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**INTRODUCTION**

*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. A diagnosis of these conditions is based on histopathologic examination of hepatic biopsy specimens. The histopathologic appearance will give clues as to the duration of the inflammation. Acute hepatitis is characterized by a combination of inflammation, hepatocellular apoptosis, necrosis, and possibly regeneration, but there is a lack of fibrosis. Chronic hepatitis (CH), on the other hand, is identified by the presence of fibrosis, proliferation of ductular structures, and regenerative nodules in addition to the inflammatory infiltrate. The type of inflammatory cellular infiltrate may give the clinician some clues regarding the etiology. Occasionally, etiologic agents will be identified within biopsy specimens. However, the etiology remains unknown for many cases of hepatitis and cholangiohepatitis in dogs and cats. This chapter will discuss the clinical presentation of animals with hepatitis and cholangiohepatitis and outline 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 127, Hepatic Failure.

**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 owner and history and thus raise the suspicion for hepatic involvement. It is important to remember that because of the large reserve capacity of the liver, a short duration of clinical signs does not necessarily indicate acute disease. Animals with CH may not show outward clinical signs until a significant portion of their 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 will 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 whereby hepatitis and cholangiohepatitis lead to hepatocellular necrosis and apoptosis is incompletely understood. 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. 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 hepatitis. Experimental work in mouse models suggests an important role for tumor necrosis factor-alpha (TNF-α) in the initiation and perpetuation of hepatitis. TNF-α, production of which is induced by 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. 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 126-1 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-Cholangiohepatitis Complex**

The feline cholangitis-cholangiohepatitis complex is one of the most common hepatobiliary disorders in cats. This syndrome has been reported in dogs but is primarily a feline disease. Several classification schemes have been proposed to define the various elements of this syndrome. Recently, the world small animal veterinary association (WSAVA) Liver Standardization Group proposed a classification system that divides feline inflammatory liver disease into two main categories: neutrophilic cholangitis and lymphocytic cholangitis.

**Neutrophilic Cholangitis**

Neutrophilic cholangitis (NC) is characterized by infiltration of neutrophils within the wall or lumen of intrahepatic bile ducts. This disease can be seen in both acute and chronic stages. In the acute stage, edema and neutrophilic inflammation may extend into the portal areas. In the chronic stage, a mixed inflammatory infiltrate may be noted in portal areas, along with varying degrees of fibrosis and bile duct hyperplasia. This syndrome was previously referred to as acute cholangiohepatitis or supplicative cholangitis-cholangiohepatitis.

Extrapolating from data using other classification schemes, it is likely that affected cats will be young to middle-aged with a male predisposition. Duration of illness is usually short (<5 days). Anorexia, weight loss, lethargy, and vomiting are common. Many cats are febrile and most animals have elevated serum alanine aminotransferase (ALT) activity at the time of presentation, with fewer numbers having elevated alkaline phosphatase (ALP) activity. Icterus is present in over 50% of cases. Cholangiohepatitis in cats has been associated with inflammatory bowel disease (IBD) and pancreatitis.

