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REVIEW

Feline cholangitis/cholangiohepatitis complex

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Cholangitis/cholangiohepatitis complex in cats is commonly encountered in clinical practice worldwide. Diagnosis and management of cats with this complex is difficult because of the ambiguity of clinical signs, diagnostic test results and commonality of comorbid disorders. These impediments can delay disease identification and treatment, which can increase morbidity and mortality. In this narrative review, we aimed to provide a thorough review of the unique physioanatomic features of the biliary system as well as clinically relevant updates on cholangitis/cholangiohepatitis complex in cats.

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INTRODUCTION

Inflammatory disease of the intrahepatic biliary system in cats is commonly encountered in clinical practice. Cholangitis/cholangiohepatitis was the most common primary histopathologic diagnosis made in 27 to 39% of feline liver biopsy submissions in recent surveys reported in Japan, UK and New Zealand (Hirose *et al.* 2014, Bayton *et al.* 2018, Fluen *et al.* 2019). Classification schemes and terminology of cholangitis/cholangiohepatitis in cats have evolved over the last two decades. Current guidelines provided by The World Small Animal Veterinary Association (WSAVA) Liver Standardisation Group includes biliary disorders grouped into four major categories: (1) neutrophilic cholangitis (NC), (2) lymphocytic cholangitis (LC), (3) chronic cholangitis (CC) associated with liver fluke infestation and (4) destructive cholangitis (DC) (Van Den Ingh *et al.* 2006). DC has been described sparingly in dogs but not yet cats. Diagnosis of cholangitis/cholangiohepatitis in cats can be difficult because of the frequent occurrence of comorbid conditions, and in many cats, clinical signs are vague and non-specific. The delay in diagnosis and subsequent lapse in therapeutic intervention can increase morbidity and mortality. Therefore, the objectives of this review were to (1) describe normal biliary anatomy and physiology and (2) summarise clinically relevant updates on NC, LC and CC.

ANATOMY AND PHYSIOLOGY OF THE BILIARY SYSTEM

The biliary system in cats is a branched arrangement of canaliculi, intralobular ducts, canal of Hering, interlobular ducts, septal ducts, hilar ducts, common bile duct (CBD), cystic duct and gall bladder (Cullen & Stalker 2016) (Fig 1). Hepatocytes are arranged in radiating fashion around a central vein and commonly used nomenclature systems are referred to as acinus or lobule. The classic lobule is a six-sided organisation of hepatocytes positioned around a central vein. The acinus is a diamond-shaped subunit divided into functional zones: *Zone 1* (*i.e.* periportal): hepatocytes are arranged around the portal tract and are nearest to oxygen/nutrient rich arterial and portal blood, *Zone 2*: transitional midzone and *Zone 3* (*i.e.* centrilobular): hepatocytes form the apex of the diamond-shaped acinus, closest to the central vein and are exposed to oxygen/nutrient-depleted blood (Cullen & Stalker 2016). The portal triad is a structure that contains ≥1 hepatic artery branch, portal vein branch and a bile duct admixed a collagenous extracellular matrix that is surrounded by a single layer of hepatocytes called the limiting plate. Portal vein inflow provides the majority of blood supply to the liver (70 to 80%) and accounts for 50% of oxygen delivery with the hepatic arteries supplying the rest (Cullen & Stalker 2016). Afferent blood from the portal triad flows to the central vein through sinusoids, while bile flows in the opposite direction.

Bile formation by the liver is an important physiological function as it facilitates excretion of endogenous/exogenous waste products and allows for the efficient digestion and absorption of lipids in the intestinal lumen. Bile acids are derived from cholesterol in the liver and the major bile acids produced in most mammals, including cats, are cholic acid and chenodeoxycholic acid. After synthesis, bile acids are conjugated in the hepatocyte with glycine or taurine forming bile salts. The conjugation of bile acids increases their polarity, which has several physiological advantages such as increased excretion into the bile, reduced toxicity and improved lipid digestion.

There are several species differences in bile acid conjugation and composition. Humans conjugate bile acids with glycine and

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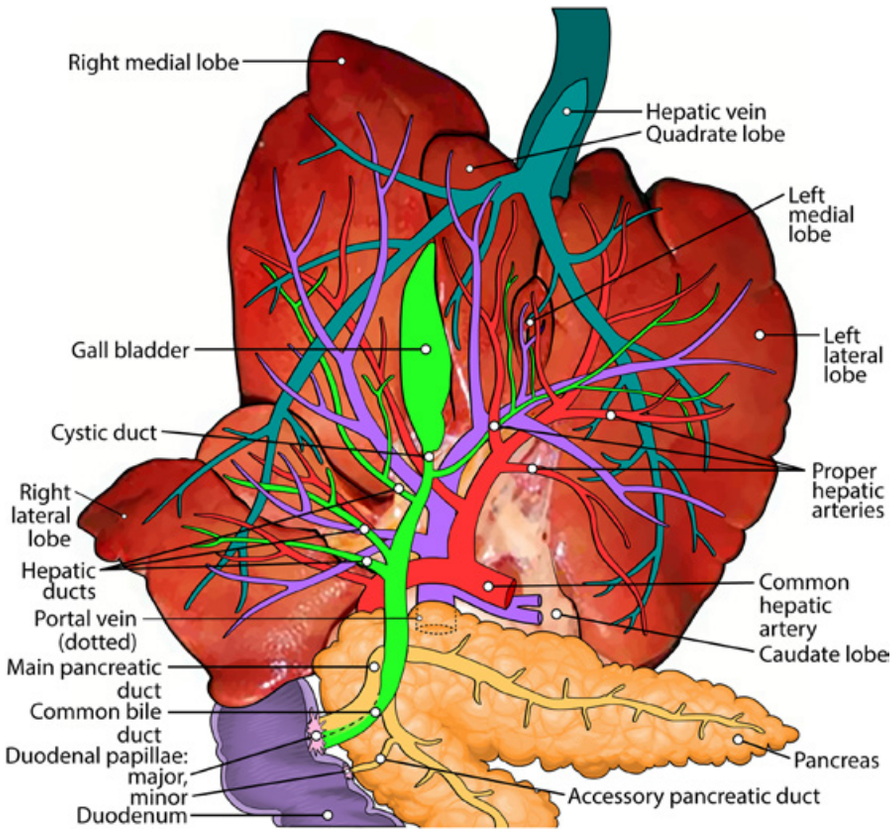

FIG 1. Schematic illustration of the feline hepatobiliary-pancreatic anatomy. Image courtesy of Brent Adrian, Senior Research Specialist, Department of Anatomy, Midwestern University, Glendale, Arizona, USA

taurine in a 3:1 ratio. Dogs predominately conjugate bile acids with taurine but can convert to the utilisation of glycine, which is in contrast to cats that undergo obligate taurine-conjugation (Kook *et al.* 2011, Miyazaki *et al.* 2019). Taurine deficiency in cats results in decreased bile acid synthesis and an altered bile acid profile characterised by increased unconjugated bile acids and reduced taurine-conjugated bile acids (Rabin *et al.* 1976, Miyazaki *et al.* 2019, Miyazaki *et al.* 2020). Collectively, the changes in bile acid metabolism in taurine-deficient cats has pathophysiologic consequences such as the induction of periportal inflammation, increased serum total bile acid concentrations and decreased serum cholesterol concentrations postulated to be secondary to lipid malabsorption (Miyazaki *et al.* 2020). Cats can become taurine-deficient easier than other species primarily because of a limited taurine biosynthetic capacity (Hayes 1988). Therefore, cats are at an increased risk to develop taurine deficiency and subsequent derangements in bile acid metabolism with prolonged inadequate nutrition or when offered a taurine-depleted diet (Rabin *et al.* 1976, Biourge *et al.* 1994, Miyazaki *et al.* 2019, Miyazaki *et al.* 2020).

Bile salts, along with glutathione, cholesterol, bilirubin, lipids, bicarbonate, proteins, sodium and metabolic wastes are secreted into the canaliculi followed by the passive diffusion of water, electrolytes and glucose. Cholangiocytes modify bile and provide approximately 30% of total bile volume as it flows through intrahepatic bile ducts. The majority of bile salts/acids are reabsorbed in the ileum (<5% lost in faeces per day) and are transported back to the liver via portal blood flow and secreted once again into bile in a process known as enterohepatic circulation. More than 90% of bile salts/acids are extracted from portal blood by hepatocytes during each passage through the liver (Center 1990). A small fraction of bile salts is deconjugated or hydroxylated by intestinal bacteria. The latter reaction results in the production of secondary bile acids such as deoxycholate and lithocholate from cholic and chenodeoxycholic acid, respectively. Deoxycholic acid is absorbed, conjugated in the liver and secreted into bile. In contrast, lithocholic acid, which is hepatotoxic, is poorly absorbed in the ileum. The small amount of lithocholic acid that is reabsorbed is sulphated in the liver, rather than conjugated, before being excreted into bile. Sulphation of lithocholic acid is protective as it hinders reabsorption in the subsequent enteric cycle.

The gall bladder is located to the right of midline between the right medial and quadrate lobes and connects to the CBD by way of the cystic duct (Fig 1). Congenital anomalies of the gall bladder in cats are rarely described in the veterinary literature; however, a single anatomic survey published in 1926, found anomalies in 12.5% of cats (Boyden 1926). The most common anomaly is the bilobed gall bladder that can further be divided into three types (Boyden 1926, Moentk & Biller 1993, Moores & Gregory 2007, Woods *et al.* 2012): (1) the external appearance of the gall bladder is normal; however, the lumen is partially divided by a septum that results in two chambers that communicate through a single cystic duct, (2) the gall bladder fundus is completely divided creating two cavities that fuse at the neck and

share a single cystic duct giving the gall bladder a valentine heart like appearance and (3) duplex gall bladders are characterised by completely separate cavities, each with independent cystic ducts that join the CBD separately. The gall bladder is the primary site of interprandial bile storage, concentration and acidification. After a meal, bile empties into the duodenum through complex neurohormonal interactions mediated primarily by cholecystokinin that results in concomitant gall bladder contraction and sphincter of Oddi relaxation (Behar & Biancani 1980, Niewiarowski *et al*. 1990).

In 80% of cats, the CBD fuses with the major pancreatic duct in an ampulla forming a "common channel" called the pancreaticobiliary duct just before inserting into the duodenum forming the major duodenal papilla (Mcclaran & Buote 2014) (Fig 1). This is in contrast to dogs in which the CBD and minor pancreatic duct travel through the head of the pancreas in parallel, but separate, and terminate into the duodenal wall forming the major duodenal papilla.

