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Infectious Hepatopathies in Dogs and Cats

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This article serves to review the various infectious diseases that affect the liver primarily or as a part of systemic infection. Although bacterial infections are probably the most common cause of infectious hepatitis, the clinician should be aware of other potential organisms and other commonly involved systems. Therefore, this article includes a description of common bacterial, mycobacterial, viral, fungal, protozoal, parasitic, and rickettsial diseases in dogs and cats.

Keywords: liver, hepatitis, Kupffer cells, canine diseases, feline diseases, infectious diseases

The liver plays a major role in guarding against infections because of its central position between the enteric and systemic circulation. Tissue macrophages (Kupffer cells), a key component in the prevention of hepatic and systemic infections, encompass approximately 35% of nonparenchymal liver cells. The liver's location, dual blood supply, and extensive sinusoidal system render it susceptible to disseminated infectious organisms, toxins, immunoreactive substances, and gut-derived debris and organisms when normal defense mechanisms fail.[1,2] This occurs despite its remarkable capacity to protect against infection. Conditions including ischemic or hypovolemic injury, cholestasis, chronic liver disease, portal hypertension, portovascular anomalies, endotoxins, and immune dysfunction all contribute to hepatic susceptibility to infection and alter the function of the reticuloendothelial system.[2,3] In addition, the extensive sinusoidal endothelium within the liver provides an ideal environment for vasculotropic organisms.

Clinical signs, biochemical and hematologic parameters, and diagnostic imaging associated with hepatobiliary infections are nonspecific and frequently do not identify the primary agent of infection. Clinical signs of hepatic disease include fever, hepatosplenomegaly, lethargy, jaundice, vomiting, diarrhea, weight loss, polyuria/polydipsia, and abdominal pain. Testing should be tailored to patient signalment, geographic location, and any specific indicators in the history and physical examination. Additional testing may be indicated based on the types of inflammatory responses identified in liver biopsies.

Bacterial Infections

Alimentary flora circulates to the liver under various clinical conditions. These bacteria are extracted by Kupffer cells, killed by neutrophils, or excreted in bile in healthy clinical states. A low-flow, low-pressure perfusion of hepatic sinusoids may allow superior removal of bacteria by phagocytes, and pressure differentials in the biliary system may limit retrograde access of enteric organisms.[2,4,5] Changes in this sinusoidal flow may decrease the effectiveness of phagocytosis when portal flow is compromised. Bowel disease, cholestasis, immunosuppression, and altered gut motility result in altered portal circulation, and the subsequently unchecked bacterial access to the liver may result in bacterial hepatitis or cholangiohepatitis. Common isolates implicated in bacterial hepatitis and cholecystitis include *Escherichia coli*, *Enterococcus* spp, *Bacteroides* spp, *Streptococcus* spp, and *Clostridium* spp.[6] Cultures can be obtained by liver aspirate, liver biopsy, and cholecystocentesis. A combination of liver and gall bladder samples (Fig 1) may increase the likelihood of identification of the offending organism(s). Surgical or laparoscopic biopsies may be more rewarding for culture growth compared with aspirates.[6] In suspected cases, broad-spectrum antibiotics for common enteric isolates should be initiated pending specific culture results.

Focal micro- and macro-abscesses have also been documented in dogs and cats.[7,8] Predisposing causes include alterations in blood flow, trauma, ascending biliary infections, liver lobe torsions,[9] immunocompromised clinical states,[10] and neoplasia.[7,11] Microabscesses are often identified in association with extrahepatic infection and sepsis.[7,12] Ultrasound has greatly enhanced the early diagnosis of hepatic abscesses.[8] Greater than 50% of solitary abscesses are polymicrobial. Antimicrobial treatment should be directed at both anaerobes and aerobes regardless of whether anaerobic cultures are negative if a polymicrobial hepatic infection is documented.[2] Bacterial isolates in hepatic abscesses are similar to those identified in diffuse bacterial hepatic disease. However, clinically rare isolates including *Klebsiella*, *Listeria*, *Salmonella*, *Brucella*, *Yersinia pseudotuberculosis*, *Actinomyces*, *Nocardia*, and *Pasturella* have also been documented.[13] Focal abscesses may require surgical drainage and antibiotic therapy. Treatment in all cases must be implemented for a minimum of 6 to 8 weeks.

