Feline Cholangitis

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Key Points

- Cholangitis is one of the commonest liver diseases in cats, defined histologically by the WSAVA standardisation group as neutrophilic cholangitis (acute and chronic forms); lymphocytic cholangitis and chronic cholangitis associated with liver fluke. However, there is very likely to be overlap between chronic neutrophilic and lymphocytic cholangitis.

- The cause of acute neutrophilic cholangitis is usually bacterial infection of bile. Some cases of lymphocytic cholangitis and, potentially, also chronic neutrophilic cholangitis may be autoimmune, but evidence is weak and there is likely to be more than one cause of chronic disease.

- Diagnosis relies on hepatic histology and cytology and culture of bile and other tissues. Clinical, clinicopathological, and imaging findings of all categories of disease are similar and concurrent inflammatory diseases of the pancreas and intestine are common, further complicating investigation.

- Treatment advice is based on very little evidence. Treatment of acute neutrophilic cholangitis involves antimicrobial therapy and surgery for conditions impacting bile flow. Lymphocytic cholangitis cases are usually treated with steroids. Antibiotics may also be used in these and chronic cholangitis cases. All cats should receive supportive therapy.

- Future studies are urgently needed to understand the causes of the chronic disease and to follow up clinical cases to understand the long-term outcome and efficacy of different treatments (220 words including key words)

Synopsis (100 words or less)

Inflammatory biliary tract disease (cholangitis) is the commonest liver disease in cats but remains poorly understood. There are chronic lymphocytic and acute neutrophilic forms together with chronic neutrophilic cholangitis which may overlap both these categories. Acute suppurative cholangitis is often associated with bacterial infections and interruptions to bile flow. Lymphocytic forms may be immune-mediated but there is evidence of heterogenicity in histological and clinical appearance and response to treatment which may suggest several distinct diseases. This review discusses current knowledge, presentation and diagnosis of feline cholangitis and suggests avenues for future research. (92 words)

Introduction

Inflammatory biliary tract disease, both acute and chronic, is common in cats. Histological studies published in the UK, New Zealand and Japan all report cholangitis as the commonest feline liver disease, although with some differences in prevalence between categories [1–3]. Historically, cholangitis was less common in the USA where hepatic lipidosis was the most common feline liver disease [4]. The reason for these epidemiological differences is unknown. Cats differ from dogs in some important ways: cats suffer more commonly from inflammatory biliary tract disease, whereas dogs usually have parenchymal hepatic disease. Cats also often have concurrent inflammatory hepatic, pancreatic, and intestinal disease ('triaditis') which has been reviewed in a recent VCNA article[5] and is not recognised in dogs. This may be partly due to the anatomic relationship of the feline bile duct which usually joins their single pancreatic duct at the sphincter of Oddi just before exiting into the duodenum[6], although this is unlikely to be the only reason. In contrast, dogs usually have two pancreatic ducts which enter the duodenum separately from their bile duct. Finally, a lack of studies of feline liver disease hampers our understanding of etiology and effective treatment.

This article will review current knowledge of feline inflammatory biliary tract disease and it's clinical implications, discuss controversies over classification of the disease, and indicate some future directions for research. Chronic cholangitis associated with liver fluke is an important differential diagnosis for cats with marked periductal and portal fibrosis on histology which live in endemic areas but will not be discussed further in this review.

Definitions

Standardized criteria for histological assessment of cholangitis in cats should allow valid comparison between different studies. The WSAVA liver standardization group suggested, nearly 20 years ago, two histological sub-categories of acquired feline biliary tract disease not associated with liver fluke: neutrophilic cholangitis and lymphocytic cholangitis[8]. This categorization is controversial because the neutrophilic group is subdivided into an acute, truly suppurative category, which is associated with documented acute bacterial infection in many cases, and a chronic neutrophilic cholangitis group with mixed lymphocytic and neutrophilic inflammation (see table 1 and figures 1, 2b, and 2c). Lymphocytic cholangitis (LC) is reserved for those cases with purely lymphocytic inflammation (fig 2a). However, splitting chronic cases of feline cholangitis into two categories based on the inflammatory infiltrate remains unsatisfactory. In some published studies, the authors clearly defined which cases were acute neutrophilic and which were chronic [7], whereas other studies simply discussed neutrophilic and lymphocytic cases which leaves room for interpretation as to which category chronic neutrophilic cases were placed in [1,2]. Furthermore, studies which pre-date the WSAVA criteria used different terms which may not map neatly to the current terms (table 1) and pathologists in early papers suggested LC may be more than one disease [8,9] . This makes it difficult to interpret differences in presentation, response to treatment, and other factors reported in different studies. The problem is compounded by the likelihood that both chronic neutrophilic and lymphocytic categories have multiple etiologies, as discussed later. In addition, most cats have a single liver biopsy at one point in