NEUTROPHILIC CHOLANGITIS/ CHOLANGIOHEPATITIS

Neutrophilic cholangitis/cholangiohepatitis vies with LC for the most common type of inflammatory biliary disorder in cats. Several observational studies have revealed either inflammatory phenotype as most common and this variability could be influenced by factors such as the circumstances that surrounded liver sample acquisition (*i.e*. biopsy *versus* necropsy), geographic region and time-period of the study (Gagne *et al*. 1996, 1999, Brain *et al*. 2006, Callahan Clark *et al*. 2011, Hirose *et al*. 2014, Fragkou *et al*. 2016, Bayton *et al*. 2018, Fluen *et al*. 2019). Histologically, NC is characterised by the presence of neutrophils in the lumen, epithelium or both, of the bile ducts (Fig 2). Lesions can affect the liver diffusely or display an irregular patchy distribution with varying severity (Van Den Ingh *et al*. 2006). The neutrophilic inflammation can occasionally extend beyond the limiting plate and into the hepatic parenchyma characterised by hepatocellular necrosis or apoptosis. Neutrophilic cholangitis/cholangiohepatitis is subclassified as acute NC (ANC) or chronic (CNC). In the acute stage, the lesion is characterised by neutrophils and oedema in the portal areas and minimal-to-mild bile duct hyperplasia, fibroplasia or fibrosis (Callahan Clark *et al*. 2011). Cases in the chronic stage are classified as CNC and will have lesions characterised by mixed neutrophilic and mononuclear inflammation in portal regions as well as moderate-to-severe bile duct hyperplasia, fibroplasia or fibrosis depending on the chronicity of disease (Callahan Clark *et al*. 2011).

Cats of any age, breed or sex can be affected. Reported median ages at the time of diagnosis are 7 to 14.5 years (range, 0.8 to 20 years) (Hirsch & Doige 1983, Gagne *et al*. 1999, Marolf *et al*. 2012, Hirose *et al*. 2014,Bayton *et al*. 2018, Fluen *et al*. 2019). Two retrospective observational studies found that cats with ANC were younger than cats with CNC; however, the small cohort sizes and tremendous overlap in age ranges render these differences clinically irrelevant (Gagne *et al*. 1999, Callahan Clark *et al*. 2011). Results from two recent epidemiologic surveys reinforced that any breed can be affected; however, several potential breed associations were identified. Breeds shown to be at an increased risk in either the UK or New Zealand included the British shorthair, Burmese, domestic longhair, Persian, Siamese and Sphynx, while domestic shorthair had a reduced risk in both regions (Bayton *et al*. 2018, Fluen *et al*. 2019). It is unclear at this time if these breed associations translate to other geographic regions. Statistical associations with sex have not been identified.

The aetiopathogenesis of NC in cats remains unclear. Two central concepts that together are purported to be responsible for the development of acute cholangitis (*i.e*. neutrophilic) in humans have potential to elucidate the mechanism underlying of NC in cats. The first, mechanical or functional biliary obstruction (partial or complete) leading to decreased bile flow and increased intraductal pressure (Sokal *et al*. 2019). Collectively, these changes increase the quantity of bacteria and promote a microenvironment that enhances the invasion of bacteria into bile duct epithelium because of the resultant adverse influences on host defence mechanisms such as Kupffer cell functions, secretory immunoglobulin A production and tight junctions (Rank & Wilson 1983, Anderson 1996, Tomioka *et al*. 2000). This concept was highlighted

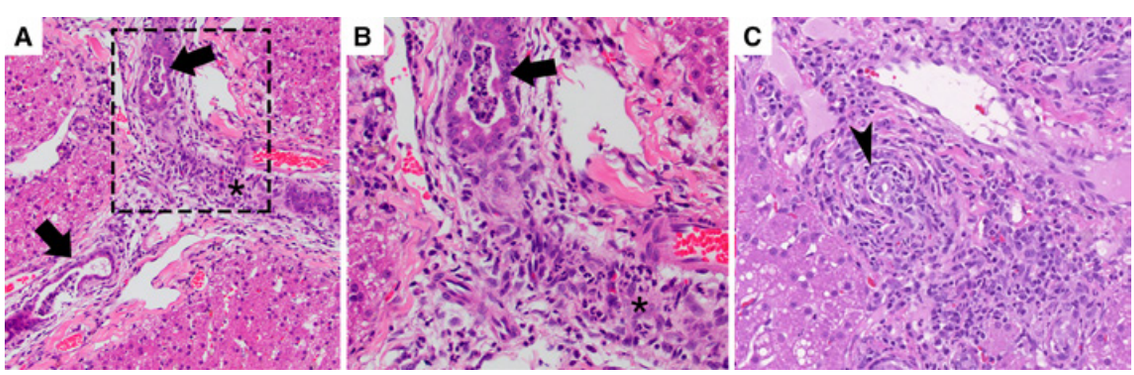

FIG 2. Neutrophilic cholangitis. Liver biopsies from cats with acute neutrophilic (A,B) and chronic neutrophilic cholangitis (C). (B) Higher magnification (×400) inset of (A), outlined by the dashed black rectangle. Infiltrating the periportal interstitium and biliary epithelium (black asterisk) as well as filling the bile duct lumina (black arrows) are moderate numbers of neutrophils (A,B). In the chronic example (C), neutrophilic infiltrates are admixed with smaller numbers of mixed inflammatory cells. Bile ducts are occasionally absent (ductopenia) and surrounded circumferentially by reactive fibrosis (black arrowhead). Haematoxylin & eosin stain. Images courtesy of John Cullen VMD, PhD, DACVP (North Carolina State University, College of Veterinary Medicine) and Sylvia Ferguson DVM, PhD, DACVP (Midwestern University, College of Veterinary Medicine).

in an experimental study in cats in which varying doses of *Escherichia coli* (*E. coli*) were infused into the splenic vein and into the portal circulation under conditions that simulated varying times of biliary obstruction (Sung *et al*. 1991b). The dose of *E. coli* needed to cause a biliary infection in those cats decreased as the time of biliary obstruction increased (Sung *et al*. 1991b). This concept is further supported by the relative frequency with which NC is reported in cats with partial or complete biliary obstruction (Hirsch & Doige 1983, Mayhew *et al*. 2002, Brain *et al*. 2006, Mayhew & Weisse 2008, Callahan Clark *et al*. 2011). Two retrospective studies found that 93 (13/14) and 100% (7/7) of cats, respectively, with extrahepatic bile duct obstruction (EHBDO) had NC (Mayhew *et al*. 2002, Mayhew & Weisse 2008).

The second essential contributing component is related to bacterial infiltration in bile. There is compelling evidence that bacteria are a primary impetus in the development of feline NC just as they are in humans with acute cholangitis. Bacteria are frequently cultured from bile, liver or both of cats with NC and even in their absence, a positive clinical response to antimicrobial therapy is noted (Hirsch & Doige 1983, Mayhew *et al*. 2002, Brain *et al*. 2006, Greiter-Wilke *et al*. 2006, Wagner *et al*. 2007, Mayhew & Weisse 2008, Callahan Clark *et al*. 2011, Twedt *et al*. 2014, Newton & Fry 2018). Further, a recent study identified bacteria within the livers of cats with NC with fluorescence in situ hybridisation (FISH) (Twedt *et al*. 2014). Not all cats have bacteria identified via traditional culture or with FISH. However, several factors in these retrospective studies could have negatively influenced the identification of bacteria such as unknown history of antibiotics, failure to grow fastidious bacteria, inconsistent methods (*e.g*. sample type, absence of anaerobic cultures or use of FISH) and the bacteriostatic effects of bile resulting in false-negative results. With that said, it is possible, though not substantiated with evidence, that a subfraction of cats with NC could have an immune-mediated aetiology with persistent inflammation in the absence of an active bacterial infection after exposure to a pathogen, drug, toxin, or other unknown trigger.

There are two possible sources of bacteria in cats with biliary infection: (1) ascendant from the duodenum and (2) translocation across the intestinal wall with haematogenous spread via the portal circulation. Both are plausible because cats have a relatively rich bacterial flora (including anaerobic bacteria) in the duodenum in addition to a "common channel" pancreaticobiliary duct (Johnston *et al*. 1993, Janeczko *et al*. 2008). These two taken together, increase the risk for the ascension of bacteria from the intestine into the pancreas and biliary system. The concept of haematogenous spread of bacteria to the biliary tract was confirmed in an experimental study in cats that had *E. coli* infused into the splenic vein (Sung *et al*. 1991b). Cats from that study developed a biliary infection when large numbers of *E. coli* were infused, corroborating that portal-venous bacteraemia can contribute to the development of NC (Sung *et al*. 1991b). Haematogenous spread of bacteria from the intestine is further supported by the commonality that bacteria of enteric origin are identified in either bile or liver tissue in cats with hepatobiliary disease (Brain *et al*. 2006, Wagner *et al*. 2007, Callahan Clark *et al*. 2011, Pashmakova *et al*. 2017, Policelli Smith *et al*. 2017).

The richness of bacteria in the duodenum and "common channel" pancreaticobiliary duct provide the foundation for several theories proposed to explain the common interplay of inflammation in the pancreas, intestine, and biliary system in cats. The syndrome known as "triaditis," or inflammation in the pancreas, intestine and bile ducts was borne from this complex physioanatomic relationship. Over the last 25 years, several retrospective case series have described concurrent inflammation in the pancreas, intestine or both, in cats with cholangitis/cholangiohepatitis (Hirsch & Doige 1983, Weiss *et al*. 1996, Brain *et al*. 2006, Mayhew & Weisse 2008, Callahan Clark *et al*. 2011). Two retrospective studies found that collectively, cats with NC had concurrent inflammation in the pancreas alone (55%, 27/49) intestine alone (58%, 29/50) or both [*i.e*. triaditis (30%, 14/46)] (Weiss *et al*. 1996, Callahan Clark *et al*. 2011). Not all cats in the aforementioned studies had biopsies procured from all three organs, so the true distribution of concurrent inflammation may not be accurate. A recent prospective study that obtained biopsy samples from liver, pancreas and intestine from cats found that only 20% (6/30) had cholangitis/cholangiohepatitis alone and the remainder had concomitant inflammation identified in the intestine alone (53%, 16/30), or in combination with pancreas [*i.e*. triaditis (27%, 8/30)] (Fragkou *et al*. 2016).

The pathomechanism responsible for the interaction of inflammation between the three organ systems in cats remains unclear; however, the prevailing theory is that the inciting event is intestinal disease that results in dysbiosis and disruption of normal mucosal barriers. Janeczko *et al*. (2008) showed that the density and composition (Enterobacteriaceae, *E. coli* and *Clostridium* species) of the mucosal flora in the duodenum was associated with the presence and severity of intestinal inflammation in cats. This seemingly more pathogenic and concentrated bacterial flora can then either migrate into the pancreas, biliary tract or both via the pancreaticobiliary duct or translocate across damaged intestinal mucosa, into the portal-venous system, and into the biliary tract. Other evidence-based scenarios have revolved around primary infection in either the biliary tract or pancreas that then causes pathology in varying combinations of the three organs (Widdison *et al*. 1994).