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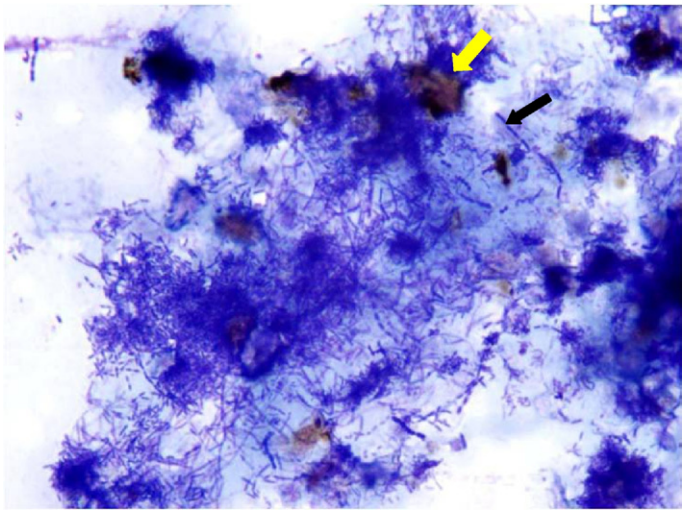

Figure 1. Fine-needle aspirate and cytology from the gallbladder of a cat with cholangiohepatitis. The aspirate consists predominantly of bacteria of mixed type. The bacteria are frequently present in chains (*black arrow*). Also, note dark brown–staining amorphous material (bile pigment: *yellow arrow*). The finding of bacteria in cytologic specimens of bile is considered abnormal. The following organisms were cultured from the bile: *Escherichia coli*, *Streptococcus pneumoniae*, an anaerobic bacterial rod, *Prevotella oralis*, and a Gram-positive rod that could not be classified. Courtesy of the Pathology Department, Angell Animal Medical Center, Boston, Massachusetts.

Leptopirosis is an extremely common nonenteric bacterial infection in the canine liver. Leptospires are thin, filamentous, spiral-shaped motile bacteria with a lipopolysaccharide outer envelope. Direct transmission occurs via contact with infected urine, venereal and placental tissues, or fluids. Indirect transmission can occur through contaminated water sources, soil, food, or bedding. The organism can stay stable for several months with the right environmental conditions. The organism initially penetrates the mucous membranes and rapidly multiplies after entry into the vascular space. Dissemination and replication occur in many tissues, including the liver. However, the organism tends to persist in the kidney and can be shed for weeks to months after infection. Certain serovars are more frequently associated with hepatic involvement and include *Leptospira icterohaemorrhagiae* and *L. pomona*. Young dogs (<6 months of age) seem to develop signs of hepatic dysfunction more frequently in disease outbreaks.[14] Profound hepatic dysfunction may occur without significant histologic changes because of subcellular damage produced by bacterial toxins. The endothelial damage, subsequent thrombosis, and possible disseminated intravascular coagulation seen in acute disease may contribute to hepatic damage. Chronic hepatitis has been reported as a sequelae to leptospiral infection.[15,16] Diagnosis is usually made based on clinical signs and serologic titers. However, leptospirosis polymerase chain reaction (PCR) performed before treatment may increase testing sensitivity given vaccinal interference and delayed seroconversion in the acute phase.[17] Penicillins are the treatment of choice in the acute phase and must be followed by appropriate antibiotics to eliminate the carrier state. Alternatively, doxycycline may be used for both the acute and carrier states.

