Bacterial Cholangitis

Allen Boyd Hardy

March 23, 2017

Advisors:

Dr. Patty Lathan, DACVIM

Dr. Harry Cridge

Introduction

Bacterial cholangitis is a bacterial infection of the gallbladder. The WSAVA guidelines describe four distinct types of cholangitis in dogs; neutrophilic, lymphocytic, destructive, and chronic cholangitis associated with liver fluke infestation.[1] Neutrophilic cholecystitis has been described both with and without bacterial infection and may occur in combination with neutrophilic cholangitis or as a solitary process.[2,3] Bile is generally considered sterile; however, the most common bacteria isolated in cases of bacterial cholangitis are *Escherichia coli* and *Enterococcus* species. [4] There are two main pathogenic theories with regard to route of infection. One route described is hematogenous spread via hepatic portal venous blood and the second potential route is an ascending infection from the duodenum.[2] Bacterial cholangitis can progress to a bacterial cholangiohepatitis, indicating liver parenchymal involvement.[2] Inflammation associated with bacterial cholangitis can lead to a post-hepatic jaundice. Yellow discoloration of the skin sclera is typically observed when the total bilirubin is $\geq$2 mg/dl.[5] The most common clinical signs of bacterial cholangitis or bacterial cholangiohepatitis are jaundice, anorexia, vomiting and pyrexia.[3] Diagnosis of bacterial cholangitis is based of bile cytology and culture, and treatment involves appropriate antimicrobial therapy in addition to supportive care. The prognosis is generally good, if the patient has not progressed to a bacterial cholangiohepatitis and liver failure.

History and Presentation

Petri Harrington, a 6-year-old neutered male Chihuahua, presented to the MSU-CVM Emergency Service on December 12, 2017, for jaundice. The owner first noted that Petri was jaundiced approximately two days prior to presentation, and Petri presented due to worsening jaundice. Petri also had a two-day history of vomiting and inappetence. Petri had previously been

evaluated for weight loss in the summer of 2017. Petri had a prior history of being diagnosed with an open fontanelle with suspected hydrocephalus. The patient was on no medications at the time of presentation.

Upon presentation, Petri was bright, alert, responsive and mentally appropriate. He weighed 2.65 kg. Physical examination revealed a yellow discoloration of the skin and sclera (jaundice), a hypermetric gait, and mild dehydration (~5%). No other indications of liver disease were noted on the physical examination.

Differential Diagnosis for Jaundice

The term jaundice describes the accumulation of bile pigment in tissues, its presence is a major clinical finding and necessitates a full diagnostic work up to determine between pre-hepatic, hepatic and post-hepatic causes of jaundice. [5]

Pre-hepatic causes of jaundice include hemolysis, where the increase in bilirubin production exceeds the ability of the hepatocytes to conjugate and excrete the bilirubin. Hepatic jaundice occurs due to diffuse diseases of the bile ducts or hepatocytes. Post-hepatic jaundice results from extrahepatic cholestasis due to impaired or obstructed flow of bile. Potential causes of pre-hepatic jaundice include immune mediated hemolytic anemia (primary or paraneoplastic), infectious hemolytic anemia or toxic hemolytic anemia (zinc, onion, methylene blue, sulfonamides, copper, penicillins or cephalosporins). These causes were considered unlikely due to the absence of anemia, and no infectious organisms seen on a blood smear. There was no history of access to any compounds or drugs that could lead to a toxic hemolytic anemia. Potential hepatic causes of jaundice include extra-hepatic biliary duct obstruction (EHBDO) due to biliary sludge, stones, pancreatitis or duodenal/pancreatic masses or cholecystitis and

cholangitis. Cholangitis may be more common than previously thought and is being diagnosed with increasing frequency based off cholecystocentesis cytology and culture.

Pathophysiology

The human gallbladder and bile are normally sterile,[6] and in dogs it is considered sterile in the absence of biliary tree pathology, although intermittent bacterial isolation from the gallbladders of healthy dogs has been described.[7] Bacterial cholangitis involves bacterial infiltration into the biliary ducts, as discussed previously there are two main possible routes of infection. The first is an ascending infection with bacteria from the duodenum or secondly hematogenously via the hepatic portal venous blood.[2]