Clinical signs and physical examination abnormalities reported in cats with NC are non-specific and have considerable overlap with other biliary pathologies including but not limited to LC as well as pancreatitis and intestinal disease. Moreover, many cats with NC have concurrent inflammatory disease in the intestine, pancreas or both, which further confound interpretation of clinical abnormalities. Callahan Clark *et al*. (2011) found no difference in the frequency of clinical signs or physical examination findings between cats with ANC and CNC. There are only four retrospective case series that provide results regarding clinical signs and physical examination findings specific to cats with histopathologic confirmed NC. Unfortunately, reporting of abnormalities was inconsistent across the four studies; therefore, a thorough summary could not be provided. However, a few relevant abnormalities were reported relatively consistently including the frequency of vomiting (73%, 8/11) (Hirsch & Doige 1983, Brain *et al*. 2006), weight loss (62%,

13/21) (Hirsch & Doige 1983, Gagne *et al*. 1999), anorexia (55%, 6/11) (Hirsch & Doige 1983, Brain *et al*. 2006), jaundice (46%, 21/46) (Hirsch & Doige 1983, Brain *et al*. 2006, Callahan Clark *et al*. 2011) and pyrexia (35%, 23/65) (Hirsch & Doige 1983, Gagne *et al*. 1999, Brain *et al*. 2006, Callahan Clark *et al*. 2011). Cranial abdominal pain was only reported in one small case series, but was relatively common (66%, 4/6) (Brain *et al*. 2006). The duration of time clinical signs is observed by owners before diagnosis is scarcely reported in the literature being limited to eight cats in two case series. The reported median duration of time clinical signs were observed was 4 days (range, 1 to 42 days) (Hirsch & Doige 1983, Brain *et al*. 2006). Most cats with NC are evaluated within 7 to 14 days of the onset of clinical signs but can occasionally linger for months in mild cases. Overall, the severity of disease can range from mild-to-life-threatening.

Biochemical analysis often reveals an increased liver enzyme activity in at least one or more of the following of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) or γ-glutamyltransferase (GGT) ranging in severity from mild to severe. However, increased liver enzyme activity may be absent in some cases. Moreover, in contrast to dogs, the liver enzyme activity pattern in cats with NC is much less predictable and often not convincingly cholestatic. The reported frequency of cats with increased activity of AST (range, 95 to 100%), ALT (range, 57 to 100%), ALP (33 to 48%) and GGT (22%) (Gagne *et al*. 1999, Brain *et al*. 2006, Callahan Clark *et al*. 2011). Hyperbilirubinemia is a relatively common feature with reported frequencies that range from 69 to 83% (Gagne *et al*. 1999, Brain *et al*. 2006, Callahan Clark *et al*. 2011). The distribution of liver enzyme activity and total bilirubin concentration parameters in one study included the following median values for cats with ANC: ALT (117 U/L; range, 26 to 212 U/L; reference interval (RI), 33 to 152 U/L), AST (100 U/L; range, 55 to 323 U/L; RI, 1 to 37 U/L), ALP (350 U/L; range, 19 to 1935 U/L; RI, 22 to 87 U/L), GGT (5 U/L; range, 5 to 7 U/L; RI, 5 to 19 U/L), total bilirubin (4.2 mg/dL; range, 2.7 to 9.1 mg/dL; RI, 0.1 to 0.8 mg/dL) and in those with CNC: ALT (214 U/L; range, 12 to 2685), AST (169 U/L; range, 37 to 3181), ALP (83 U/L; range, 11 to 697 U/L), GGT (16 U/L; range, 5 to 41 U/L) and total bilirubin (1.4 mg/dL; range, 0.3 to 24.9 mg/dL) (Callahan Clark *et al*. 2011). The authors of that study did not identify any clinically relevant differences in biochemical parameters between cats with ANC and CNC. Haematology results vary and are reflective of the magnitude of systemic inflammation. Abnormalities that can be identified include leucocytosis, leukopenia band neutrophils, toxic changes to neutrophils and mild-to-moderate non-regenerative anaemia (Hirsch & Doige 1983, Gagne *et al*. 1999, Brain *et al*. 2006, Callahan Clark *et al*. 2011).

Coagulation status should be assessed in all cats with suspected hepatobiliary disease, especially before procedures including percutaneous cholecystocentesis (PUC), fine-needle aspiration of the liver and collection of liver biopsy samples. Cholestatic disease can result in unpredictable changes characterised by a rebalanced haemostatic homeostasis with abnormalities in at least one or more of primary and secondary haemostasis as well as fibrinolysis, which can result in hyper- or hypocoagulable states. Decreased bile flow can result in malabsorption of fat-soluble molecules including vitamin K, and in humans, the severity of deficiency correlates with the magnitude of cholestasis (Strople *et al*. 2009, Kloek *et al*. 2010). Coagulation factors II, VII, IX and X as well as anticoagulant mediators including protein C and protein S all require vitamin K to become active; therefore, vitamin K deficiency mediated hypocoagulability has potential to develop in cats, as it does in humans (Harvey 2012). Results from one recent study found that 28% (5/18) of cats with cholestatic liver disease were hyperfibrinolytic (Kakar *et al*. 2020). Minimum coagulation tests that should be performed include prothrombin time, activated partial thromboplastin time and platelet count. Thromboelastography should be performed if available because it might more accurately predict haemostatic disorders than conventional coagulation testing alone (Kakar *et al*. 2020).

There is a lack of information in the veterinary literature that describes sonographic features associated with specific inflammatory phenotypes of cholangitis/cholangiohepatitis in cats. Instead, retrospective observational studies reported sonographic characterisations as a collective group of inflammatory biliary disorders (Fig 3). Overall, the sonographic appearance of liver parenchyma is variable, non-specific and can be unremarkable; therefore, it cannot be used to reliably exclude or diagnose NC in cats (Newell *et al*. 1998, Gagne *et al*. 1999, Callahan Clark *et al*. 2011, Marolf *et al*. 2012). Marolf *et al*. (2012) reported that cats with cholangitis/cholangiohepatitis had normal (69%, 18/26), large (27%, 7/26) or small sized (4%, 1/26) livers. Echogenicity of the liver is reported to be normal (range, 39 to 54%), hyperechoic (range, 13 to 38%) or hypoechoic (8 to 48%) (Newell *et al*. 1998, Marolf *et al*. 2012). Focal or multi-focal nodules are uncommonly identified (8 to 17%) (Newell *et al*. 1998, Marolf *et al*. 2012). Imaging findings of the biliary tract can be unremarkable (48%, 11/23) (Newell *et al*. 1998) or various abnormalities can be identified such as dilation of intra/extrahepatic bile ducts, gall bladder distension, increased gall bladder "sludge" and thickening of the gall bladder wall or bile duct walls (Newell *et al*. 1998,Brain *et al*. 2006, Callahan Clark *et al*. 2011, Marolf *et al*. 2012). The normal CBD diameter in cats is ≤4 mm (Leveille *et al*. 1996). Normal gall bladder wall thickness in cats is less than 1 mm (Hittmair *et al*. 2001). Commonly reported sonographic biliary tract abnormalities irrespective of inflammatory phenotype include increased gall bladder wall thickness (15 to 83%), CBD distension (31 to 50%) and increased gall bladder "sludge" (33 to 38%) (Brain *et al*. 2006, Callahan Clark *et al*. 2011, Marolf *et al*. 2012).

Results from one recent study suggest that the sonographic appearance of the gall bladder in cats with suspected hepatobiliary disease could be useful in the prediction of bile culture positivity (Policelli Smith *et al*. 2017). Because studies have suggested that the presence of bactibilia of cats is pathogenic, bacterial culture positivity of bile could be used as a diagnostic puzzle piece to support a suspected diagnosis of NC, cholecystitis or both in cats with assumed hepatobiliary disease (Sung *et al*. 1990, Sung

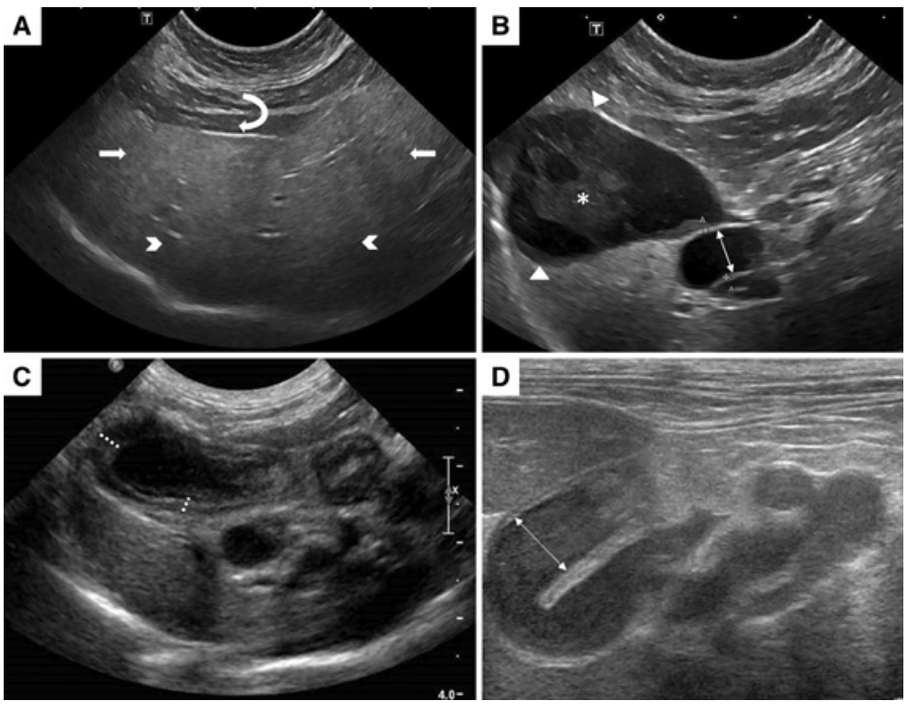

FIG 3. Ultrasonographic images from cats with cholangitis/cholangiohepatitis. (A,B) Eight-year-old female-spayed, domestic shorthair cat with neutrophilic cholangitis/cholecystitis and hepatic lipidosis. (A) The hepatic parenchyma is diffusely hyperechoic (solid white arrows) with hyperattenuation of the ultrasound signal in the deep field (white chevrons). The liver is hyperechoic relative to the falciform fat pad (curved white arrow). (B) There is mild diffuse thickening of the gall bladder wall (solid white arrow). There is lobular, amorphous echogenic material within the lumen of the gall bladder (white asterisk). There is dilation of the cystic duct (double-headed white arrow). An ultrasound-guided PUC was performed and bacteriology revealed growth of *Enterococcus* species. The cat was hospitalised and treated successfully with supportive care, supplemental nutritional support via oesophagostomy tube and susceptibility-guided antibiotic administration. (C,D) Thirteen-year-old, female-spayed, domestic shorthair cat with chronic cholangitis/cholecystitis associated with *Platynosomum* species. (C) Diffusely thickened, hyperechoic gall bladder wall that measured up to 2.0 mm (dashed white line). The lumen contained predominately anechoic material. (D) Severe diffuse dilation of the cystic duct (double-headed white arrow) and CBD (9.1 mm) with no obstruction identified. The cat lived indoors with access to a fenced enclosure. Baseline biochemical parameter abnormalities consisted of increased liver enzyme activities, AST [320 U/L; reference interval (RI), 13 to 43 U/L], ALT (222 U/L; RI, 32 to 83 U/L), ALP (433 U/L; RI, 11 to 60 U/L), hyperbilirubinemia (6.3 mg/dL; RI, 0.1 to 0.4 mg/dL), hypoalbuminemia (1.8 mg/dL; RI, 2.2 to 3.4 g/dL) and hyperglobulinemia (7.1 g/dL; RI, 3.4 to 5.3 g/dL). *Platynosomum* species, ova were identified via faecal sedimentation. The cat was hospitalised for 3 days and treated successfully with supportive care and praziquantel (20 mg/kg, subcutaneously once every 24 hours for 4 days). Images courtesy of Eric T. Hostnik DVM, MS, DACVR-DI, DACVR-EDI (Ohio State University, College of Veterinary Medicine) and Andrew Specht DVM, DACVIM (University of Florida, College of Veterinary Medicine).

et al. 1991a, Savary-Bataille *et al*. 2003, Brain *et al*. 2006, Byfield *et al*. 2017). Importantly, bactibilia is not an exclusive finding in cats with NC and/or cholecystitis because bacterial infection can occasionally occur in cats with other hepatobiliary disorders such as LC, CC, hepatic lipidosis or neoplasia (Byfield *et al*. 2017, Pashmakova *et al*. 2017).