Bartonella spp are Gram-negative fastidious bacteria and are well adapted for the intracellular environment. A recent case report documented *B. henselae* and *B. clarridgeiae* DNA in the liver of 2 dogs with granulomatous inflammation. Both had a positive clinical response to azithromycin and demonstrated biochemical reduction in hepatocellular enzymes.[18] Another dog with peliosis hepatitis (a rare vascular condition characterized by multiple, randomly distributed blood-filled cavities throughout the liver) had *B. henselae* DNA amplified from multiple hepatic specimens by PCR.[19]

Helicobacter canis has been isolated from the liver of a single dog with hepatitis.[20] *Helicobacter* spp have also been amplified from hepatic tissue in cats with cholangiohepatitis. Further studies are required to determine whether these organisms are associated with inflammatory liver disease. These organisms are difficult to culture, and this failure may reflect the fastidious nature of these bacteria. PCR positivity may reflect the presence of intestinal helicobacter from the enterohepatic circulation or transient colonization rather than a true disease association.[21]

Francisella tularensis (tularemia) is a pleomorphic, Gram-negative, nonspore-forming bacillus. This disease frequently occurs as a result of exposure to ticks or wildlife. Macrophages are the primary host cells, and bacteremia with multiorgan involvement is common. Lungs, spleen, liver, and skin are common sites for embolic spread, resulting in microabscesses and granulomatous disease. Puppies and young cats appear more susceptible to infection, and dogs are generally more resistant to infection. Clinical findings include depression, oral/lingual ulceration, regional or generalized lymphadenomegaly, hepatosplenomegaly, panleukopenia with severe toxic neutrophil changes, hyperbilirubinemia, and bilirubinuria.[22–24] Examination for evidence of microscopic agglutinating antibody is most frequently used for diagnosis, although indirect fluorescent antibody testing may be useful as well.[24] Aminoglycosides are the primary treatment in humans. However, tetracyclines (doxycycline), chloramphenicol, and quinolones are commonly used in dogs and cats. Unfortunately, clinical relapse is common with these antibiotics.

Tyzzer's disease (*Clostridium piliforme*) is caused by a flagellated, spore-forming, Gram-negative intracellular parasite. Although spores have been identified in rodent species, interspecies transmission via ingested feces has not been documented. However, spontaneous disease has been documented in dogs and cats.[25–28] Colonization of the liver results in multifocal, periportal hepatic necrosis and may result from a currently unidentified toxin.[29] Minimal inflammation may be present despite extensive necrosis.[30] Death usually occurs within 24 to 48 hours once the organism is in the liver.[31–37]

Rhodococcus is a soil-borne pleomorphic, Gram-positive bacteria normally associated with suppurative infections in

domestic livestock. Inhalation from soil or wound inoculation are the suspected routes of transmission. Disseminated infection and death have been reported in a single dog.[38] Clinical reports are rare in cats.

Mycobacterial Infections

Mycobacterium spp are aerobic, nonspore-forming, nonmotile bacteria with a wide host affinity and pathogenic potential. They are typically classified based on growth in culture and by the pathologic production of tubercles or granulomatous disease. *Mycobacterium tuberculosis* and *M. bovis* are the most pathogenic, and humans are reservoirs for these species. Aerosolized organisms in sputum are considered the primary mode of transmission. However, *M. bovis* can be acquired via uncooked meats and wildlife reservoirs. Mycobacterial disease is often subclinical in dogs and cats, but signs may be associated with granuloma formation in various organs.[39,40]

Nontuberculous mycobacterium, including those in the *Mycobacterium avium* complex, are saprophytic opportunistic organisms primarily implicated in disseminated disease in cats[41–45] and occasionally in dogs.[46–53] No clear associations have been identified with retroviral diseases. Canine and feline breeds with potentially increased susceptibility include Basset hounds,[51] Miniature schnauzers,[53] Siamese,[45] and Abyssinians.[42] Dogs with *M. avium* complex–induced disease will often demonstrate extensive granulomatous disease of the intestine, spleen, liver, and mesenteric lymph nodes. Animals undergoing immunosuppressive drug therapy with inhibition of cell-mediated immunity may be at risk for disseminated disease, including renal transplant patients.[43] Acid-fast cytology can demonstrate bacilli, although false negatives can occur. Negative bacterial images may be identified on routine stains (Fig 2). PCR may provide greater sensitivity and safety than culture.[52] Combination therapies are often required, because organisms build resistance quickly, particularly with disseminated disease. Although not a risk for immunocompetent individuals, dogs and cats infected with saprophytic mycobacterium pose a risk for immunodeficient people.