time, so the progression of disease is often unknown, and biliary pathology is also recognized to have an irregular distribution in the liver[10]. For all these reasons and because of the potential overlap, this review article will not only discuss neutrophilic cholangitis (NC) and lymphocytic cholangitis (LC) but will also split the neutrophilic cholangitis group into acute neutrophilic cholangitis (ANC) and chronic neutrophilic cholangitis (CNC).

Table 1 – Pathological Classification of feline biliary tract disease- see also figure 1 and figure 2
Note: if inflammation traverses the limiting plate, the term 'cholangiohepatitis' is used

WSAVA Criteria	WSAVA histological description	Historical and alternative names	Potential problems with WSAVA criteria
Neutrophilic cholangitis NC	Acute stage: neutrophils surrounding and invading bile ducts	Suppurative or exudative cholangitis/ cholangiohepatitis	No problem with truly acute form In this review, will be termed 'acute neutrophilic cholangitis' ANC
	Chronic neutrophilic cholangitis –mixed inflammatory infiltrate in portal areas – neutrophils, lymphocytes and plasma cells and possibly fibrosis and bile duct proliferation	Non-suppurative cholangitis-cholangiohepatitis. Overlap with category 2	Potential overlap in pathology with lymphocytic cholangitis – see fig 1 In this review, will be termed 'chronic neutrophilic cholangitis' CNC
Lymphocytic cholangitis LC	Infiltration of lymphocytes into portal areas often associated with variable portal fibrosis and biliary proliferation. Lymphocytes centre on bile ducts and may infiltrate biliary epithelium, but not necessarily.	Lymphocytic cholangiohepatitis; lymphocytic portal hepatitis [11]; Chronic cholangiohepatitis[11]; non-suppurative cholangitis/cholangitis-cholangiohepatitis [12] Sclerosing cholangitis [13]	Potential overlap in pathology with CNC – see fig 1 Lymphocytic portal hepatitis reported in 1996 with no biliary tract involvement may or may not be the same disease[4]
Destructive cholangitis	Dogs only? Destruction and loss of bile ducts in smaller portal triads with	N/A	No problems except bile duct destruction/ ductopenia recognised in some chronic cholangitis cases[12,14]

	subsequent inflammation and fibrosis – postulated usually due to a drug reaction or viral infection		
Chronic cholangitis associated with liver fluke	Common in cats in endemic areas. Dilated larger bile ducts. Marked periductal and portal fibrosis. Mild to moderate mixed inflammation. Number of eosinophils is variable	N/A	None

Etiology and pathogenesis of cholangitis in cats

Acute and chronic neutrophilic (suppurative) cholangitis

Neutrophilic cholangitis (NC) was first reported in the veterinary literature over 40 years ago, with the first small case series of 5 Canadian cats published in 1983[15] . It was the commonest feline liver disease identified by recent pathology studies in the UK and Japan (20.5% and 28% of cases respectively)[1,3] and the second commonest in a pathology study in New Zealand (9.7%)[2] . All these studies included both ANC and CNC in one category which, as discussed above, has a potential overlap with lymphocytic cholangitis (figure 1). In a US pathology study of 44 cats, the categories were split: 7 cats had ANC and 33 had CNC [7]. The largest case series of NC was recently published in two papers documenting 168 cats seen by one author in the USA over nearly 40 years [16,17]. This study also included both ANC and CNC, documenting criteria for inclusion as a predominance of portal, duct-centric neutrophils.

ANC is believed to be due to bacterial infection in the biliary tract, either ascending from the small intestine or hematogenous which may be in the portal blood or systemically. Concurrent cholecystitis is common [18] . A study using eubacterial fluorescent *in situ* hybridisation (FISH) in liver biopsies from 39 cats with inflammatory liver disease and 19 normal cats found significantly more of the inflammatory cases were positive for bacteria and had intrahepatic bacteria. However, surprisingly, bacteria were most often localised to portal vessels, venous sinusoids and the parenchyma, rather than the bile duct, supporting translocation in the portal vein rather than ascending biliary tract infection [19].

