. Symptomatic therapy and supportive care are therefore the primary therapeutic options.

Infectious canine hepatitis

Infectious canine hepatitis is caused by canine adenovirus type I. This disease has become rare because of extensive vaccination protocols using the cross-reacting adenovirus type II vaccine. As such, the disease is seen only in young, unvaccinated dogs. The degree of antibody response determines the severity of disease, with a poor

response resulting in an acutely fatal syndrome. Animals that mount an appropriate response may recover or develop CH. Corneal edema and anterior uveitis may develop in animals that recover from acute illness. The diagnosis is made by histopathologic identification of large basophilic to amphophilic intranuclear inclusion bodies within hepatocytes and Kupffer cells that are identified during the first week of infection.[15] Histopathology also reveals multifocal coagulative necrosis and a neutrophilic inflammatory infiltrate that may not be present in animals with severe acute infection.

Feline infectious peritonitis

Feline infectious peritonitis (FIP) is caused by the feline enteric coronavirus. FIP can affect any organ in the body. Cats with hepatic involvement often have increased activities of ALT and AST and develop hyperbilirubinemia as the disease progresses. Histologic lesions include multifocal necrosis (often around blood vessels) with associated infiltration with neutrophils and macrophages. Pyogranulomatous lesions may be noted on the liver capsule.[17] Immunohistochemistry can be performed on liver biopsy specimens to confirm the presence of virus.[22] When hepatic involvement occurs, the disease is uniformly fatal. Because there is no definitive treatment, supportive care is the mainstay of therapy.

Bacterial Causes
Leptospirosis

Leptospirosis is caused by any one of several serovars of spiral bacteria belonging to the species *Leptospira interrogans* sensu lato. The commonly isolated serovars in small animals include *Leptospira icterohaemorrhagiae, Leptospira canicola, Leptospira pomona, Leptospira hardjo, Leptospira grippotyphosa,* and *Leptospira bratislava.* Infection in dogs most commonly results in acute renal failure, although hepatic involvement may occur in 20% to 35% of cases.[3,23] Other clinical manifestations of infection include pulmonary hemorrhage, uveitis, and acute fever.[24] Infection in young animals and infection with serovars *L. icterohaemorrhagiae* and *L. pomona* are more likely to result in hepatic involvement.[25] Affected dogs may show acute hepatitis or develop chronic hepatitis with subclinical acute infection. Although cats are generally resistant to leptospirosis, experimental infection with *L. pomona* has caused hepatic lesions in this species.[3] Patients with hepatic involvement show increased activity of hepatic enzymes (ALT, AST, ALP), although ALP often is affected most severely. Hyperbilirubinemia and signs of hepatic failure may occur. Diagnosis of leptospirosis usually is based on clinical suspicion because of renal and hepatic involvement combined with serologic evidence of infection. However, antibody titers may be negative during the first week of infection, and antibody production may persist for only 2 to 6 weeks.[3] Suspected patients with negative antibody titers and a short duration of illness should be treated as though they have leptospirosis, and antibody titers should be repeated in 2 weeks. Histopathologic changes in the liver of affected animals may include coagulative necrosis and infiltration of lymphocytes and plasma cells with lesser numbers of neutrophils and macrophages. Organisms may be identified in biopsy specimens with silver staining, but this is an insensitive diagnostic test. Polymerase chain reaction (PCR) techniques to detect organisms in blood and urine samples are available. These techniques have not been well studied in dogs with clinical disease, but they are likely to make this diagnosis less challenging in the future. Historically, treatment recommendations have included penicillin to eliminate the leptospiremic stage, followed by doxycycline to eliminate the carrier state. However, treatment with doxycycline alone is effective for the leptospiremic stage and carrier state (5 mg/kg PO/IV q12h).[24] Penicillins may be used in animals that do not tolerate doxycycline. Alternative antibiotic choices include azithromycin, ceftriaxone, and cefotaxime.[24] Prognosis is typically good, but patients often require intensive supportive care, including hemodialysis in animals with oliguric or anuric renal failure. Pulmonary involvement worsens prognosis.