Mycobacterium lepraemurium was considered the main causative agent for feline leprosy until recently. However, *M. visibilis* has been associated with feline multisystemic granulomatous mycobacteriosis, resulting in diffuse cutaneous disease and widespread dissemination to multiple internal organs.[54]

Fungal Infections

Organisms responsible for disseminated fungal infections include *Histoplasma capsulatum*, *Coccidioides immitis*, *Blastomyces dermatitides*, *Aspergillosis* sp, *Cryptococcus*sp, and *Sporothrix schenckii*. Most are dimorphic, saprophytic, opportunistic fungi that exist in the mycelial stage in the environment. Spores are produced in the mycelial stage and become pathogenic on inhalation, ingestion, or inoculation. Dissemination occurs via the hemolymphatic system. Specific environmental conditions are required for the individual organisms, and this dictates their geographic range.

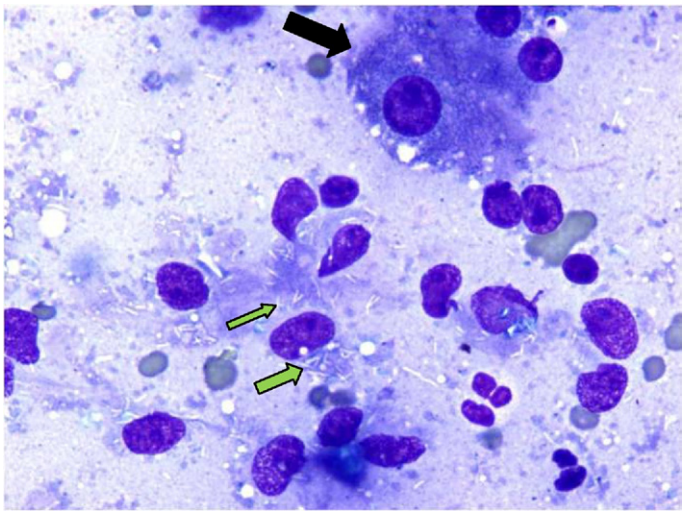

Figure 2. *Mycobacterium* in the liver of a cat. The aspirate consists of hepatocytes (*black arrows*) admixed with inflammatory cells that include macrophages and fewer small lymphocytes, plasma cells, and neutrophils. Numerous extracellular and intracellular (within macrophages) negative images of bacterial rods are seen (*green arrows*). Courtesy of the Pathology Department, Angell Animal Medical Center, Boston, Massachusetts.

Histoplasma capsulatum is located primarily in the temperate and subtropical areas of the world. Organisms are phagocytized by mononuclear cells and replicate intracellularly once they are inhaled and converted to the yeast phase. The primary clinical signs in dogs are associated with the gastrointestinal system (diarrhea, tenesmus, mucous, fresh bloods in stools). Clinical signs in cats are vague. Dissemination to other visceral organs (including the liver) has been documented in both species.[55–57] Clinically affected animals are usually young (1-4 years of age). Diagnosis is usually achieved with fine-needle aspirate or exfoliative cytology of affected organs.

Aspergillosis is primarily associated with rhinitis. However, several reports have documented systemic infections in German shepherds and in non-shepherd breeds. *Aspergillus terreus*[58–62] and *A. deflectus*[63,64] have been most frequently implicated in systemic infection. Predisposing factors include optimal climatic conditions, access to a partial strain, or subtle defects in mucosal immunity.[65] Disseminated aspergillosis has also been documented in cats.[66,67] Neurologic deficits, spinal column pain, urinary system disorders, and respiratory pathology are the primary presenting clinical signs.