**Box 126-1 Causes of Hepatitis and Cholangiohepatitis in Dogs and Cats**

| Idiopathic                                      | Leishmaniasis                   |
|-------------------------------------------------|---------------------------------|
| Canine chronic hepatitis                        | Cytaxozoonosis                  |
| Feline cholangitis-cholangiohepatitis complex    | Hepatocoxoniosis                |
| Nonspecific reactive hepatitis                   | Schistosomiasis                 |
| Lobular dissecting hepatitis                     | Coccidiosis                     |
| **Viral**                                        |                                 |
| Infectious canine hepatitis (adenovirus type 1)  |                                 |
| Acidophil cell hepatitis                         |                                 |
| Herpesvirus (neonates)                          |                                 |
| Feline infectious peritonitis                    |                                 |
| **Bacterial**                                    |                                 |
| Feline cholangitis-cholangiohepatitis complex    |                                 |
| Leptospirosis                                    |                                 |
| Bartonellosis                                    |                                 |
| Tyzzer's disease (*Clostridium piliformis*)      |                                 |
| Salmonellosis                                    |                                 |
| Listeriosis                                      |                                 |
| Tularemia                                        |                                 |
| Brucellosis                                      |                                 |
| Yersiniosis                                      |                                 |
| *Helicobacter* spp                              |                                 |
| Mycobacteria                                     |                                 |
| Septicemia                                       |                                 |
| **Rickettsial**                                  |                                 |
| Ehrlichiosis                                     |                                 |
| Rocky Mountain spotted fever                     |                                 |
| **Protozoal**                                    |                                 |
| Toxoplasmosis                                    |                                 |
| Neosporosis                                      |                                 |
| **Parasitic**                                    |                                 |
| Visceral larval migrants                         |                                 |
| Dirofilariasis (caudal vena caval syndrome)      |                                 |
| Liver fluke migration                            |                                 |
| **Fungal**                                       |                                 |
| Histoplasmosis                                   |                                 |
| Blastomycesis                                    |                                 |
| Coccidioidomycosis                              |                                 |
| Aspergillus (disseminated)                       |                                 |
| Phycomycosis                                     |                                 |
| Algal                                            |                                 |
| Protothecosis                                    |                                 |
| **Select Drugs and Toxins**                      |                                 |
| Amiodarone                                       |                                 |
| Aspirin                                          |                                 |
| Carprofen                                        |                                 |
| Halothane                                       |                                 |
| Ketonazol                                       |                                 |
| Lomustine                                        |                                 |
| Methimazole                                      |                                 |
| Phenobarbital                                    |                                 |
| Phenytoin                                        |                                 |
| Primidone                                        |                                 |
| Trimethoprim/sulfadiazene or sulfamethoxazole    |                                 |
and many investigators believe that NC is the result of an ascending bacterial infection from the gastrointestinal (GI) tract. However, bacterial organisms have been isolated inconsistently from cases reported in the literature. When isolated, common bacterial species include *Escherichia coli*, *Enterococcus* spp, *Clostridium* spp, *Bacteroides* spp, *Actinomyces* spp, and *Streptococcus* spp. Hepatic tissue, bile, or both should be submitted for aerobic and anaerobic culture as part of the diagnostic workup for any cat suspected of having hepatitis. Treatment with a broad-spectrum antibiotic combination aimed at enteric flora is recommended pending results of culture and sensitivity 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 by a mixed inflammatory infiltrate (typically small lymphocytes, or lymphocytes and plasma cells) within portal areas with associated signs of chronicity including bile duct proliferation, bridging fibrosis, and pseudodolobule formation. Inflammation within the walls or lumens of intrahepatic bile ducts may be present, but is not a specific hallmark of the disease. LC probably includes a wide spectrum of clinical diseases with varying severity and clinical significance. LC likely includes syndromes that have previously been referred to as chronic cholangiohepatitis, nonsuppurative cholangitis-cholangiohepatitis and lymphocytic portal hepatitis. Extrapolating from data using other classification schemes, it seems that cats with LC tend to be older than those with NC. Clinical signs are similar to those seen in NC with the exceptions that fever is uncommon, the onset of illness is more insidious, and the duration of illness tends to be longer in cats with LC. Elevations of serum ALT, ALP, and total bilirubin are common as in NC, but cats with LC tend to have higher ALP than those with NC. The etiology 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. Active infection has been rarely documented in cats with LC. 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.

**Canine Chronic Hepatitis**

Although many causes of chronic hepatic inflammation in dogs have been identified, the term *chronic hepatitis* (CH) describes a progressive necroinflammatory disease of unknown etiology that is common in the canine population. Evidence supports an immune-mediated process as the perpetuating factor, although it is unclear whether the disease is autoimmune in nature or if an outside insult incites the 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 elevated hepatic enzyme activity that is noted on routine serum biochemical screening.

Animals of any age and sex are affected, although middle-aged female dogs may be overrepresented. CH is seen with increased frequency in certain breeds (Box 126-2), suggesting a familial predisposition. No specific diagnostic findings separate CH from other causes of hepatitis. Ultimately, the diagnosis is based on histopathologic examination of liver tissue revealing inflammation (usually lymphocytic and plasmacytic), piecemeal or bridging necrosis, and possibly fibrosis and/or hyperplasia of ductular structures and the absence of an identifiable underlying cause. The optimal treatment protocol for animals with CH has not been well studied, but immunosuppressive therapy is the mainstay of treatment. Corticosteroids are the only class of drug shown to potentially benefit 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. 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 CH is unclear. Elevated hepatic copper levels have been identified in many dogs with CH, but because biliary excretion is the major mechanism of maintaining copper homeostasis, any cause of cholestasis would be expected to increase hepatic copper levels. However, it has been shown in the Bedlington Terrier that elevated copper levels (caused by an inherited defect in excretion) will lead to CH and cirrhosis. 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 CH has been described for many breeds in addition to the Bedlington Terrier, and these are listed in Box 126-2.

A suspected primary hepatic copper storage disorder has also been reported in one cat. Whether the copper accumulation is a primary or secondary event, it is possible that 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 CH. It is recommended that hepatic tissue be harvested 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.