Bartonellosis

Bartonella species are arthropod-transmitted bacteria that have been associated with multiple clinical syndromes in veterinary medicine.[26] *Bartonella henselae* and *Bartonella clarridgeiae* have been identified as causes of hepatic disease in dogs.[27] Clinical findings are similar to those of dogs with other causes of hepatitis. Histologic examination of hepatic tissue from dogs with *B. henselae* infection has revealed peliosis hepatis[28] and granulomatous hepatitis,[27] both of which have been described in infected humans. Diagnosis was made via identification of *Bartonella* DNA using PCR techniques on hepatic biopsy specimens. This is the preferred method of diagnosis because serologic assays impart information only regarding exposure, and granulomatous hepatitis may be caused by other agents. The cause of granulomatous hepatitis in dogs frequently is unknown, although reported causes include fungal infection, mycobacterial infection, dirofilariasis, lymphoma, histiocytosis, and intestinal lymphangiectasia.[29] Azithromycin is the antibiotic of choice for treatment of bartonellosis, although its use in dogs with hepatic disease caused by *Bartonella* spp. has not been evaluated thoroughly. Other antibiotics that may be effective include doxycycline (high dose, 10 to 15 mg/kg q12h), enrofloxacin, and rifampin (in combination with doxycycline or enrofloxacin).[26]

Septicemia

An important cause of hepatitis in critically ill dogs and cats is bacterial seeding of the liver secondary to bacteremia or via translocation from the GI tract. Commonly isolated aerobic bacteria include *Staphylococcus* spp., *Streptococcus* spp., and enteric gram-negative organisms. Commonly identified anaerobes include *Bacteroides* spp., *Clostridium* spp., and *Fusobacterium* spp.[3] The diagnosis of bacteremia can be difficult in veterinary patients (see Chapter 91). Septicemia-induced hepatitis should be suspected in critically ill animals that develop clinicopathologic evidence of hepatic disease while hospitalized, especially those in which bacterial infection or severe GI disease have been documented. Treatment with broad-spectrum antimicrobials (pending sensitivity testing), along with aggressive supportive care, are vital to a successful outcome.

Drugs and Toxins

The liver is particularly susceptible to toxic injury because it receives blood from the portal circulation. Histologic changes in the liver secondary to toxic injury vary and may include no changes, hepatocellular swelling, steatosis, necrosis, cholestasis, inflammation, and/or fibrosis.[2] Several substances reported to cause hepatotoxicity are noted in Box 115-1, but this is by no means an exhaustive list. Because of the varying and nonspecific nature of histologic changes, diagnosis of hepatotoxicity often is made on the basis of clinical suspicion (biochemical alterations, such as marked increases in liver enzyme activity) with or without a history of known exposure. Treatment involves removal of the offending agent and aggressive supportive care. S-Adenosylmethionine (SAMe) (20 mg/kg PO q24h) has been effective in treating acetaminophen toxicity.[30,31] Although its effectiveness against other forms of hepatotoxicity has not been evaluated, it is a logical choice for supportive care in animals suffering any hepatotoxic insult, mainly because of its ability to increase hepatic glutathione levels, which may increase antioxidant and repair abilities.