Prototheca is a saprophytic, achlorophyllous alga found in the southeastern United States. Three species of *Prototheca* have been identified, but *P. zopfii* is the only one associated with disseminated disease. The organism is associated with

sewage, slime flux of trees, and animal waste. Transmission generally occurs through ingestion or penetration of injured skin or mucosa. Disease can develop with diminished host resistance or concurrent diseases.[68] Concomitant large intestinal diarrhea and ocular signs should prompt clinical consideration of *Prototheca* infection. Dissemination via blood or lymph to other organs including the liver is common. Various stages of development of the organism may be identified on cytology or histopathology. Urine culture and sediment are also useful in organism identification.[69] This disease is invariably fatal, although disease progression may be delayed with various antifungal and antibacterial agents.[70–73]

Coccidioides immitus is a dimorphic fungus with preference for the alkaline sandy soil environment found in the lower Sonoran life zone in the southwestern United States, western Mexico, and Central and South America. Mycelia are produced during rainfall, but arthroconidia develop with soil drying and become airborne under dry and windy conditions. Inhalation is the primary mode of infection in dogs and cats. The spherule (tissue parasitic form) undergoes division with eventual rupture. The severity and extent of clinical disease depend on immunocompetence and range from a mild, asymptomatic, pulmonic form to severe, life-threatening disseminated disease. Dissemination most commonly involves the axial and appendicular skeleton and overlying skin. Tissues from abdominal viscera, the central nervous system (CNS), pericardium, myocardium, and prostate can also be involved.[74,75] Cytology or histology may reveal spherules, although diagnosis is often made based on history, clinical signs, and positive serology. Antigens for sero-testing commonly use tube precipitin and complement fixation with agar gel immunodiffusion.

Sporothrix schenckii causes a chronic granulomatous disease of worldwide distribution. Infection is usually the result of trauma and inoculation with infective conidiophores. The skin is the primary target organ. However, disseminated disease has been reported, particularly in the cat. No clear dissemination pattern has been identified because of low case numbers, but affected organs include the internal lymph nodes, liver, lungs, eyes, bone, muscles, and CNS.[76,77] Diagnosis is frequently made by cytology.

Blastomyces dermatitidis is found primarily in Mississippi, Missouri, the Ohio River Valley, the mid-Atlantic states, and some Canadian provinces. Growth of the organism requires sandy, acidic soil with some proximity to water. Preferred sites for dissemination include the skin, eyes, bones, and lymph nodes, although dissemination to the liver has been reported.[78,79] *Cryptococcus neoformans* has a worldwide distribution. Inhalation may be the primary mode of infection, and sites of infection tend to be areas of the body with cooler temperatures, including the respiratory passages and subcutaneous tissues. The fungus is occasionally disseminated to the kidneys and rarely to the liver.[80]

Treatment of most disseminated fungal infections involves the use of triazoles, including itraconazole and fluconazole, as well as amphoterocin B.[59,81–85] Clinical signs may resolve in many cases, but relapses occur and patients with severe clinical illness generally have a poor prognosis.

Protozoal Infections

Leishmania, transmitted by the sandfly (*Lutzomyia* in the New World, *Phlebotymus* in the Old World), frequently causes cutaneous and visceral lesions in the dog. Promastigotes transmitted by the female sandflies become amastigotes in the vertebrate and are phagocytized by mononuclear cells. The organism travels through hemolymph organs to remote dermal sites and other organs. Clinical signs will not develop in all exposed animals, and the immune response at the time of infection appears important in determining development of disease. *Leishmania* infection should be considered in dogs from endemic areas with marked hyperglobulinemia or in those with a travel history to endemic areas. Mild increases in liver enzymes are often noted. However, unlike the kidneys, the liver is not a primary target organ. Infection can be associated with chronic hepatitis.[86] Definitive diagnosis is made by demonstration of organisms on cytology or histopathology, or by serology, culture, or PCR. Amphotericin B in a soybean oil lipid emulsion has been intravenously administered for higher clinical cure success rates and greater numbers of negative posttreatment parasitologic tests compared with other treatments. Other less successful treatment options include allopurinol and the pentavalent antimonials.[87]