**Box 126-2 Breeds Predisposed to Chronic Hepatitis**

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

*Proven or suspected copper-associated hepatopathy.
**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. 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 quite rare owing to extensive vaccination protocols using the cross-reacting adenovirus type II. As such, the disease is only seen 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 inclusions within hepatocytes and Kupffer cells that are identified during the first week of infection. Histo-pathology will also reveal multifocal coagulation 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 elevated activities of ALT and aspartate aminotransferase (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. When hepatic involvement occurs, the disease is uniformly fatal. Because there is no definitive treatment, supportive care is the mainstay of treatment.

**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 *L. icterohaemorrhagiae*, *L. canicola*, *L. pomona*, *L. hardjo*, *L. grippotyphosa*, and *L. bratislava*. Infection in dogs most commonly results in acute renal failure, although hepatic involvement may occur in 20% to 35% of cases. It has been suggested that infection in young animals and infection with serovars *L. icterohaemorrhagiae* and *L. pomona* are more likely to result in hepatic involvement. Affected dogs may show acute hepatitis or develop CH with subclinical acute infection.

Although cats are generally resistant to leptospirosis, experimental infection with *L. pomona* has caused hepatic lesions in this species. Patients with hepatic involvement will show elevated levels of hepatic enzymes (ALT, AST, ALP), although ALP is often most severely affected. Hyperbilirubinemia and signs of hepatic failure may occur. Diagnosis of leptospirosis is usually based on clinical suspicion due to 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. 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 very insensitive. Molecular techniques such as polymerase chain reaction (PCR) are likely to make this diagnosis less challenging in the future. Optimal treatment includes penicillin to eliminate the leptospiroemic stage, followed by doxycycline or enrofloxacin to eliminate the carrier state. (Note: the use of enrofloxacin in dogs that cannot tolerate doxycycline has not been well studied.) Prognosis is typically good, but patients often require intensive supportive care, including hemodialysis in animals with oliguric or anuric renal failure.

**Bartonellosis**

*Bartonella henselae* and *Bartonella clarridgeiae* have been identified as causes of hepatic disease in dogs. These arthropod-transmitted bacteria are the etiologic agents of cat-scratch disease in humans and have been isolated from approximately 30% of healthy cats. 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 and granulomatous hepatitis, 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 is frequently unknown, although reported causes include fungal infection, mycobacterial infection, dirofilariasis, lymphoma, histiocytosis, and intestinal lymphangiectasia. 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 thoroughly evaluated.

**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. The diagnosis of bacteremia can be difficult in veterinary patients. 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 main histologic lesion associated with toxic hepatic injury is diffuse centrilobular necrosis. Depending on the temporal relationship between toxin ingestion and tissue biopsy, necrosis may be accompanied by apoptosis or inflammation. Lymphocytic or plasmacytic cellular infiltrates may occur later in the course of disease and have been described commonly with amiodarone, carprofen, and lomustine intoxications. Phenobarbital, primidone, and phenytoin may cause CH that can progress to cirrhosis with prolonged use. Several other drugs reported to cause hepatitis are noted in Box 126-1, but this is by no means an exhaustive list. 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. Although its efficacy 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.

SUGGESTED FURTHER READING*

Center SA: Acute hepatic injury: Hepatic necrosis and fulminant hepatic failure. In Guilford WG, Center SA, Strombeck DR, Williams DA, Meyer DJ, editors: Strombeck’s small animal gastroenterology, ed 3, Philadelphia, 1996, Saunders. An excellent review chapter. Although from an older text, most information current. Gives information regarding several causes of acute hepatitis.

Center SA: Chronic hepatitis, cirrhosis, breed-specific hepatopathies, copper storage hepatopathy, suppurative hepatitis, granulomatous hepatitis, and idiopathic hepatic fibrosis. In Guilford WG, Center SA, Strombeck DR, Williams DA, Meyer DJ, editors: Strombeck’s small animal gastroenterology, ed 3, Philadelphia, 1996, Saunders. Another excellent review from this older text discussing the causes of CH in dogs and cats in great detail.

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, 1999. A retrospective study describing the clinical signs and clinicopathologic findings in cats with inflammatory liver disease. Diseases classified as acute cholangiohepatitis, chronic cholangiohepatitis, or LPH.

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, 2003. A case series describing two cases of canine hepatic disease where Bartonella species were isolated from hepatic tissue via polymerase chain reaction.

Johnson SE: Chronic hepatic disorders. In Ettinger SJ, Feldman EC, editors: Textbook of veterinary internal medicine, ed 6, St Louis, 2005, Saunders. An excellent review of workup and treatment for animals with chronic hepatic disorders containing particularly useful information regarding canine CH.

*See the CD-ROM for a complete list of references.