Policelli Smith *et al*. (2017) reported that cats with at least one or more abnormal gall bladder sonogram finding were 21 times more likely to have positive bacterial culture results compared to cats that had an unremarkable gall bladder appearance. Specific gall bladder ultrasonogram abnormalities associated with increased odds of culture positivity included a thickened gall bladder wall (OR, 6.7; 95% CI, 2.2 to 20.5) or the presence of "sludge" (OR, 3.2; 95% CI, 1.1 to 9.3) (Policelli Smith *et al*. 2017). Overall, ultrasonogram findings had a sensitivity (96%; 95% CI, 78 to 99.9%), specificity (49%; 95% CI, 34.1 to 63.9%), positive predictive value (PPV; 48% (95% CI, 41 to 55%) and negative predictive value (NPV; 96%; 95% CI, 77 to 99%) to predict bile culture positivity in cats with suspected hepatobiliary disease (Policelli Smith *et al*. 2017). The high NPV (96%) indicates that if a cat had a normal gall bladder on ultrasonogram, it was highly unlikely that bile culture would yield a positive result. Furthermore, the low PPV (48%) suggests that if a cat had an abnormal gall bladder on ultrasonogram, it was unreliable in predicting culture positivity. These results must be interpreted with caution because several variables in that retrospective study were not accounted for that could have led to false-negative culture results and thus inflated the NPV and lowered the PPV. Ultrasonography will also provide information regarding the presence of concurrent disease or complications such as pancreatitis, intestinal disease (*i.e*. IBD or lymphoma), cholecystitis, cholelithiasis, biliary rupture or EHBDO; all of which could affect clinical decisions and prognosis.

The diagnosis of EHBDO in cats can be difficult, but is essential in deciding whether a cat requires emergent surgical intervention or medical therapy. Sonographic criteria used to facilitate a diagnosis of EHBDO include CBD dilation of more than 5 mm in diameter, dilation of intrahepatic biliary ducts and the identification of an obvious source of obstruction (*e.g*. choledocholithiasis, inspissated bile plugs, neoplasia) (Leveille *et al*. 1996, Gaillot *et al*. 2007) (Fig 3). Gall bladder size is not a reliable indicator of EHBDO as it can appear normal in cats with confirmed

obstruction and dilated in cases without (Gaillot *et al*. 2007, Callahan Clark *et al*. 2011).

The collection of bile and subsequent submission for cytological examination and aerobic/anaerobic bacterial culture can provide integral diagnostic and actionable information and should be performed in cats with suspected NC. Bile can be procured either via ultrasound-guided PUC or by cholecystocentesis performed at the time of exploratory laparotomy or laparoscopy. Percutaneous ultrasound-guided cholecystocentesis has the advantage of being minimally invasive, is relatively safe, and can provide clinically relevant information early in the diagnostic investigation. Major complications related directly to a PUC procedure are uncommonly encountered when performed by trained individuals and high-risk (*e.g*. emphysematous cholecystitis, severe coagulopathy, haemodynamically unstable) cats are avoided (Savary-Bataille *et al*. 2003, Brain *et al*. 2006, Koster *et al*. 2016, Policelli Smith *et al*. 2017). A description with visual aide of the PUC procedure can be found in Griffin (2019).

Cytological examination of bile offers the clinician several advantages such as (1) guiding initial antimicrobial therapy, (2) detection of difficult to culture bacteria (*e.g. Helicobacter* species), (3) identification of mixed populations of bacteria that can be missed due to being overgrown by *E. coli* in culture, (4) neutrophilic inflammation in the absence of bacteria is still clinically relevant and (5) non-bacterial pathogens (*Platynosomum* species, *Toxoplasma gondii*, *Candida albicans*) or (6) neoplastic cells are occasionally identified (Boomkens *et al*. 2004, Koster *et al*. 2016, Pashmakova *et al*. 2017, Lo Piccolo *et al*. 2019, Palermo *et al*. 2019) (Fig 4).

There is a paucity of information regarding the frequency of bacterial culture positivity in cats with NC. The available literature is limited, most importantly, by its retrospective nature and resultant uncontrolled variables that skew the interpretation of reported results. Details regarding specific inflammatory phenotype, antibiotic history and culture methodology are rarely reported. Investigators from one small case series of cats with cholecystitis or acute NC reported that all six cats had growth of at least one bacterial isolate (Brain *et al*. 2006). Another study reported 71% (5/7) of cats with pancreatitis-associated EHBDO and NC had growth of at least one bacterial isolate (Mayhew & Weisse 2008). Other retrospective case series have reported lower rates of positive bile and/or liver bacteriology results (14 to 48%), but were reflective of cats with all hepatobiliary diseases rather than just cats with NC (Wagner *et al*. 2007, Twedt *et al*. 2014, Peters *et al*. 2016, Byfield *et al*. 2017, Pashmakova *et al*. 2017, Policelli Smith *et al*. 2017). A recent retrospective study found that 50% (6/12) of cats with NC had intrahepatic bacteria identified using FISH (Twedt *et al*. 2014). These results highlight the potential complementary role that FISH could have in the identification of intrahepatic bacteria in cats with NC that have negative bacterial culture results.

Histopathology of liver biopsy samples is required for a definitive diagnosis and can be obtained via laparotomy, laparoscopy or by the ultrasound-guided percutaneous needle core (*i.e*. Tru-Cut) method. Each technique has advantages and disadvantages that must be taken into consideration on a case-by-case basis. Wedge liver biopsy during laparotomy is the optimal method for obtaining a diagnosis and is recommended for cats with suspected EHBDO (Cole *et al*. 2002). Laparotomy also has the added benefit of visualising and sampling extrahepatic structures but is associated with greater morbidity than other methods and may not be suitable for cats that are not stable. Laparoscopy has emerged as a minimally invasive diagnostic and therapeutic alternative to laparotomy (Robertson *et al*. 2014, Mitchell *et al*. 2017, Conceicao *et al*. 2018, Lafuente *et al*. 2018, Sakals *et al*. 2018). Robertson *et al*. 2014 recommends liver biopsy acquisition using laparoscopy in cats with suspected hepatobiliary disease without EHBDO; however, there is a lack of published data comparing the diagnostic accuracy of laparoscopic liver biopsies with wedge biopsies. Consideration should be given to the concomitant acquisition of biopsy samples from small intestine and pancreas in cats that remain stable under anaesthesia after collection of liver biopsies. The relatively high frequency that concurrent inflammatory disorders (or alimentary lymphoma) are diagnosed in those organs support the rationale for their acquisition as it could affect

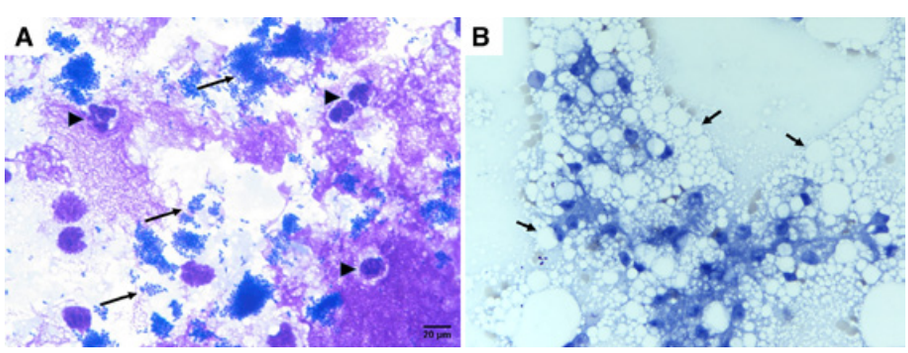

FIG 4. Cytological description of bactibilia (A) and hepatic lipidosis (B) in cats with neutrophilic cholangitis/cholecystitis. (A) Cytocentrifuge preparation made from aspiration of bile from a 16 year old, male-neutered, domestic shorthair cat with a history of triaditis. Present within the sample are several degenerate neutrophils (black arrowheads) and aggregates of 1×2-µm bacterial rods (black arrows) amongst variable amounts of hazy, amorphous, blue material (bile). Organisms were identified as *Escherichia coli* by aerobic bacterial culture. Modified Wright's stain, ×100 objective. Scale bar = 20 µm. (B) Liver sampling with fine-needle aspiration diagnosis of hepatic lipidosis in an eight-year-old female-spayed, domestic shorthair cat. Lipid accumulation and droplets (black arrows) amongst hepatocytes. Wright-Giemsa stain, ×50 objective. Images courtesy of Clark Broughton DVM (Texas A&M University, College of Veterinary Medicine), Mary Nabity DVM, PhD, DACVP (Texas A&M University, College of Veterinary Medicine) and Nina Randolph DVM (Ohio State University, College of Veterinary Medicine).

long-term prognosis and treatment. The Tru-Cut needle core method has several appealing features that have contributed to the commonality of its use in cats with hepatobiliary disease including rapid sample acquisition, low-risk for complications when performed by trained individuals, and is usually less-expensive than other methods (Pavlick *et al*. 2019). While complications related to the Tru-Cut needle core biopsy method in cats are uncommon, they can be life threatening when they do occur. The primary disadvantage is that samples representative of the primary liver disease may not be retrieved. Tru-Cut needle core biopsy diagnoses were reported in one study to correlate with wedge biopsies in only 48% of cases (Cole *et al*. 2002). A thorough review of liver biopsy techniques can be found in Rothuizen & Twedt (2009). Regardless of sampling method, biopsies should be obtained from multiple liver lobes because disease severity can vary greatly in individual cats.

Cytological examination of liver via ultrasound-guided fine-needle aspiration should be considered in cats that are not stable or when cat-owners are averse to liver biopsy collection. Cytology can support a diagnosis of lymphoma or concurrent hepatic lipidosis (Roth 2001, Wang *et al*. 2004) (Fig 4). Clinicians cannot exclude infiltrative liver disease when cytological examination of the liver detects hepatic lipidosis alone (Willard *et al*. 1999). Neutrophilic inflammation can occasionally be detected but this is a non-specific finding and bacteria are rarely identified (Roth 2001, Wang *et al*. 2004, Masserdotti 2020). Therefore, the primary purpose of cytological evaluation of liver is to rule out other clinically relevant infiltrative disorders or to determine if the cat also has hepatic lipidosis. Peritoneal effusion is occasionally present but may not become apparent until the cat is rehydrated. The fluid should be sampled and submitted for fluid analysis, cytological examination and possibly bacteriology if indicated. Fluid cytology findings consistent with bile peritonitis include golden, green or black-brown pigments free or within macrophages or lakes of mucinous material (white bile). If bile peritonitis is suspected but fluid cytological evaluation is unclear, then assessment of bilirubin concentrations in the fluid is indicated. Peritoneal fluid bilirubin concentration, that is more than two times concurrent blood bilirubin concentration, is confirmatory.