Hepatozoon canis is a worldwide protozoal disease reported in domestic dogs and is most prevalent in subtropical and temperate climates. The primary vector is the *Rhipicephalus sanguineous* tick, which is primarily located in warm and temperate regions. Transmission occurs through ingestion of ticks containing mature protozoal oocyts. Sporozoites are released in the intestine on tick ingestion and penetrate the gut wall, invade mononuclear cells, and disseminate. Target organs include the bone marrow, spleen, and lymph nodes but can involve other internal organs such as the liver, kidney, and lungs.[88,89] The most striking clinicopathologic abnormality is leukocytosis with evidence of parasitemia of the white cells on peripheral blood smears. Clinical findings can range from incidental hematologic findings to severe life-threatening illness. Hepatitis, glomerulonephritis, and pneumonitis have all resulted from *H. canis* infection.[90] Coinfections with other protozoal diseases (*Toxoplasma*, *Leishmania*, and *Babesia* spp) or other tick-borne diseases (*Ehrlichia* spp) and immunosuppressive states can predispose animals to clinical illness. The hepatitis is associated with developing meronts within the liver and their associated neutrophilic and mononuclear inflammation. *Hepatozoon* has also been documented in felines.[91-93] Microscopic detection of gamonts in peripheral blood smears is the most frequently used diagnostic test. Imidocarb is the treatment of choice in dogs. Subcutaneous or intramuscular injections are administered every 14 days until gamonts are no longer visualized in the leukocytes.

A new species, *Hepatozoon americanum*, was identified in 1997, with the *Amblyomma maculatum* tick as its definitive

host.[94] This emerging disease has spread to the north and the east since its initial identification in the Gulf Coast region. Clinical signs are often severe, even in the absence of other diseases or in the presence of immunosuppression. Waxing and waning clinical signs are attributed to repeated cycles of asexual reproduction and pyogranulomatous inflammation. The primary site of infection for the merozoites is the cardiac and skeletal muscle. However, single zoites can enter circulation and reproduce asexually at distant locations.[95] Diagnosis is most often made with muscle biopsy, although a recent study has identified promise in the use of PCR testing.[96] An enzyme-linked immunosorbent assay has been developed with sporozoites as the antigen.[97] No treatment effectively eliminates the tissue stages of *H. americanum*. However, treatment with trimethoprim-sulfadiazine, clindamycin, and pyrimethamine followed by long-term administration of decoquinate resulted in extended survival times and an excellent quality of life.[98]

The microsporidial parasite *Encephalitozoon cuniculi* is an obligate intracellular protozoan. Infection likely occurs by inhalation or ingestion of spores from contaminated urine or feces shed by infected hosts. The organism undergoes asexual reproduction or binary fission after infecting host cells and ruptures, leading to infection of new cells or shedding of resistant spores into the environment. Typical organs of localized infection include the kidney, liver, lungs, and brain with resultant granulomatous inflammation.[99,100] Cats and older dogs are not commonly affected, and renal disease predominates in young dogs. Cytological examination of fluids (particularly urine) is important in making a diagnosis in animals with disseminated disease as other tests are commercially unavailable.

Cytauxzoon felis is a tick-borne protozoal disease of domestic and wild cats. The bobcat is the natural reservoir in North America and is usually asymptomatic despite persistent erythroparasitemia. The tissue phase of infection consists of the development of large schizonts in mononuclear phagocytes. The schizonts line the lumens of vessels in most organs, eventually leading to vessel occlusion. Merozoites are released into blood or tissue fluid once the host cells rupture and infect red blood cells. Late-stage parasitemia can often be detected on blood films at about 1 to 3 days before death. Most clinical signs, including those associated with liver abnormalities, are due to schizont-associated mechanical obstruction. However, parasite by-products may also be toxic, pyogenic, and vasoactive. The anemia is regenerative but mild in comparison with clinical icterus. This may be useful in differentiating this infection from hemotropic mycoplasmas. Demonstration of piroplasms in Wright's-stained or Giemsa-stained blood films most frequently provides a definitive diagnosis. Histopathology reveals schizont-laden mononuclear phagocytes in the veins of the lungs, liver, and spleen. The prognosis is generally considered poor, but different geographic strains may have varying virulence.[101] Treatment with diminazene or imidocarb has been somewhat successful.[102]