REFERENCES

1. Johnson SE: Parenchymal disorders. In Washabau RJ, Day MJ, editors: Canine and feline gastroenterology, St Louis, 2013, Elsevier Saunders.
2. van den Ingh TSGAM, Van Winkle T, Cullen JM, et al: Morphological classification of the parenchymal disorders of the canine and feline liver. In Rothuizen J, Bunch SE, Charles JA, et al, editors: WSAVA standards for clinical and histological diagnosis of canine and feline liver disease, Edinburgh, 2006, Saunders Elsevier.
3. Center SA: Acute hepatic injury: hepatic necrosis and fulminant hepatic failure. In Guilford WG, et al, editors: Strombeck's small animal gastroenterology, ed 3, Philadelphia, 1996, WB Saunders Company.
4. Zhou F, Ajuebor MN, Beck PL, et al: CD154-CD40 interactions drive hepatocyte apoptosis in murine fulminant hepatitis, Hepatology 42:372-380, 2005.
5. Gagne JM, Weiss DJ, Armstrong PJ: Histopathologic evaluation of feline inflammatory liver disease, Vet Pathol 33:521-526, 1996.
6. Forrester SD, Rogers KS, Relford RL: Cholangiohepatitis in a dog, J Am Vet Med Assoc 200:1704-1706, 1992.
7. van den Ingh TSGAM, Cullen JM, Twedt DC, et al: Morphological classification of biliary disorders of the canine and feline liver. In Rothuizen J, Bunch SE, Charles JA, et al, editors: WSAVA standards for clinical and histological diagnosis of canine and feline liver disease, Edinburgh, 2006, Saunders Elsevier.
8. Center SA: The cholangitis/cholangiohepatitis complex in the cat. In Proceedings, 12th Am Coll Vet Intern Med, 766-771, 1994.
9. 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 209:1114-1116, 1996.
10. Rondeau MP: WSAVA classification and role of bacteria in feline inflammatory hepatobiliary disease. In Proceedings, Forum Am Coll Vet Intern Med, 590-591, 2009.
11. Morgan M, Rondeau M, Rankin S, et al: A survey of feline inflammatory hepatobiliary disease using the WSAVA classification, J Vet Intern Med 22:860A, 2008.
12. 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 214:513-516, 1999.
13. Callahan Clark JE, Haddad J, Brown DC, et al: Feline cholangitis: a necropsy study of 44 cats (1986-2008), J Feline Med Surg 13:570-576, 2011.
14. Rondeau MP: Intrahepatic biliary disorders. In Washabau RJ, Day MJ, editors: Canine and feline gastroenterology, St Louis, 2013, Elsevier Saunders.
15. Day MJ: Immunohistochemical characterization of the lesions of feline progressive lymphocytic cholangitis/cholangiohepatitis, J Comp Pathol 119:135-147, 1998.
16. Warren A, Center S, McDonough S, et al: Histopathologic features, immunophenotyping, clonality, and eubacterial fluorescence in situ hybridization in cats with lymphocytic cholangitis/cholangiohepatitis, Vet Pathol 48:627-641, 2011.
17. Center SA: Chronic hepatitis, cirrhosis, breed-specific hepatopathies, copper storage hepatopathy, suppurative hepatitis, granulomatous hepatitis, and idiopathic hepatic fibrosis. In Guilford WG, et al, editors: Strombeck's small animal gastroenterology, ed 3, Philadelphia, 1996, WB Saunders Company.
18. Boisclair J, Doré M, Beauchamp G, et al: Characterization of the inflammatory infiltrate in canine chronic hepatitis, Vet Pathol 38:628-635, 2001.
19. Strombeck DR, Miller LM, Harrold D: Effects of corticosteroid treatment on survival time in dogs with chronic hepatitis: 151 cases (1977-1985), J Am Vet Med Assoc 193:1109-1113, 1988.
20. Meertens NM, Bokhove CA, van den Ingh TSGAM: Copper-associated chronic hepatitis and cirrhosis in a European Shorthair cat, Vet Pathol 42:97-100, 2005.
21. Mandigers PJ, van den Ingh TSGAM, Bode P, et al: Improvement in liver pathology after 4 months of D-penicillamine in 5 Doberman Pinschers with subclinical hepatitis, J Vet Int Med 19:40-43, 2005.
22. Giori L, Giordano A, Giudice C, et al: Performances of different diagnostic tests for feline infectious peritonitis in challenging clinical cases, J Small Anim Pract 52:152-157, 2011.
23. Adin CA, Cowgill LD: Treatment and outcome of dogs with leptospirosis: 36 cases (1990-1998), J Am Vet Med Assoc 216:371-375, 2000.
24. Sykes JE, Hartmann K, Lunn KF, et al: 2010 ACVIM small animal consensus statement on leptospirosis: diagnosis, epidemiology, treatment and prevention, J Vet Intern Med 25:1-13, 2011
25. Greene CE, Sykes LE, Moore GE, et al: Leptospirosis. In Greene CE, editor: Infectious diseases of the dog and cat, ed 4, St Louis, 2012, Elsevier Saunders.
26. Breitschwerdt EB, Chomel BB: Canine bartonellosis. In Greene CE, editor: Infectious diseases of the dog and cat, ed 4, St Louis, 2012, Elsevier Saunders.
27. Gillespie TN, Washabau RJ, Goldschmidt MH, et al: Detection of *Bartonella henselae* and *Bartonella clarridgeiae* DNA in hepatic specimens from two dogs with hepatic disease, J Am Vet Med Assoc 222:47-51, 2003.
28. Kitchell BE, Fan TM, Kordick D, et al: Peliosis hepatic in a dog infected with *Bartonella henselae*, J Am Vet Med Assoc 216:519-523, 2000.
29. Chapman BL, Hendrick MJ, Washabau RJ: Granulomatous hepatitis in dogs: nine cases (1987-1990), J Am Vet Med Assoc 203:680-684, 1993.
30. Wallace KP, Center SA, Hickford FH, et al: S-adenosylmethionine (SAMe) for the treatment of acetaminophen toxicity in a dog, J Am Anim Hosp Assoc 38:246-254, 2002.
31. Song Z, McClain CJ, Chen T: S-Adenosylmethionine protects against acetaminophen-induced hepatotoxicity in mice, Pharmacology 71:199-208, 2004.