The gallbladder has mechanical defense mechanisms that help to prevent bacterial cholangitis. These defense mechanisms include the antegrade flow of bile, the sphincter of Oddi which acts as a mechanical barrier, bacteriostatic effects of bile salts and local immunological defense mechanisms, including mucous, Kupffer cells and IgA.[4] There have been cases reported in which an acute enteritis can lead to a secondary bacterial cholangitis, via an ascending infection.[8] Factors that predispose to biliary infection include factors that impair the natural defense mechanisms including biliary stasis and increased biliary pressure with partial obstructions of bile flow.[9] Following infiltration with bacteria, inflammation and neutrophilic infiltration take place, and if bacteria continue to ascend from the biliary ducts to the gallbladder itself, inflammation of the gallbladder, which is called cholecystitis, can occur.[1] The inflammation leads to impairment of bile outflow from the gallbladder, and development of a post-hepatic jaundice. The relationship between bacterial cholangitis and cholecystitis has not yet been clearly defined.

Cases of bacterial cholangitis can present with vomiting, anorexia, lethargy, jaundice, and abdominal discomfort.[2] Not all signs are present in every case. Complete or partial biliary obstruction can lead to hyperbilirubinemia and visible jaundice. Alterations to bile outflow can decrease vitamin K absorption, which can lead to impaired coagulation.[10]

Diagnostic Approach

A standard diagnostic approach to a patient with jaundice includes evaluation of routine bloodwork including a complete blood count (CBC), serum biochemistry and urinalysis. In addition to routine bloodwork, evaluation of liver function in addition to clotting times may be performed. A jaundiced patient should also have abdominal radiographs and an abdominal ultrasound performed with or without aspirates of the liver and/or gallbladder depending on the abnormalities detected.[11] The aim of the bloodwork and diagnostic imaging is to determine whether there is a pre-hepatic, hepatic or post-hepatic jaundice. If abdominal discomfort is present, a canine snap cPL test or alternative pancreatic lipase assay may be performed to determine if pancreatitis could be a cause of EHBDO.[10] In cases of bacterial cholangitis, the CBC can be normal or show a leukocytosis. A serum biochemistry often reveals elevated liver enzymes (ALP, ALT), hypercholesterolemia, and hyperbilirubinemia.[12] Hyperglobulinemia has also been reported.[2] In a previous study, 17/19 cases had at least one of the following findings; neutrophilia, monocytosis or hyperglobulinemia, thus when a patient has an increased bilirubin and an inflammatory leukogram the index of suspicion for cholangitis should increase.[2]

There are two commonly utilized liver function tests; bile acids and the ammonia tolerance test. Bile acids should not be performed in the presence of hyperbilirubinemia due to artifact. The results of these tests are elevated in hepatic dysfunction/failure.[11] In cases of liver

or biliary disease clotting times may be prolonged either as a result of primary liver disease or secondary to cholestasis and decreased vitamin K absorption.

Imaging is the next step in the diagnostic approach. Abdominal radiographs can reveal the presence of choleliths and anatomical abnormalities such as hepatomegaly; however, a thorough abdominal ultrasound is critical in evaluation of these patients. Common findings in cases of bacterial cholangitis include distention of the common bile duct, thickening of the gallbladder wall, gallbladder sludge, changes to the hepatic parenchyma echogenicity, and gallbladder mucocele formation.[2] Obstruction can be definitively diagnosed on ultrasound, but bacterial cholangitis requires further diagnostic testing including cytology and culture and sensitivity. Cytological examination can reveal the presence of bacteria and inflammatory cells, and visualization of bacteria on cytology indicates a minimum of 1,000 to 100,000 bacteria/mL of fluid.[4] Culture and sensitivity should be used to ensure proper antibiotic choice. This is due to the high frequency of resistant strains identified in cases of bacterial cholangitis[2] and due to the fact that although *Escherichia coli* and *Enterococcus* spp are the most common isolates, other bacteria including *Citrobacter freundii*, *Clostridium sordelli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, and methicillin-resistant *Staphylococcus pseudintermedius* have also been isolated from bile samples in dogs.[12] A cytology should always be performed in addition to the culture and sensitivity, because cytology can detect low yields that may not be positive on culture and are less effected by prior antimicrobial administration.