Toxoplasma gondii is an obligate intracellular coccidian parasite that infects almost all warm-blooded animals. Domestic cats are the definitive hosts and excrete the infective oocyts. Three stages of the life cycle are considered infectious, including oocyst sporozoites, tissue cyst tachyzoites, and tissue cyst bradyzoites. Transmission can occur through ingestion of oocysts or tissue cysts and via congenital transmission. Other reported modes include lactation, transfusions, and transplantation.[103] A higher frequency of disease is reported in dogs and cats fed raw meat or those in a rural/feral environment. The extra-intestinal life cycle is the same in all hosts, and sporozoites encyst in the intestinal lumen, penetrate cells, and divide into tachyzoites. The tachyzoites can form cysts in the CNS, muscle, and visceral organs, and may persist for the life of the host. Clinical signs were diverse in 100 cats with histologically confirmed toxoplasmosis, and more than 90% had pulmonary, CNS, and liver manifestations.[104,105] In dogs, disseminated infection is most often associated with canine distemper, other infections including ehrlichiosis and immunosuppression, or vaccination with live attenuated vaccines.[106] Clinical cases in cats have been seen with steroids, cyclosporine use, hemotropic mycoplasms, and viral disease.[107–109] Liver and lung involvement is associated with quicker mortality than other organ involvement. Tachyzoites may be detected on cytology of various organs and body fluids. However, diagnosis is most frequently based on clinical signs, serology (immunoglobulin G, immunoglobulin M), and response to treatment. Clindamycin is the treatment of choice.

Neospora caninum is a protozoan similar to *Toxoplasma*. Dogs and coyotes are considered definitive hosts, and deer and cattle are intermediate hosts. The predominant mode of transmission is transplacental in the dog, and clinical signs are usually secondary to exacerbation of a congenital infection. Acute phases of infection include widespread dissemination to many organs, including the liver, whereas chronically infected animals are restricted to muscular and neuronal sites.[103] Serology and muscle biopsy often provide a diagnosis, although tachyzoites may be detected in other parasitized tissue or body fluid.[110]

Sarcocystis canis is an apicomplexan protozoan with no particular geographic distribution. Infection results in disseminated disease, including protozoal hepatitis.[111,112] Many reports involve puppies, suggesting the presence of congenital infection. However, the life cycle is still unknown. *Sarcocystis canis* is the only *Sarcocystis* species known to form schizonts in canine tissue.

Viral Disease

Infectious canine hepatitis (ICH) is caused by adenovirus type 1. This is the only virus with primary tropism for the liver.[113] Infection leads to severe hepatic necrosis and can also cause ocular and renal changes. The virus localizes in the tonsils after oronasal exposure, spreads to regional lymph nodes, and disseminates via the thoracic duct. Hepatic parenchymal cells and vascular endothelial cells are the prime targets of viral localization, and injury leading to centrilobular to panlobular hepatic necrosis ranges from self-limiting to

fatal. Most affected dogs are less than 1 year of age and unvaccinated. Severely affected dogs can become moribund and die within hours of disease onset and with few predictive clinical signs. If patients survive the acute phase, they may develop clinical signs including vomiting, diarrhea, and abdominal pain.[114,115] Those that survive may go on to develop chronic hepatitis and fibrosis, likely secondary to self-perpetuating liver inflammation rather than chronic infection.[116] Diagnosis is frequently made based on clinical signs and serology, although the virus can be isolated in cell cultures. This disease is rarely encountered because of the high efficacy of vaccination.

Canine acidophil hepatitis is believed to be caused by a viral agent. However, the specific agent is not yet identified. Disease has been reproduced via injections of sterile liver homongenates from spontaneously affected animals. Acute infections can lead to acute to chronic hepatitis, cirrhosis, and hepatocellular carcinoma. Diagnosis is made on histology because acidophils are scattered throughout lesions. This disease has only been reported in Great Britain.[117,118]

Canine herpesvirus causes tissue necrosis and localized mucosal or generalized systemic infections in young or immunocompromised animals. The virus only infects dogs because of specific cell-surface receptors. Replication occurs via viral DNA synthesis within the host nucleus. Transmission occurs through direct contact with mucosal secretions from the respiratory or genital tract of animals. Factors predisposing to infection in puppies include hypothermia and a poorly developed immune system. Newborns can acquire disease in utero, during passage through the birth canal, during contact with infected littermates, from oronasal secretions of the dam, and from fomites. Puppies less than 1 week of age are more susceptible to generalized fatal infections. Dissemination leads to hemorrhagic necrosis in several organs including the adrenal glands, kidney, liver, lungs, and spleen. Clinical signs include loss of interest in nursing, loss of body weight, soft yellow-green feces, abdominal discomfort, and dullness. A marked increase in alanine aminotransferase is often noted on biochemistry profile. Definitive diagnosis is by viral isolation.[119]