The commonest bacteria identified with conventional culture are of gut origin particularly *E. coli* and enterococcus species [19] . The commonest anaerobes are *Bacteroides* and *Clostridium* [17]. A study of 6 cats with biliary tract bacterial infection documented on cytology

and culture of bile found *E. coli* in 4 cases, co-infecting with *Streptococcus* species in one case and *Clostridium* in one case; *Streptococcus* in one case and *Salmonella enteritica* serovar typhimurium in one case [20] . Unusual infections such as *Providencia* species can also be found [21], so it is important to culture cases whenever possible (see section below). Bile-tolerant *Helicobacter* species have been isolated in a few cats with cholangiohepatitis but also in the bile of cats without liver disease, so their significance is unknown [22].

The WSAVA criteria suggest that CNC is also caused by bacterial infection. This may be true in some cases, but others may be due to chronic biliary tract obstruction or lymphocytic cholangitis with secondary hepatic necrosis or infection. There is strong evidence in the literature that the bacterial infection of the feline biliary tract is predisposed by interruptions to bile flow, and it is important to look for these during investigations. Bacteria arriving in the liver either in the biliary tract or hematogenously are removed by liver resident macrophages (Kupffer cells) and excreted in bile and any disruption of bile flow may predispose to colonisation. In the earliest published case series, 4/4 cats with CNC had documented or potential biliary obstruction (two had choleliths and two histologically confirmed chronic pancreatitis) and 1/1 cat with ANC had a gallbladder cyst[15] . In the recent large study of NC, 53% of cats had a documented extrahepatic biliary obstruction (EHBO) and 42% had choleliths – only 58% of which were found on diagnostic imaging [16]. Ductal plate malformations were found in 44% of cats. There was biopsy-confirmed chronic inflammatory enteropathy (IBD) in 60/68 and pancreatitis in 41/44. Twenty-eight of these cats with pancreatitis had EHBO and 20 of 28 had documented cholelithiasis. Only a small number of affected cats had documented predisposing factors for bacterial infections, such as dentals procedures, being fed raw food, being FIV positive, or receiving immunosuppressive medication. However, these predisposing factors should be considered to reach a diagnosis.

Lymphocytic cholangitis/ non-suppurative cholangitis/cholangitis-cholangiohepatitis
Chronic idiopathic cholangitis not associated with liver fluke was first reported in the USA in 1982 in 3 cats[8] followed by a series of 21 cats from the UK[23] . Since then, there have been several case series of the disease which was initially commoner in the UK but is now also widely recognized in the USA[9,12,24]. LC is the commonest form of cholangitis in some studies [2]but less common than neutrophilic in others (table 2). The cause is suggested to be immune-mediated. This is likely in a proportion of cases, but feline chronic biliary tract disease likely represents a syndrome of diseases which look similar on histology but have different etiopathologies[6]. In fact, the early literature on the disease suggested there was more than one histological form, with acute and chronic stages of LC and a histologically distinct lymphocytic portal hepatitis [4,9]. Age and breed predispositions vary between reports as do clinical presentation and response to treatment (table 2).

An immune-mediated etiology was supported by an early histological study of LC which showed periportal lymphocytes were predominantly CD3 positive T cells, with some infiltrating the bile duct epithelium and some piecemeal necrosis in acute cases [9]. The largest study of immunohistochemistry of feline LC compared 51 cases of LC with 27 cases of hepatic lymphoma and found that 68.6% of cases of LC were T cell predominant whereas 29.4% of cases had an equal mix of B and T cells and only 1 case was B cell predominant. Bile

duct targeting of inflammatory cells and ductopenia were also reported in that study, suggestive of immune-mediated duct destruction.

A recent Master's Degree Thesis at the University of Cambridge described novel work using indirect immunofluorescence on frozen liver sections from a normal cat to look non-specifically for feline anti-liver antibodies in serum from 34 cats with chronic cholangitis (both LC and CNC) and 12 control cats with non-inflammatory liver disease [14] . Seven of the 34 cases were positive for anti-liver antibodies, 4 with a nuclear staining pattern typical of anti-nuclear antibodies and 3 with cytoplasmic staining, whereas none of the controls were positive. While this does not prove immune-mediated disease, it is certainly supportive. Other features of the histology in some cases, such as ductopenia and concentric peribiliary fibrosis (both typical of human primary sclerosing cholangitis, PSC) also suggest immune-mediated disease. However, this study differed from previous studies in finding a B cell predominance in 40% of the cases. The reason is unclear but might partly reflect the inclusion of CNC in this study.