Treatment and Management

After determining bacterial cholangitis as the cause of jaundice, medical management is initiated. Appropriate treatment plans include antibiotic therapy, fluid therapy, nutritional support, and choleretic therapy. Duration of treatment can range from 4 to 12 weeks.[2] Where

possible, antimicrobial therapy should be guided by an anaerobic and aerobic culture and sensitivity, due to the high frequency of antimicrobial resistance. A recent study showed 2/3^{rds} of *E. coli* isolates being resistant to amoxicillin clavulanic acid and a high frequency of resistance to fluoroquinolones and 1st generation cephalosporins. Despite the documented resistance, empirical antibody selection often includes a fluoroquinolone and amoxicillin clavulanate potassium.[2]

As oxidative injury is often a primary or secondary component of liver injury, supportive treatment often includes antioxidant therapy including SAMe, vitamin E and silymarin. If patients cannot tolerate SAMe (oral) then N-acetylcysteine (NAC) is commonly used in its place (IV). SAMe plays a central role in the synthesis of glutathione and the transsulfuration pathway.[13] Its main role is to prevent oxidative damage by preventing hepatic glutathione depletion. SAMe is also thought to have some anti-inflammatory properties, modulate apoptosis and be anti-carcinogenic. SAMe is available as a combination product with silybin, called Denamarin.[14] N-acetylcysteine acts as a free radical scavenger by being a thiol donor.[10] It is a formulation of L-cysteine that helps replenish hepatic intracellular cysteine and glutathione concentrations, helping to protect against oxidative injury. This medication is given parenterally.

Ursodeoxycholic acid (UDCA) is a hydrophilic bile acid, that displaces more toxic hydrophobic bile acids from the circulating pool, it also has a choleretic effect[13], and is given at 15 mg/kg PO twice a day until signs resolve.[15]

Additional supportive care includes fluid therapy and antiemetic medication. Intravenous fluid resuscitation is important to correct fluid losses from vomiting and diarrhea in addition to correcting electrolyte disturbances.[10] As cholestasis can reduce absorption of vitamin K, many clinicians supplement Phytonadione (Vitamin K1), to prevent an acquired coagulopathy from

clotting factor 2,7,9 or 10 deficiency. Phytonadione can be supplemented between 2.5 and 5 mg/kg/day SQ until sufficient bile outflow has returned for adequate vitamin K absorption.[14]

Case Outcome

For Petri, blood samples were collected for a CBC, serum biochemistry, and coagulation profile. The CBC revealed a mild lymphopenia with a normal hematocrit. There was no evidence of auto-agglutination, and as such a pre-hepatic jaundice was considered unlikely. The serum biochemistry revealed a profound elevation in ALP and marked elevations in total bilirubin and ALT. The serum chemistry also revealed a mild hypercholesterolemia in addition to electrolyte abnormalities. Clotting times were within normal limits. A urinalysis was performed that revealed a urine specific gravity of 1.030 and bilirubin crystalluria. An ammonia tolerance test was performed, and the results were within normal limits. Due to the presence of abdominal discomfort and concern about EHBDO a snap cPL was performed and was normal. Leptospira PCR and serology were submitted to rule out Leptospirosis, and the results of these tests were negative.

Abdominal radiographs and an abdominal ultrasound were then performed. The abdominal radiographs revealed the presence of mineralized gallbladder debris. An abdominal ultrasound showed mineralized gallbladder sludge, likely associated with cholestasis, and the liver echogenicity and echotexture appeared normal. Due to the significant elevation of ALP relative to ALT, and the ultrasonographical evidence of gallbladder disease a cholecystocentesis was offered but was not pursued at the time, due to the perceived risks of hemorrhage, gallbladder rupture, bile peritonitis and vagally induced hypotension. Fine needle aspirates of the liver were collected for cytology and culture and sensitivity. The cytology revealed mild lipid accumulation, and the liver culture was negative. Supportive care for suspected post-hepatic

jaundice and gallbladder disease was pursued. Liver protectants (N-acetylcysteine, ursodiol), GI medications (Cerenia, pantoprazole), antibiotics (metronidazole, Clavamox), and Phytonadione were initiated.

Petri clinically improved with supportive care, and he was scheduled to be discharged on day 4 of hospitalization. However, a serum chemistry was submitted prior to scheduled discharge, which revealed an increase in ALP, ALT and total bilirubin. Clotting times were rechecked, and the results were normal. A repeat abdominal ultrasound was performed, which showed no significant changes in the gallbladder sludge, and a cholecystocentesis was offered again, and was pursued at this time. Gallbladder cytology revealed neutrophilic infiltration, and an aerobic and anaerobic culture and sensitivity revealed growth of *Aeromonas caviae.* This organism was sensitive to enrofloxacin and TMS. Petri was diagnosed with a bacterial cholangitis, and TMS was added to the treatment plan. He remained hospitalized, and serum biochemistries on days 6, 8, 9, and 11 revealed that the liver enzymes were steadily decreasing towards normal. On day 12, he was discharged on oral liver protectants, GI medications, antibiotics, and Phytonadione.