While histopathology is considered the gold standard criterion for establishing a diagnosis of NC, liver biopsies are often not obtained due to factors such as high risk to an unstable patient or lack of owner consent. In lieu of histopathology, clinicians are forced to utilise a combination of clinical signs, physical examination findings, haematology/biochemistry results, imaging results, bile/liver cytological examination, bacteriology and response to therapy to establish a presumptive diagnosis.

A consensus on optimal therapy has not been determined; therefore, the following recommendations are based on anecdotal clinical experience and review of available literature. Cats with suspected NC should be admitted to the hospital. Outpatient therapy can be considered in stable cats with mild disease (*e.g.* euhydrated and mild clinicopathologic abnormalities). Therapeutic intervention is then dictated by the severity of disease, comorbid disorders and the presence of clinically relevant complications that could require surgical intervention such a cholecystitis, cholelithiasis, biliary tract neoplasia, EHBDO and biliary rupture. Antibiotics are the foundation of therapy and drug selection should be based on bacteriology and susceptibility test results. Antibiotics with broad-spectrum coverage (Gram-negative, Gram-positive, aerobes and anaerobes) should be administered in moderate to severe cases while bacteriology results are pending and in those same cats that do not have cultures performed. A single antibiotic can be used initially in mild cases without cultures performed and alterations made, if needed, based on clinical and clinicopathologic response. Antibiotic administration in these cats should not be postponed to collect bile for bacteriology testing. The risk for clinical decompensation and death far outweigh the possibility of obtaining false-negative bacterial culture results. The most commonly isolated bacteria from bile and/or liver tissue are aerobic and anaerobic bacteria of enteric origin including *E. coli*, *Enterococcus* species, *Clostridium* species and others (Brain *et al*. 2006, Wagner *et al*. 2007, Mayhew & Weisse 2008, Twedt *et al*. 2014, Peters *et al*. 2016, Byfield *et al*. 2017, Pashmakova *et al*. 2017, Policelli Smith *et al*. 2017).

Antimicrobial sensitivity results for bacterial isolates cultured from bile and/or liver from dogs and cats with suspected hepatobiliary disease were reported in Wagner *et al*. (2007) and Pashmakova *et al*. (2017). Wagner *et al*. (2007) found that 67 and 82% of *E. coli* isolates were susceptible to amoxicillin/clavulanate and ciprofloxacin, respectively. In that same study, 100 and 86% of *Enterococcus* species, isolates were susceptible to amoxicillin/clavulanate and ciprofloxacin, respectively. The Pashmakova *et al*. (2017) study found that *E. coli* isolates had the following antimicrobial susceptibility results; amoxicillin/clavulanate (percentage, total number of isolates tested; 33%, 6), cefpodoxime (66%, 6), enrofloxacin (83%, 6), tetracycline (83%, 6) and trimethoprim sulfamethoxazole (100%, 6). Distribution from that study for *Enterococcus* species, isolates included ampicillin (83%, 6), chloramphenicol (86%, 7), enrofloxacin (14%, 7) and tetracycline (57%, 7). Susceptibility testing of *Enterococcus* species, to amoxicillin/clavulanate, cefpodoxim and trimethoprim sulfamethoxazole were not performed. These bacterial susceptibility results should be interpreted with caution because of the unknown affect that time and the subsequent emergence of antimicrobial resistance could have on their direct application to cats currently.

The current recommendation is to treat with antimicrobials for 4 to 6 weeks, but evidence to support this duration of treatment is lacking. The topic of duration of antimicrobial administration in humans with acute (neutrophilic) cholangitis is controversial. The Tokyo Guidelines 2018, an international reference that describes therapy for acute cholangitis in humans, suggests that antibiotics be administered for 4 to 7 days after control of the source of infection, except with respect to *Enterococci* species, or *Streptococci* species, for which 2 weeks is recommended (Gomi *et al*. 2018). The French Infectious Disease Society proposed antibiotics be administered for 3 days after source control of infection with therapeutic bile drainage (Wintenberger *et al*. 2017). Source control

of infection in humans generally translates to therapeutic bile drainage, temporary diversion via cholecystostomy tube or cholecystectomy for suspected cholecystitis or cholelithiasis. Currently, "source control" is not accomplished in most cats with NC, so adoption of the short-course antibiotic regimen used in humans cannot be used in cats. It is also important for clinicians to search for and treat diseases that would predispose cats to recurrent episodes of NC such as cholelithiasis, pancreatitis, intestinal disease (IBD or lymphoma) or partial EHBDO.

Nutritional support is required in most cats to treat or prevent concurrent hepatic lipidosis and is best achieved with the placement of an oesophagostomy tube or nasoesophageal/gastric tubes. Nasoesophageal/gastric tubes are viable short-term options for unstable cats or when cat-owners are averse to the placement of an oesophagostomy tube. A review of oesophagostomy and nasoesophageal/gastric tubes that includes visual aid for placement can be found in Webb (2018). The administration of oral appetite stimulants can be attempted in stable cats with mild disease but should be abandoned in favour of an oesophagostomy tube if voluntary food consumption does not amount to ≥80% of resting energy requirements (RER) within 5 to 7 days (Chan 2020). Calculation of daily energy requirements for cats that weigh more than 2 kg: 70×(body weight in kg)$^{0.75}$ and cats ≥2 kg: 70+(body weight in kg) (Chan 2020). Diets formulated for cats that are easily digestible, high protein (5 to 6 g per 100 kcal), fat and low carbohydrate, such as standard canned or liquid "recovery" or "maximum-calorie" diets are generally successful (Chan 2020). The optimal type of diet is unclear and will vary with concurrent comorbid disorders. For example, diets fed to cats with hepatic encephalopathy or severe azotaemia should have lower protein (3 to 4 g per 100 kcal) (Chan 2020). Regardless of the type of diet, it should be reintroduced slowly as to mitigate the risk for refeeding syndrome (Cook *et al*. 2021). The specific timeline that 100% RER is achieved will vary on a case-by-case basis. It is generally recommended to aim to reach full RER within 3 to 4 days, but adjustments are made based on serial assessments that include weight, physical examination and clinicopathologic results (Center 2005). Supplemental feeding should continue until the cat voluntarily consumes ≥75% of its RER (Chan 2020).

Intravenous crystalloid fluids are indicated in the majority of cats. Electrolyte derangements (*e.g*. deficiencies in phosphorous, potassium and magnesium) are common and should be corrected intravenously. Other commonly used treatments include anti-emetics (*e.g*. maropitant and ondansetron) as well as hepatoprotective agents such as ursodeoxycholic acid (UDCA), S-adenosylmethionine (SAMe), N-acetylcysteine (NAC), silymarin and vitamin E. A thorough review of cytoprotective agents in cats with hepatobiliary disease can be found in Webster & Cooper (2009). Specific treatment considerations for cats with hepatic encephalopathy can be found in Lidbury *et al*. (2016). The liver is essential for storage and activation of many water soluble vitamins in cats including thiamine and cobalamin; therefore, hepatobiliary disease with or without hepatic lipidosis increases the risk for deficiency. Therefore, it is commonly recommended to supplement these cats with cobalamin (starting with 250 µg subcutaneously once every 7 days) and a fortified B-complex solution (2 mL mixed with each litre of fluids) (Center 2005, Webb 2018).

Corticosteroids administered at anti-inflammatory dosages [prednisolone; (1.0 to 1.5 mg/kg once every 24 hours)] could be indicated in some cats with NC that fail to substantially improve clinically within 2 weeks of antibiotics and other ancillary interventions, or if clinical deterioration occurs before that time. If clinical deterioration occurs, then comorbid disorders or complications that could require surgery such as biliary rupture or EHBDO must be excluded before initiation of corticosteroid therapy. Antibiotics and other supportive care treatments should be continued concurrently with prednisolone. The optimal duration of therapy with prednisolone will vary on a case-by-case basis, but generally aim to gradually wean the cat off completely within 4 to 8 weeks or to the lowest effective dosage to mitigate clinical signs. Some cats can be gradually weaned off, while others require long-term therapy. The specific reason that some cats with NC benefit from corticosteroids is not known but some theories include (1) concurrent chronic pancreatitis or intestinal disease (*e.g*. IBD or lymphoma), (2) potential immune-mediated mechanism of disease and (3) improved bile flow from reduced tissue oedema. An elimination diet trial is eventually recommended in cats with confirmed or suspected concurrent chronic intestinal inflammation.

Prompt surgical intervention is needed for cats with fixed EHBDO such as choledocholithiasis, inspissated bile plugs or neoplasia (*e.g*. CBD, pancreatic or duodenal). Consideration should be given to therapeutic ultrasound-guided PUC as a bridge to eventual surgical intervention when the cat is stable. In addition, emergent surgical intervention is required for cats with bile and/or septic peritonitis as well as in cases with imaging results that are diagnostic for or suggestive of biliary rupture. Surgery is also recommended when imaging results are indicative of severe and/or emphysematous cholecystitis even in the absence of EHBDO. Suspected partial or transient EHBDO, such as pancreatitis or cholangitis, should be treated medically and only taken to surgery in refractory cases. Surgical techniques to restore bile flow include (1) temporary procedures: choledochal stenting and cholecystostomy tube placement or (2) permanent procedures: cholecystectomy and biliary-enteric diversion. The specific technique is often heavily influenced by intraoperative findings.

Published outcome data in cats with NC are scarce. Prognosis for cats with NC is generally good if treated aggressively, but can be influenced by serious concurrent disorders such as EHBDO, neoplasia, acute necrotising pancreatitis, sepsis, multiple organ dysfunction syndrome or biliary rupture (Hirsch & Doige 1983, Gagne *et al*. 1999, Mayhew *et al*. 2002, Brain *et al*. 2006, Mayhew & Weisse 2008). Gagne *et al*. (1999) reported an overall mean survival time for cats with NC of 29.3 months, with 47% (7/15), 40% (6/15) and 13% (2/15) of cats surviving less than 1 year, 1 to 5 years and more than 5 years, respectively. The majority of cats (71%; 5/7) that survived less than 1 year had a serious concurrent disorder that could have directly or indirectly

contributed to their death (*e.g.* feline infectious peritonitis, lymphoma, chronic kidney disease, diabetes mellitus and IBD). Given the high perioperative mortality rate, it is reasonable to presume that cats with NC and EHBDO that require surgical intervention have a worse prognosis than cats that do not need surgery. Mayhew *et al.* (2002) found that the mortality rates of cats with EHBDO and underlying neoplasia or inflammatory disease (*e.g.* cholangitis, pancreatitis, cholelithiasis, cholecystitis) was 100% within 3 days, and 40% within 7 days of surgery, respectively. A more recent study found that prognosis for cats with inflammatory disease as the underlying cause for EHBDO can do well postoperatively, with 69% (9/13) of cats surviving to hospital discharge and an overall median survival time of 255 days (range, 4 to 2196 days) (Buote *et al.* 2006).