Feline leukemia virus is a single-stranded retrovirus that replicates in many tissues. Clinical illness is generally related to the hematopoietic system and the immune system. Feline leukemia virus has also been associated with icterus and various inflammatory and degenerative liver diseases including focal liver necrosis.[120]

Feline infectious peritonitis (FIP) is a feline coronavirus that has undergone frequent RNA mutations, resulting in an ability to enter and replicate in macrophages. An immune-mediated vasculitis occurs if the virus is not eliminated. Affected cats develop signs related to target organ lesions (kidney, liver, CNS, intestine) or due to fluid redistribution. Abnormal liver enzymes can occur because of hepatitis, hepatic lipidosis, or prehepatic sequalae of vasculitis, erythrocyte destruction, and hypoxia. Hyperbilirubinemia is common and usually secondary to vasculitis in the liver.[121] Histopathology is required for definitive diagnosis but is supported by history, physical examination, and laboratory findings. A new PCR test may also prove useful in the diagnosis of FIP.[122] Treatment is generally unrewarding. Conflicting information exists on the usefulness of feline recombinant interferon, although it may be beneficial for a subpopulation of FIP-infected cats.[123,124]

Rickettsial Diseases

The most common agents encountered in dogs with clinical evidence of liver involvement include the *Ehrlichia* sp, *Rickettsia rickettsii*, and *Borrelia burgdorferi*. These organisms can infect either hepatocytes or endothelial cells. Hepatic involvement in *Erhlichia* infections occurs in more than 80% of human patients, leading to mild transient increases in transaminases.[125] Liver injury may be related to organism proliferation in hepatocytes and stimulation of immunologic and nonspecific inflammatory mechanisms. Rocky Mountain Spotted Fever is vasculotropic in nature and can cause moderate increases in transaminases. Experimental evidence with *Borrelia* suggests direct hepatic invasion by the spirochetes in conjunction with cellular and humoral immunologic mechanisms.[126] An association with *Borrelia* was observed and confirmed with liver biopsy in 2 dogs. Lesions were consistent with lobular dissecting hepatitis and mixed multifocal inflammation leading to focal pyogranulomas in the other.[2]

Parasitic Diseases

Chronic cholangitis associated with liver fluke infestation in endemic areas is primarily observed in cats and less frequently in dogs. Most infections are due to *Opistorchus* and *Metorchis*, which require 2 intermediate hosts. The first hosts are water snails, and the second hosts include a wide variety of fish with encysted metacercariae. The final host acquires infection by ingestion of fish, and the young liver flukes migrate to the liver through the bile ducts. This results in bile duct thickening and dilation. Rarely, cysts may be formed as well.[127] A slight to moderate inflammation may be seen both within the ducts and in the portal areas. Although eosinophils may be present, they are usually limited in numbers. The number of liver flukes and eggs within the dilated bile ducts varies markedly, and often only limited evidence of liver flukes or eggs is identified.

Platynosomum concinnum is a trematode of the feline biliary system. Terrestrial snails, lizards, toads, and terrestrial isopods act as intermediate hosts based on geographic location. Disease is most prevalent in the tropical and subtropical climates. Clinical cases involve adult indoor or indoor-outdoor cats. The severity of clinical signs is proportional to the number of adult flukes as well as to the duration of parasitemia. Early diagnosis can be difficult. However, diagnosis is easier when eggs have been identified in the bile.[128] Treatment of *P. concinnum* and liver fluke infections is best accomplished with praziquantel.

Conclusions

There are many infectious diseases that ultimately affect the liver. Few, however, have primary tropism for hepatic tissue. Testing should be directed based on signalment, geographic locale, and primary presenting complaint. Cytology and/or histopathology of the liver will most frequently provide a definitive diagnosis in clinical situations with liver involvement. The prognosis is guarded with many disseminated infections.

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