However, the outcome and response to treatment was not investigated in any of these studies so the clinical relevance of these findings is unknown.

Signalment and Clinical Signs of Cholangitis

The signalment and clinical signs of ANC, CNC and LC in published papers are summarised in table 2, noting the difficulty in separating CNC from ANC and LC in many studies. There is considerable overlap between groups. Any age or breed can be affected, although most are middle aged and older. This may reflect an underlying chronic disease or biliary obstruction in many cases of NC. Early reports suggested LC was more common in younger cats, but more recent studies suggest it affects cats of all ages including older cats. One study found cats with cholangitis alone were significantly younger than those with concurrent disease in the gut and pancreas [25]. There is no obvious sex predisposition for any form of cholangitis in most studies. Some suggest an increased risk of NC in pedigree breeds including Persian, British Shorthair, Burmese, and Siamese. DSH were the commonest affected in the most recent study of NC whereas they were under-represented in a UK prevalence study. Early studies of LC suggested Persian cats were at increased risk whereas more recent studies suggest either no breed risk or an increased risk in Burmese and Siamese. Differences between studies may represent sampling or other bias, different histological categorisation and disease overlaps, and differences in geographical location or era.

Typical clinical signs (table 2) are lethargy, hyporexia, and vomiting. Jaundice is less common and fewer than half of the reported cases of neutrophilic cholangitis are pyrexic. Abdominal pain is also uncommon but may be under-recognised as cats are notoriously adept at hiding their pain. However, cats may also be asymptomatic with nearly half of the cats with cholangitis (both NC and LC) in one recent study having no clinical signs [25] . Cats in that study were significantly more likely to have clinical signs if they had concurrent IBD and pancreatitis and given the high prevalence of concurrent disease including pancreatitis and cholelithiasis, it is impossible to know which signs are specific to cholangitis and which result from concurrent diseases. Early reports, particularly from the UK, showed several cats with LC presenting with ascites.

Signs can be present for a wide range of time prior to presentation, with an overlap between NC and LC and cats with NC do not always present acutely.

Table 2 – Signalment and clinical signs of cats with neutrophilic and lymphocytic cholangitis

Study; number of cases; and country	Diagnosis method	Age	Breed and sex	Clinical signs
Neutrophilic cholangitis				
Hirsch and Doige [15] 5 cats Canada	Biopsy or PM all cases. 2 case reports; 3 histology database	Median 13 years; range 10-17 years	2 Siamese; 3 DSH. 2 female, 3 male	One cat signs for 2 weeks, one 2 days 5/5 icterus; vomiting, weight loss. 2/2 pyrexia; 2/5 polydipsia; 1/2 hypersalivation
Brain et al[20]– 6 cats (1/6 GI lymphoma) Australia	Cystocentesis cytology and culture alone 3 Histopathology 3.	Mean 7.7 years; median 8 years; range 4-12 years	2 Burmese; 2 Abyssinian; 1 Russian Blue; 1 DSH	All cats signs 1-5 days * Pyrexia. Lethargy; anorexia; inappetence; vomiting; diarrhea; 4/6 jaundice and abdominal pain
Center et al[16] 168 cats suppurative cholangitis (ANC + CNC - neutrophils predominant cell type) USA	Histology of liver biopsies reviewed by author	Median 10 years; range 0.5-20 years. Cats with ductal plate abnormality were younger	No control group to calculate OR. 123 DSH. 19 DLH; 10 Siamese; 3 Manx; 2 each Persian and BSH; 1 each of 7 other pedigree breeds.	Signs median 30 days (range 1-1,460 days). Hyporexia; lethargy; vomiting all 80%. Jaundice 67%. Pyrexia 43%. Hepatomegaly 34%; abdominal