LYMPHOCYTIC CHOLANGITIS/ CHOLANGIOHEPATITIS

Lymphocytic cholangitis/cholangiohepatitis competes with NC as the predominant inflammatory hepatobiliary disease in cats (Gagne *et al.* 1996, Gagne *et al.* 1999, Callahan Clark *et al.* 2011, Hirose *et al.* 2014, Fragkou *et al.* 2016, Bayton *et al.* 2018, Fluen *et al.* 2019). The WSAVA Liver Standardisation Group characterised LC histologically as infiltration of small lymphocytes in the portal region with varying degrees of fibrosis and bile duct proliferation. Lymphocytes can also be identified around or within biliary epithelium, but is not a required feature for the disease (Van Den Ingh *et al.* 2006) (Fig 5). Working within the confines of this definition, there is a wide spectrum of congruent histologic features that has contributed to the diverse terminology used to describe the disorder (*i.e.* non-suppurative cholangitis/cholangiohepatitis, lymphocytic portal hepatitis and progressive lymphocytic cholangitis/cholangiohepatitis). Presently, it is unclear if the range in histologic features could reflect disease chronicity, or perhaps, distinct phenotypic entities within a larger LC syndrome. A relatively common combination of histologic changes includes infiltration of small lymphocytes primarily in the portal region, a varying magnitude of portal fibrosis and biliary or oval cell proliferation (Gagne *et al.* 1996, 1999, Weiss *et al.* 1996). Some cats have lymphocytes that infiltrate within or immediately adjacent to biliary epithelium (*i.e.* bile duct targeting), and have varying degrees of inflammation, peribiliary fibrosis and progressive ductopenia (Prasse *et al.* 1982, Lucke & Davies 1984, Day 1998, Warren *et al.* 2011). Then, there are cats that have an expansion of infiltrating lymphocytes that is difficult to discern from a well-differentiated lymphoma (Van Den Ingh *et al.* 2006).

Cats of any age, breed or sex can be diagnosed with LC. Reported median/mean ages at the time of diagnosis are 4.4 to 15 years (range, 0.4 to 21 years) (Prasse *et al.* 1982, Lucke & Davies 1984, Day 1998, Gagne *et al.* 1999, Warren *et al.* 2011, Marolf *et al.* 2012, Hirose *et al.* 2014, Otte *et al.* 2014, Bayton *et al.* 2018). Collectively, several retrospective studies have

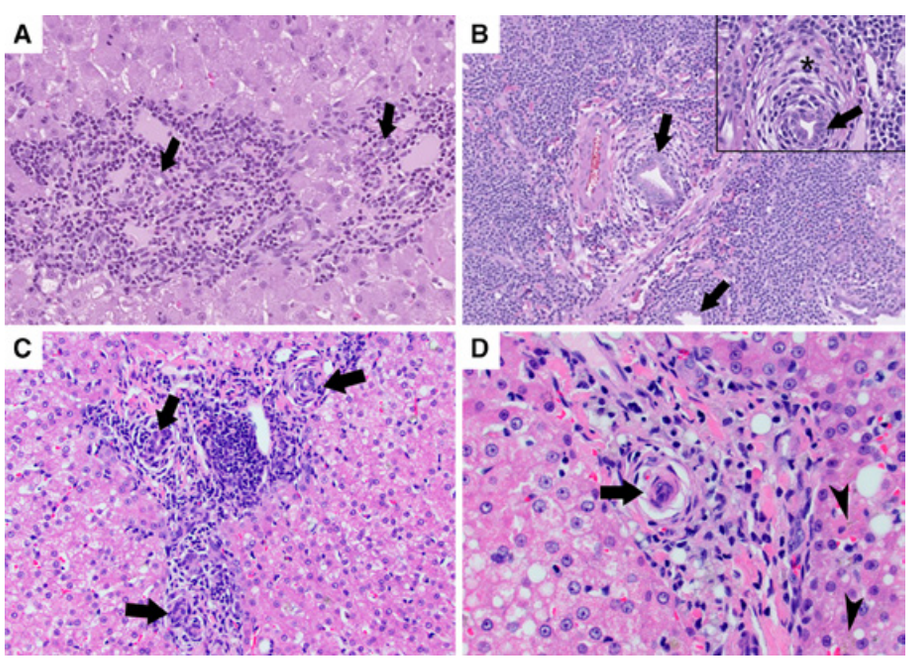

FIG 5. Lymphocytic cholangitis. Liver biopsies from cats with lymphocytic (A) and chronic lymphocytic (B to D) cholangitis; images (C) and (D) are from the same case. Infiltrating and expanding the periportal interstitium and variably infiltrating into the surrounding hepatic parenchyma are aggregates of small lymphocytes (A to D). Accompanying these lymphocytes are increased numbers of biliary profiles (bile duct hyperplasia; black arrows). In the chronic lymphocytic examples, bile ducts are either lined by irregular cuboidal to columnar biliary epithelium (B) and frequently surrounded circumferentially by moderate amounts of fibrosis (highlighted by black asterisk in B but also present in C and D). In (C) and (D), bile ducts are irregular/damaged that could lead to ductopenia and periportal hepatocytes contain small quantities of yellow-brown pigment (secondary copper accumulation; D, black arrowheads). In addition to lymphocytic infiltrates, the periportal interstitium is infiltrated by small numbers of foamy macrophages (D). Haematoxylin & eosin stain. Images courtesy of John Cullen VMD, PhD, DACVP (North Carolina State University, College of Veterinary Medicine) and Sylvia Ferguson DVM, PhD, DACVP (Midwestern University College of Veterinary Medicine).

reported an overrepresentation of Persian breed cats (Prasse *et al*. 1982, Lucke & Davies 1984, Day 1998). Results from a recent epidemiologic survey found that Siamese and Burmese cats were at an increased risk for LC in New Zealand (Fluen *et al*. 2019). Similarly, a retrospective study from the Netherlands found that the Norwegian Forest Cat was predisposed (Otte *et al*. 2013). Breed associations were not identified in another epidemiologic survey from the UK (Bayton *et al*. 2018). Male and female cats appear to be equally represented (Prasse *et al*. 1982, Warren *et al*. 2011, Bayton *et al*. 2018, Fluen *et al*. 2019), although two studies suggest a possible male predominance (Day 1998, Otte *et al*. 2013).

The specific cause for the development of LC in cats remains elusive, but an immune-mediated pathogenesis is suspected based upon a collective evaluation of the literature that includes (1) the predominance of $CD3^+$ T-lymphocytes that surround bile ductules and infiltrate the portal/periportal region and biliary epithelium, (2) portal distribution of $CD79^+$ B-lymphocyte aggregates, (3) regional expression of major histocompatibility complex class II, (4) bile duct destruction and ductopenia and (5) clinical and histologic improvement with immunosuppression (Day 1998, Center 2009, Warren *et al*. 2011, Otte *et al*. 2014). While evidence for an immune-mediated aetiology is compelling, the underlying trigger(s) that initiates and/or perpetuates the aberrant inflammatory process is unknown.

Some authors have proposed a corollary with primary sclerosing cholangitis (PSC), an autoimmune inflammatory biliary disorder in humans, which could provide potential pathomechanistic insight for LC in cats (Prasse *et al*. 1982, Lucke & Davies 1984, Day 1998, Center 2009). Histologically, PSC is characterised by lymphocytic inflammation in the portal region with or without infiltrates in the biliary epithelium in the early stage of disease that progresses in severity to include the hepatic parenchyma, ductopenia and fibrosis (Angulo *et al*. 1999). Genetic and environmental factors are important causes, but definitive triggers of disease have not been identified. A large genome-wide association study found a strong link with human leukocyte antigen that supports a pathogenic role for T-lymphocytes (Liu *et al*. 2013). Similar genome-based studies have not been performed in cats, but a variable geographic distribution of high-risk breeds (*e.g*. Persian, Siamese, Burmese and Norwegian Forest Cat) could also support a similar interplay between genetics and environment.

The most important clinical risk factor for PSC is the presence of IBD, present in approximately 70% of humans with the disease (Wiesner *et al*. 1989). Concurrent inflammatory disorders in the intestine, pancreas or both are reported to occur in cats with LC (Weiss *et al*. 1996, Fragkou *et al*. 2016). Investigators of a recent prospective study found that 80% (20/25) of cats with LC from Greece had a concurrent inflammatory disorder with coexistence of either IBD alone (60%, 15/25) or in combination with chronic pancreatitis (*i.e*. triaditis; 20%, 5/25) (Fragkou *et al*. 2016). In humans, intestinal dysbiosis and inflammatory mediators are purported to be at the centre of this inflammatory disorder coupling (Dyson *et al*. 2018). Intestinal dysbiosis can result in microbes navigating to the biliary system via ascension through the CBD or portal circulation. Bacteria can then either alter the biliary microbiome and contribute to the loss of tolerance or act as a direct infectious pathogen inciting a cascade of inflammation that persists after their clearance (Bergquist *et al*. 2008). The "common channel" pancreaticobiliary duct and IBD-related dysbiosis in cats could increase the likelihood that microbes and/or inflammatory mediators end up in the biliary system. Evidence supportive of a direct infectious link in cats is lacking. While bacteria are rarely identified in bile/liver in cats with LC at the time of diagnosis, their absence does not preclude the possibility of an initial direct bacterial trigger (Warren *et al*. 2011, Twedt *et al*. 2014). Moreover, the biliary microbiological composition in cats with LC has not been explored.

Cats with LC can be subclinical with diagnostic investigations initiated after the incidental detection of abnormal liver enzyme activities on routine examination. This is in contrast to cats with NC that uniformly demonstrate clinical sign(s). Interestingly, up to 50% of humans with PSC are initially asymptomatic and are diagnosed after identification of increased liver enzyme activities (Broome *et al*. 1996). The majority of cats with LC that demonstrate clinical signs have a protracted history of slow progression over weeks to years, but most of these cats have had clinical signs noted by owners for several months before evaluation (Day 1998, Center 2009). Clinical signs can be episodic and include weight loss, polyphagia, anorexia, hyporexia, vomiting, jaundice and lethargy. Clinical signs most frequently recorded in one study were weight loss (78%, 18/23), jaundice (65%, 15/23), anorexia (52%, 12/23), vomiting (48%, 11/23) and listlessness (48%, 11/23) (Otte *et al*. 2013). Details regarding reported physical examination findings are scarce and when present, are not complete or consistent. Two retrospective studies that included only cats with LC identified ascites and hepatomegaly in 38% (15/40) and 30% (12/40) of cats, respectively (Lucke & Davies 1984, Day 1998). Lucke & Davies (1984) did not identify pyrexia in any of the 21 cat cohort. Both these studies included cats with similar histologic abnormalities; therefore, it is possible the reported examination findings are unique to a specific morphologic entity or stage of disease. Generally, physical examination findings can be unremarkable in some, and in others include dehydration, ascites, jaundice, hepatomegaly, pyrexia, as well as signs consistent with hepatic encephalopathy (*e.g*. seizures, dull mentation, ptyalism).

Biochemical parameter abnormalities are similarly variable to cats with NC. Most cats, but not all, have an increase in at least one or more of the following of ALT, AST, ALP or GGT that can range from mild to severe. There are only two retrospective studies with cohorts less than three cats that provided comprehensive biochemical results. From those studies, the frequency of cats with increased activity of either ALP or ALT ranged from 32 to 64% and 52 to 64%, respectively (Lucke & Davies 1984, Gagne *et al*. 1999). The previously mentioned studies only included a total of 39 cats with biochemical data and did not include GGT or AST enzyme activity. Hyperbilirubinemia is inconsistently identified and can be episodic in

presence and severity (Prasse *et al*. 1982, Lucke & Davies 1984, Gagne *et al*. 1999, Callahan Clark *et al*. 2011). Moreover, hyperbilirubinemia can occasionally be present in the absence of increased liver enzyme activity. At diagnosis, 28% (7/25) to 43% (6/14) of cats were reported to be hyperbilirubinemic (Lucke & Davies 1984, Gagne *et al*. 1999). Hyperglobulinemia is common but not distinguishable from NC or other hepatobiliary diseases. Haematology results vary but are commonly unremarkable, which is contrast to cats with NC (Prasse *et al*. 1982, Lucke & Davies 1984, Gagne *et al*. 1999, Callahan Clark *et al*. 2011).