On January 2, 2018, Petri presented for a recheck appointment. At this time Petri was clinically improved. The CBC was normal but the serum biochemistry revealed a substantially increased ALT with unchanged ALP and TBili. It was suspected that Petri experienced hepatic necrosis as an idiosyncratic drug reaction, and as such TMS was discontinued and replaced with enrofloxacin. He was maintained on liver protectants, GI protectants, antibiotics, and Phytonadione with rechecks every week to assess his improvement. On January 11, 2018, his serum biochemistry showed improvement with mildly elevated ALP, ALT, cholesterol and TBili. Phytonadione was discontinued.

References

1. Cullen JM. Summary of the World Small Animal Veterinary Association Standardization Committee Guide to Classification of Liver Disease in Dogs and Cats. Vet Clin Small Anim 2009; 39:395-418.
2. Tamborini A, Jahns H, McAllister H, Kent A, Harris B, Procoli F, Allenspach K, Hall EJ, Day MJ, Watson PJ, O'Neil EJ. Bacterial Cholangitis, Cholecystitis, or both in Dogs. J Vet Intern Med 2016; 30:1046-1055.
3. O'Niell E.J., Day M.J., Hall E.J., Holden D.J., Murphy K.F., Barr F.J. and Pearson G.R. Bacterial cholangitis/cholangiohepatitis with or without concurrent cholecystitis in four dogs. JSAP 2006; 47: 325-335.
4. Pashmakova MB, Piccione J, Bishop, MA, Nelson WR, Lawhon SD. Agreement between microscopic examination and bacterial culture of bile samples for detection of bactibilia in dogs and cats with hepatobiliary disease. JAVMA 2017; 250(9):1007-1013.
5. Cullen JM. Liver, Biliary System, and Exocrine Pancreas. In: McGavin MD and Zachary JF. Pathologic Basis of Veterinary Disease, 4th ed. St. Louis:Mosby-Elsevier, 2007; 393-462.
6. Sung JY, Costerton JW, Shaffer EA. Defense system in the biliary tract against bacterial infection. Dig Dis Sci 1992;37:689– 696.
7. Kook PH, Schellenberg S, Grest P, et al. Microbiologic evaluation of gallbladder bile of healthy dogs and dogs with iatrogenic hypercortisolism: A pilot study. J Vet Intern Med 2010; 24:224
8. Watson PJ, Bunch SE. Hepatobiliary and Exocrine Pancreatic Disorders. In: Nelson RW and Couto CG. Small Animal Internal Medicine, 4th ed. St. Louis:Mosby-Elsevier, 2009; 485-606.
9. Carpenter HA. Bacterial and Parasitic Cholangitis. Mayo Clinic Proc 1998; 73:473-478.
10. Weingarten MA, Sande AA. Acute liver failure in dogs and cats. J Vet Emerg Crit Care 2015; 25(4):455-473.
11. Kumar V, Kumar A, Varshney AC, Tyagi SP, Kanwar MS, Sharma SK. Diagnostic Imaging of Canine Hepatobiliary Affections: A Review. Vet Med Internation 2012; 2012:1-15.
12. Harrison JL, Turek BJ, Brown DC, Bradley C, Clark JC. Cholangitis and Cholangiohepatitis in Dogs: A Descriptive Study of 54 Cases Based on Histopathologic Diagnosis (2004-2014). J Vet Intern Med 2018; 32:172-180.
13. Lidbury JA. General Principles in the Treatment of Liver Disease. In Ettinger SJ, Feldman CJ and Cote E (eds): Textbook of Veterinary Internal Medicine 8th Edition. St. Louis, MO: Elsevier; 2017: 1621-1627.
14. Papich MG. Saunders Handbook of Veterinary Drugs, 4th ed. St. Louis:Elsevier, 2016.
15. Gupta AR, Panigraphi PN, Manisha D. Therapeutic Management of Hepatitis associated with Cholangitis in a Dog. Intas Polivet 2013; 14(I):121-122.
16. Lester C, Cooper J, Peters RM, Webster CRL. Retrospective evaluation of acute liver failure in dogs (1995-2012): 49 cases. J Vet Emerg Crit Care 2016; 26(4):559-567.