			No sex predisposition	pain 23%; diarrhea 19%.
Lymphocytic cholangitis				
Prasse et al [8] 3 cats USA	Histology of liver (3 cats) and pancreas (2 cats) examined by one pathologist	3 yo, 3.5 yo, and 9 yo	2/3 DSH 1/3 Persian All male	3/3 Intermittent anorexia, weight loss 2/3 hepatomegaly 1/3 jaundice 1/3 ascites
Lucke and Davies[23] 21 cats UK	Histology examined by one pathologist. 10 postmortem; 13 surgical wedge biopsy (overlap with PM)	Range 6 months to 10 years. 14/21 4 years or less	6/21 Persian (3 from one breeder) No sex predisposition	Ascites 11 cats, of which 9 bright; 2 anorexia and weight loss Jaundice 10 cats 2 cats both ascites and jaundice 1 cat episodic neurological signs No cats pyrexic
Day [9] 20 cats Uk	Histology of 14 surgical wedge biopsies and 6 PM examined by one pathologist	Mean 4.4 years, range 0.5– 12 years	14 DSH 2 Persian 1 DLH 1 Siamese 2 unknown 12 males; 6 females; 2 unknown	Duration known in 8 cases: median 3.5 months range 2 weeks to 5 months Signs reported 19 cases: Jaundice 14 Hepatomegaly 6 Weight loss 5 Ascites 4 Inappetence 3

				Acute collapse 2 Neurological signs 2
Warren et al[12] 51 cats with LC to compare with 27 cats with lymphoma USA	Histology of wedge biopsies (62); Tru-cut biopsies (14), or at postmortem (4)	LC group median age 10.5 years, range 1-19 years Lymphoma older but not significant	No breed or sex predisposition	Not reported
Otte et al[26] 26 cats Netherlands	Histology of Tru-cut biopsies	Median age 12.3 years, range 1.2- 21 years)	17 European shorthair, 3 BSH; 3 Norwegian forest; 1 each Persian; Siamese; mixed breed 20 males, 6 females Significant male predisposition	Weight loss 18/23; icterus 15/23; anorexia 12/23; vomiting 11/23
Both neutrophilic and lymphocytic cholangitis				
Gagne et al[11] – total 41 cats – 25 lymphocytic portal hepatitis LPH (assume equivalent to LC); 7 ANC; 9 CNC USA	Histology of liver biopsies	Mean LPH 8.2 yrs; median 7.1 years; range 0.4-17.4 years Mean ANC 5.7 years; median 3.3 years; range 1-17 years	12/25 LPH pure bred 5/16 CNC purebred No sex predisposition	Anorexia, weight loss, lethargy and vomiting common ANC 6/7 weight loss 5/7 pyrexic CNC 3/9 weight loss

		Mean CNC 9.7 years; median 9 years range 1.2-20 years		1/9 pyrexic LH significantly lower bodyweight than NC
Clark et al[7]– total 44 cats: 7 ANC; 33 CNC; 3 LC; 1 liver fluke USA	Histology at necropsy	Median all groups 9 years (range 6 weeks to 19 years). ANC significantly younger than CNC.	38/44 DSH No sex predisposition	All groups together: lethargy 75%; vomiting 66%; weight loss 58%; hypoxia 50%; pyrexia 22% (1/7 ANC); icterus 34% (2/5 ANC; 1/2 LC)
Marolf et al[27] Ultrasound study of 14 LC; 12 NC (ANC+CNC) USA	Cats with both histology and ultrasound	ANC+CNC- mean 10.7 years (range 4-17 years); LC mean 11.4 years (range 4-11 years)	22/26 DSH or DLH	All groups together: anorexia and weight loss most common; vomiting and lethargy next most common
Hirose and others 71 feline liver biopsies: NC (ANC+CNC) 23.9%; LC 14.1% Japan	Histology of liver biopsies	Median: NC 10 years 11 months; LC 5 years 1 month – difference not significant	No breed predisposition. 41/71 Japanese domestic cats No sex predisposition	Not reported
Fragkou et al [25] Cholangitis in 30/47 cats in study No cases ANC CNC 5/30 LC 25/30 Greece	Histology of surgical biopsies of liver as part of a larger study also of pancreas and gut	Median age LC+CNC no concurrent disease 3.5 years (range 3-10) Median age LC + CNC with concurrent IBD and pancreatitis significantly	Not reported	16/27 symptomatic 14/20 non symptomatic Cats with concurrent IBD and pancreatitis significantly more likely to