Many of the ancillary diagnostic tests such as abdominal ultrasonogram, coagulation testing and serum cobalamin/folate concentrations overlap with those described for NC. There are no sonographic features that distinguish LC and NC (Marolf *et al*. 2012). Ultrasonography can provide information regarding the presence of concurrent disease. Concurrent EHBDO is possible, but occurs much less frequently than NC. Coagulation status should be assessed, especially before procedures. Bile should be collected via ultrasound-guided PUC or cholecystocentesis performed during laparotomy/laparoscopy and submitted for cytological examination and bacteriology testing because cats with LC can be complicated by a secondary bacterial infection (Fig 4).

Histopathology of liver biopsy samples is required for a definitive diagnosis. The presence and severity of disease can vary greatly within individual cats' livers and thus biopsy samples should be obtained from multiple liver lobes (Warren *et al*. 2011). A minimum staining panel in cats with suspected LC should include routine haematoxylin and eosin, Masson's trichrome and immunohistochemistry to detect T-lymphocytes, B-lymphocytes and biliary epithelium (cytokeratin) (Warren *et al*. 2011). This combination of stains and immunohistochemical testing improves characterisation of the disease and facilitates discrimination from well-differentiated small cell lymphoma. Warren *et al*. (2011) found that bile duct targeting, ductopenia, peribiliary fibrosis, B-lymphocyte aggregates and portal lipogranulomas were significantly more common in cats with LC and thus, could aid in distinguishing LC from hepatic lymphoma. In that same study, T-cell receptor was deemed helpful as an adjunct diagnostic procedure but should be avoided as a standalone test. Consideration should be given to the acquisition of biopsy samples from small intestine and pancreas in cats that remain stable under anaesthesia after collection of liver biopsies. The relatively high frequency that concurrent inflammatory disorders (or lymphoma) are diagnosed in those organs support the rationale for their acquisition as it could affect long-term prognosis and treatment.

Large clinical trials investigating optimal therapy for cats with LC are lacking; therefore, the following recommendations are based on results from small uncontrolled retrospective case series and anecdotal clinical experience. The initial therapeutic approach to cats with LC is similar to that described for cats with NC in regards to administration of broad-spectrum antimicrobials, supplemental enteral nutrition, hepatoprotective agents, B vitamins, intravenous fluids with electrolyte support and any other ancillary interventions that will vary on a case-by-case basis. Antimicrobial therapy is tailored to the sensitivity results of cultured bacteria from bile/liver tissue and continued for 3 to 4 weeks. It is recommended that antibiotics be administered for 2 weeks in cats with negative bacteriology results.

Long-term therapy requires immunomodulation that can be initiated after histopathologic confirmation of disease. This study recommends that prednisolone be administered at anti-inflammatory dosages (1.0 to 1.5 mg/kg per day) in conjunction with antimicrobials in cats with a concurrent bacterial infection. Immunosuppressive dosages of prednisolone (2 to 4 mg/kg per day) are recommended in cats with negative bacteriology results and in cats after complete treatment of bacterial infection. Ursodexoychilic-acid is a common component of long-term therapy because of its theoretical immunomodulatory effects and extrapolated benefit demonstrated in humans with PSC. Investigators from one retrospective study found that treatment with prednisolone resulted in greater histologic improvement compared to UDCA in cats; however, cats treated with UDCA in that study had less severe baseline histopathologic inflammation and the cohort was small (prednisolone, n = 5; UDCA, n = 4) (Otte *et al*. 2014). In another small retrospective study by the same investigators, cats treated with prednisolone alone had longer survival times compared with UDCA monotherapy (Otte *et al*. 2013). Center (2009) suggested that consideration be given to coadministration with metronidazole for its potential immunomodulatory properties and assistance with control of associated IBD. Response to therapy is based upon evaluation of clinical signs and biochemical parameters rather than repeat histopathological examination of liver biopsy samples. A complete response is characterised by resolution of signs as well as normalisation of liver enzyme activity and total bilirubin concentration; however, transient cyclical mild elevations in liver enzyme activity and total bilirubin concentration can occur in some cats. Potential complications related to LC over time include bacterial cholangitis, cholelithiasis, cholecystitis and biliary strictures. Serial examinations are recommended to occur once every 4 to 6 months as biochemical changes can precede overt clinical signs. The dosage of prednisolone is gradually decreased over 4 to 6 months until the lowest dose that prevents clinical signs and maintains normal liver enzyme activity and total bilirubin concentration is identified. Hepatoprotective agents are administered long term.

Cats that fail to respond completely to prednisolone or that relapse while being treated could require additional immunosuppressive therapy. Chlorambucil is the most commonly used second-line immunosuppressive drug in cats with LC. Optimal dosing has not been established, but Center (2009) recommended (2 mg orally, once every 24 hours initially, and then titrated to every other day). Center (2009) also recommended immunosuppression with methotrexate in severe refractory cases as a third-line option. Methotrexate imparts profound immunosuppression and should be used with extreme caution and vigilant monitoring for drug-associated complications.

Cats with LC have a variable prognosis. A collective review of the literature supports this with some cats not surviving to hospital discharge and others surviving for up to 7 years after

initial diagnosis (Prasse *et al*. 1982, Lucke & Davies 1984, Gagne *et al*. 1996, 1999, Day 1998, Otte *et al*. 2013). Even cats with severe clinical signs (*e.g*. jaundice, ascites) and morphologic abnormalities (*e.g*. biliary destruction, ductopenia, fibrosis) can respond to treatment and live for many years (Prasse *et al*. 1982, Lucke & Davies 1984). Investigators from one retrospective survival study found that the overall median survival of cats with LC treated with either prednisolone or UDCA as 795 days and the survival rates for 1, 2 and 3 years were 74, 56, and 35%, respectively (Otte *et al*. 2013). In that same study, purebred cats (hazard ratio (HR), 84, 95% CI, 3.1 to 2279.4) and cats treated with UDCA (HR, 25.1; 95% CI, 1.0 to 652.2) were more likely to have shorter survival times than domestic shorthair cats and cats treated with prednisolone, respectively (Otte *et al*. 2013). Several prognostic variables have been identified in humans with PSC that warrant future investigation in cats with LC such as histological stage, age and coexistence of IBD at diagnosis as well as total bilirubin concentration and liver enzyme activity during treatment (Karlsen *et al*. 2017).

CHRONIC CHOLANGITIS/CHOLANGIOHEPATITIS ASSOCIATED WITH LIVER FLUKE INFESTATION

Liver flukes reported to infect cats include trematode species of the families Opisthorchiidae (*Opisthorchis* species, *Metorchis* species, *Amphimerus* species and *Clonorchis* species) and Dicrocoeliidae (*Platynosomum* species). *Platynosomum* species is the most commonly reported liver fluke to affect cats and will be the focal point of this section of the review. This fluke is found worldwide and endemic in tropical and sub-tropical regions. Platynosomosis has been reported in Brazil, British Guyana, Cayman Islands, Colombia, Cuba, Curacao, Bonaire and Aruba, Indonesia, Malaysia, Mexico, Papa New Guinea, Nigeria, Puerto Rico, St. Kitts, Thailand, Venezuela, Trinidad and Tobago and in various regions of the USA (*e.g*. Florida and Hawaii) (Basu & Charles 2014). The prevalence of infection varies with geographic region and the density of free roaming cats. Countries with the highest reported prevalence include Malaysia (73%), St. Kitts (81%), Mexico (45%) and Brazil (43%) (Retnasabapathy & Prathap 1971, Rodriguez-Vivas *et al*. 2004, Krecek *et al*. 2010, Braga *et al*. 2016). There is a precipitous decline in occurrence in regions with owned cats that are confined predominately indoors. For example, prevalence in free roaming cats and owned-cats in St. Kitts was reported to be 81 and 6.8%, respectively (Krecek *et al*. 2010, Ketzis *et al*. 2020). This pattern was also reported in a study from Brazil that found free roaming cats (42%) had significantly greater occurrence of infection than confined cats (7.1%) (Salomão *et al*. 2005).

Lizards, geckos and marine toads are implicated in the transmission of the infective form to cats through predation. A recent experimental study demonstrated that mice could also be a contributory host (Pinto *et al*. 2014). After consumption of the infected intermediate host, the infective metacercaria excysts and migrates through the minor duodenal papilla, to the CBD and eventually the gall bladder and small intrahepatic bile ducts. Maturation to adult parasites requires 8 to 12 weeks at which time eggs are released into the bile and intestine (Taylor & Perri 1977). The median parasite burden reported in one study was 7 flukes/cat (range, 1 to 219 flukes/cat) and were more commonly found in the intrahepatic bile ducts (82.1%) than in gall bladders (6.8%) (Braga *et al*. 2016). However, parasite burden is variable, demonstrated by the results of another study that reported a mean of 110.4 flukes/cat (range, 1 to 843 flukes/cat) (Rodriguez-Vivas *et al*. 2004).

Most cats with platynosomosis in endemic regions are subclinical (Greve & Leonard 1966, Retnasabapathy & Prathap 1971, Palumbo *et al*. 1974, Taylor & Perri 1977). The severity of clinical signs is purported to be dependent on parasite burden, chronicity of infection and the individual immune response to the infection (Basu & Charles 2014). Cats with low parasite burden (*i.e*. <125 flukes/cat) are unlikely to demonstrate clinical signs and even high burdens (>1000 flukes/cat) are generally well tolerated (Taylor & Perri 1977). Reported clinical signs in cats with naturally occurring infection include anorexia, weight loss, lethargy, diarrhoea, vomiting and jaundice (Barriga *et al*. 1981, Haney *et al*. 2006, Xavier *et al*. 2007, Montserin *et al*. 2013).

Cats with naturally occurring platynosomosis that are presented for evaluation of clinical illness are expected to have increased liver enzyme activities and total bilirubin concentration (Greve & Leonard 1966, Haney *et al*. 2006, Xavier *et al*. 2007, Montserin *et al*. 2013). Experimentally infected cats can have transient derangements in liver enzyme activity and total bilirubin shortly after inoculation (Taylor & Perri 1977). A subfraction of cats in that experimental study had resurgence of clinicopathologic abnormalities that coincided with recrudescence of clinical signs in the chronic phase (Taylor & Perri 1977).

Similar to cats with NC or LC, abdominal ultrasonogram can be unremarkable or non-specific changes can be identified (Salomão *et al*. 2005, Koster *et al*. 2016) (Fig 3). Investigators from one recent study found that 30 (8/27) and 56% (15/27) of cats with platynosomosis had normal ultrasonogram appearance of the liver and CBD, respectively (Koster *et al*. 2016). Of the 19 cats with liver abnormalities on ultrasonogram, the most common changes included hyperechogenicity (59%, 16/27), heterogenicity (48%, 13/27) and enlargement (22%, 6/27) (Koster *et al*. 2016). The median CBD diameter was 3.9 mm (IQR, 2.85 to 5.25 mm) with 22% (6/27) of cats with CBD diameter greater than 5 mm (Koster *et al*. 2016). The gall bladder wall was thickened (*i.e*. ≥ 1 mm) in all cats and was more than 2-mm thick and hyperechoic in 26% (7/27) of cats (Koster *et al*. 2016). Gall bladder "sludge" was identified in 37% (10/27) of cats.

Detection of eggs via faecal examination or cytological evaluation of bile can be used to obtain a diagnosis (Fig 6). Occasionally, eggs can be identified cytologically via ultrasound-guided fine-needle aspiration of the liver (Fig 6). At least four different faecal methods have been shown to diagnose platynosomosis in cats including direct smear, zinc sulphate, formalin-ether sedimentation and double centrifugation with Sheather's sugar flotation solution with the latter touted by investigators from a

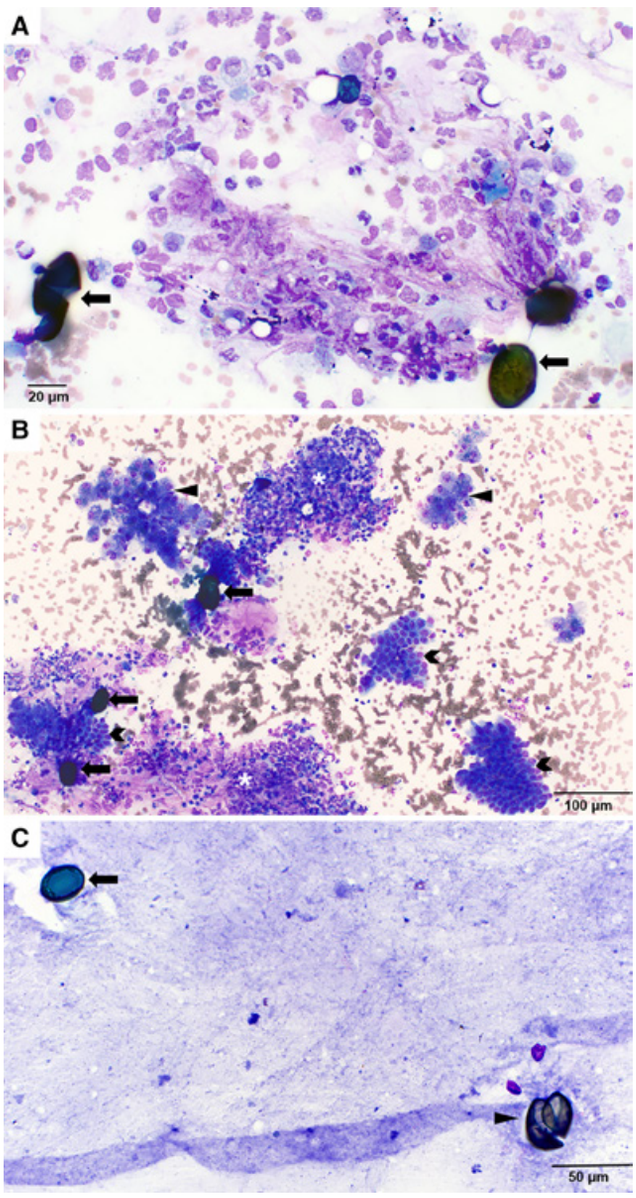

FIG 6. Cytological description of (A,B) ultrasound-guided fine needle aspirates from hyperechoic liver nodules and (C) bile from cats with platynosomsis. (A,B) Seven-year-old, female-spayed, domestic shorthair cat with a several-month history of anorexia, weight loss and increase liver enzyme activities. Numerous large, round-to-oval structures, consistent with *Platynosomum fastosum* ova (black arrows), were seen admixed with neutrophils enmeshed in nucleoproteinaceous material (white asterisk). Several clusters of uniform-appearing biliary epithelium (black chevron) were also noted, consistent with biliary hyperplasia, along with a few cohesive sheets of mildly atypical hepatocytes (black arrowheads). Wright-Giemsa stain, (A) ×50 objective, (B) ×20 objective. (C) Five-year-old, female-spayed, domestic shorthair cat with a week history of hyporexia and increased liver enzyme activities. The preparation consisted of amorphous to streaming, occasionally globular lavender to variably basophilic material on a pale basophilic background. A few, oval, yellowish-brown to green structures measuring approximately 25 to 30 µm×35 to 40 µm are observed, with morphology consistent with *Platynosomum* species ova (black arrows). These had a glossy appearance with a thin dark brown-green rim and an occasional granular internal structure. Hollow/ruptured forms were also noted (black arrowhead). A faecal sedimentation test recovered rare *Platynosomum concinnum* ova. Wright-Giemsa stain, ×40 objective. Images courtesy of Kamila Sandoval DVM (University of Florida, College of Veterinary Medicine) and Francisco O. Conrado DVM, MSc, DACVP (Tufts University, Cummings School of Veterinary Medicine).

recent study as being the most sensitive technique (Eisenbraun *et al.* 2020). Faecal examination may not identify eggs because of variable shedding density with low parasite burden, inconsistent egg morphology (immature and embryonated forms) and sporadic egg passage especially with the development of EHBDO. The inconsistent sensitivity for a single faecal examination to detect eggs was highlighted in one study in which eggs were identified in only 35% (77/222) of cats with platynosomosis (Retnasabapathy & Prathap 1971). Serial faecal examinations or cytological evaluation of bile are indicated in cats with negative faecal egg counts but clinical suspicion for platynosomosis remains high (Koster *et al.* 2016). Investigators from a recent study identified eggs on cytological evaluation of bile in all cats with platynosomosis and egg counts in bile were significantly greater than faeces (Koster *et al.* 2016).

Histopathologic examination of liver typically shows varying degrees of cholangitis/cholangiohepatitis, cholangiectasis, biliary hyperplasia and fibrosis (Fig 7). The inflammatory cell infiltrate consists of a diverse spectrum of inflammatory cells that can vary depending on chronicity, secondary bacterial cholangitis and the immune response in the individual cat. Some cats have predominately lymphocytes and plasma cells, while others have considerable infiltration with eosinophils and neutrophils (Greve & Leonard 1966, Retnasabapathy & Prathap 1971, Haney *et al.* 2006, Xavier *et al.* 2007, Montserin *et al.* 2013, Braga *et al.* 2016, Cullen & Stalker 2016, Koster *et al.* 2016). Eggs and adults can be identified within the lumen of dilated bile ducts (Braga *et al.* 2016, Koster *et al.* 2016). Histologic evidence of chronic cholecystitis is common (Braga *et al.* 2016, Cullen & Stalker 2016, Koster *et al.* 2016).

Praziquantel administered at a dosage of 20 mg/kg intramuscularly once every 24 hours for three consecutive days is the recommended treatment (Lathroum *et al.* 2018). Cats can continue to shed eggs intermittently for up to 9 weeks after treatment despite successful elimination of adults. Lathroum *et al.* (2018) suggested that a repeat treatment 12 weeks after the first could be beneficial as it would provide enough time for metacercariae consumed near the time of the initial treatment to mature. Adjunctive therapy to be considered will depend on severity of disease but generally include prednisolone (1 to 1.5 mg/kg orally, once every 24 hours), hepatoprotective agents and broad-spectrum antibiotics. Concurrent bacterial neutrophilic cholangitis/cholecystitis has been reported; although its overall prevalence has not been investigated (Koster *et al.* 2016). Additional supportive care measures including intravenous fluid therapy, correction of electrolyte abnormalities, anti-emetics and nutritional support should be provided when indicated.

Prognosis depends on the magnitude of clinical illness of the infected cat at the time of diagnosis. Cats that are subclinical and are diagnosed after an incidental identification of increased liver enzyme activities or faecal examination on routine wellness evaluations are expected to have a good prognosis. Most cats, even with severe changes to the biliary tract and severe cholecystitis, with a high parasite burden, often lack clinical signs and respond to praziquantel without the need for additional supportive care

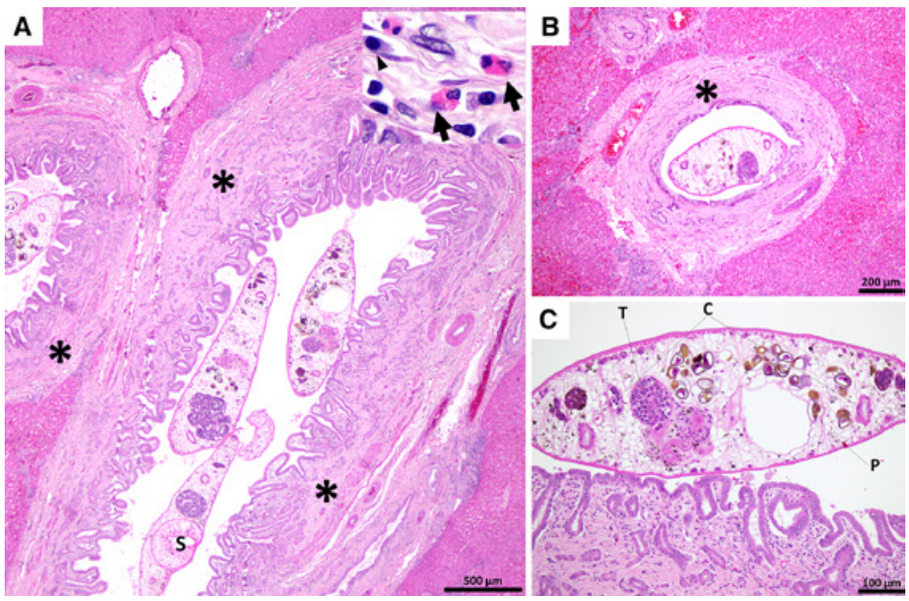

FIG 7. Chronic cholangiohepatitis, fibrosing, lymphoplasmacytic and eosinophilic, with intraductal adult trematodes in a cat, compatible with *Platynosomum fastosum*. (A,B) Portal areas are multi-focally expanded and result in the compression of adjacent hepatic parenchyma. Bile ducts are dilated with an increased number of bile ductules (biliary hyperplasia) and surrounded by marked fibrosis (black asterisk), sometimes bridging adjacent portal areas. Admixed within the proliferating fibrous connective tissue there is mild to moderate lymphoplasmacytic and eosinophilic infiltration (inset; arrowhead indicates plasma cells; black arrows indicate eosinophils). (C) Within the lumen of the bile ducts are longitudinal and tangential cross sections of adult trematodes (up to 1.7 cm long in histological sections) with an outer tegument, testis (T), a digestive tract consisting (paired blind ceca – C), a spongy parenchyma (P), suckers (S), uterus with multiple, asymmetrical, yellow-brown, up to 40-µm-long, thick-shelled eggs containing miracidia. Haematoxylin & eosin stain. Images courtesy of Pompei Bolfa DVM, MSc, PhD, DACVP (Ross University, School of Veterinary Medicine).

[Liza Koster, personal communication, BCSc, MMedVet(med), DECVIM-CA (internal medicine and cardiology)]. Therefore, if a cat becomes clinical from platynosomosis, then more profound liver dysfunction and complications have developed, and prognosis is guarded (Haney *et al*. 2006, Xavier *et al*. 2007, Montserin *et al*. 2013).

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Conflict of interest

The author of this article does not have a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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