		older 7.5 years (range 3-14)		be symptomatic
Fluen and others 154 liver biopsies of which 39 LC 19 NC (ANC + CNC) New Zealand	Histology of liver biopsies at diagnostic pathology lab in New Zealand	Mean/median ANC+CNC 7 years range 0.25 to 14 years Mean/median LC 10 years range 3-17 years	Increased OR NC (ANC+CNC) Persian; Sphinx; reduced OR DSH Increased OR LC Burmese and Siamese	Not reported
Bayton et al [1] 1217 liver biopsies of which 258 NC (ANC+CNC) 85 LC UK	Histology of liver biopsies at diagnostic pathology lab in UK.	Median (ANC+CNC) 9.2 years; range 4 months to 18.5 years. Median age LC 11 yo range 11 months to 19.5 years	Increased OR NC (ANC+CNC) in British shorthair; Burmese; Siamese; DLH. DSH reduced risk No breed risk identified for LC No sex predisposition any category	Not reported

NC = neutrophilic cholangitis; ANC = acute neutrophilic cholangitis; CNC = chronic neutrophilic cholangitis; LC = lymphocytic cholangitis; LPH = lymphocytic portal hepatitis; DSH = domestic shorthair; DLH = domestic longhair. PM = postmortem; OR = odds ratio; USA = United States of America; UK = United Kingdom; IBD = inflammatory bowel disease.

*Except lymphoma case which had signs for 6 weeks

Clinical investigation of suspected feline cholangitis

Definitive diagnosis of ANC, CNC, and LC is made on histology of liver biopsy, preferably combined with culture and cytology of bile and other tissues as discussed below. It is possible to make a diagnosis of bacterial cholangitis/cholecystitis and presumptive ANC simply with liver ultrasound and a bile aspirate for cytology and culture [20]. This allows effective treatment of the bacterial infection but does not identify if it is primary or secondary to an underlying liver disease. Therefore, if the cat continues to show clinical signs after treatment, further investigations including liver biopsy are strongly

recommended. The clinical signs (table 2) and clinical pathology (table 3) and imaging findings (table 4) for all types of feline cholangitis overlap with each other and with IBD and pancreatitis which may be present concurrently, making diagnosis a particular challenge.

Clinical pathology

Changes on clinical pathology in published studies are summarised in table 3. Neutrophilia is recognised in less than half of cases, and increases in ALT activity are more common than those of ALP. The degree of elevation of liver enzyme activities is highly variable between cats. Increased bilirubin is common, but it is important to note that both bilirubin and liver enzyme activities can remain within reference ranges in some cases. Leukocytosis and band neutrophils may be more common in NC but are not seen in all cases. Cats with LC may show an increase in gamma-globulin concentration, making feline infectious peritonitis an important differential diagnosis. Coagulation times are not often measured but are frequently increased when they are.

Diagnostic imaging

Findings on abdominal ultrasound in cats with cholangitis are summarised in table 4. Ultrasonographic abnormalities of the liver and biliary tract are common, as are abnormalities in the pancreas and gut. However, one study of cats with cholangitis noted that most cases had normal hepatic and biliary tract ultrasound [27] and it is clear from table 4 that finding a normal liver does not rule out either LC or NC. It is also clear that no findings on diagnostic imaging reliably differentiate NC from LC. It is important to look carefully for disease in other organs, particularly the pancreas, GI tract and kidneys and also to check the gallbladder and for evidence of diseases impacting bile flow, such as choleliths, EHBO, or cystic liver disease, noting that small concretions at the sphincter of Oddi can be missed on imaging [16], and overlying gas in the small intestine may also obscure choleliths .

Cytology of bile and liver biopsy

A sample of bile should be taken for cytology and culture if possible. Histopathology of the liver alone is not enough to diagnose acute bacterial infection because the disease may be confined to the biliary tract and hepatic histopathological changes may be mild and non-specific. Cholecystocentesis to obtain bile for cytology and culture can be performed under ultrasound guidance or at laparoscopy or surgery and appears to be relatively safe in both normal and diseased cats [28,29]. In one study of ultrasound-guided cholecystocentesis including 70 cats, a positive bile culture was much more likely in cats with an abnormal gallbladder although specificity of this ultrasound finding for biliary bacterial growth was only 49%. However, having a normal gallbladder on ultrasound gave a 96% negative predictive value for negative culture [30]. Published papers suggest it is unlikely that bacteria would be cultured from bile in normal cats, unless they are contaminants. Recent studies also suggest that cats do not have a core bile microbiome [31].

In the recent large case series of NC, only 80% of the 168 cats had bacterial culture and novel immunohistochemical markers of bacterial infection were used on histology in all cats. Bacterial culture was positive in 93 of 135 cats (69%) even though many had prior antibiotic treatment. However, using the immunohistochemical markers, suggested bacterial infection in 142/151 cases (94%) [17].

It is important to request cytology in addition to culture because finding neutrophils in bile and intracellular bacteria greatly increases confidence that this is a primary infection and not a contaminant [18]. Bile culture appears to be more sensitive than culture of liver histology or liver aspirates [29] . An increase in sensitivity has been reported when samples from multiple sites were combined (liver, gall bladder bile, choledochal cyst, crushed choleliths, or gallbladder wall scrape or section)[17] .

Histology

Histological examination of a liver biopsy is the 'gold standard' for diagnosis of NC and LC. It is important to check coagulation times prior to biopsy and pre-treatment with vitamin K_1 for 2-3 days prior to biopsy is wise because of the high prevalence of vitamin K responsive coagulopathy in cats particularly when there is concurrent pancreatic and intestinal disease [32] .

Wedge biopsies collected at laparotomy or laparoscopy are likely to be the most representative and allow at least visual inspection, and potential biopsy, of the pancreas and gut. Ultrasound-guided Tru-Cut needle biopsies may also be taken. However, the use of semi-automatic Tru-Cut guns should be avoided in cats because of reports of fatality likely due to vagally induced shock [33] .

Treatment and prognosis

The lack of prospective treatment studies combined with poor understanding of the cause of the disease means that treatment of feline cholangitis, particularly chronic forms, remains empirical and unproven. More than 10 years ago, one paper noted that determining the histological subtype of disease did not help with evidence-based treatment or prognosis [7] , and the same remains true now.

Acute neutrophilic cholangitis: Cats with documented biliary tract infection should be treated with an appropriate antibiotic based ideally on the results of culture and susceptibility testing. The optimal length of course is unknown – 4-6 weeks are traditionally recommended. Amoxycillin or potentiated amoxycillin is a good initial choice as it is concentrated in bile and many isolates are sensitive. However, culture and susceptibility testing is wise to identify resistance both at the beginning of the course and after several weeks of treatment if the cat is not responding as expected. Ursodeoxycholic acid is given as an additional choleretic and anti-inflammatory agent and S-adenosylmethionine could also be justified. Both are logical but there are no studies demonstrating efficacy.

In one recent study of NC, it was controversially suggested that cats should receive 1-6 months of antibiotic treatment and lifelong antibiotics for cats with ductal plate malformation [16] . In the author's experience, intermittent courses of antibiotics can also be effective in these cats and may only be necessary infrequently. Intravenous imipenem was also used at surgery in some cats, which would not be permitted under most European and Scandinavian responsible antibiotic use policies.

Septic or extremely sick cats may require hospitalization for intravenous fluid and intravenous antibiotic administration during the initial stages of therapy. Careful attention should be paid to feeding anorexic cats to avoid the concurrent development of hepatic

lipidosis; a diet designed for feline chronic enteropathy, or a high-protein diet designed for feline critical care would be much more appropriate in these animals than a protein-restricted liver diet. Tube-feeding should be instituted if necessary.

Consideration should be given to surgical treatment of any identified underlying cause such as choleliths or chronic gall bladder disease. The prognosis is generally good and affected cats usually recover completely provided they are treated early and appropriately. In the recent study, median survival time ranged from 240 to 694 days and surgery for choleliths and cholecystectomy was associated with an increased survival time in cats with choleliths [16] .

Chronic neutrophilic and Lymphocytic cholangitis:Treatment of CNC and LC is largely empirical and relies on various combinations of steroids, antibiotics, ursodeoxycholic acid, antioxidants, and nutritional support. Papers are largely descriptive and lack long term follow up. In the only published retrospective treatment study, 10 cats treated with prednisolone alone lived significantly longer than 13 cats treated with ursodeoxycholic acid alone [26] , supporting the use of steroids. However, no control group, an unusual patient population with a large male predominance and inclusion of the two treatment groups enrolled over different time periods mean other confounding variables were possible. Repeat biopsies after treatment in 5 of the prednisolone treated and 4 of the ursodeoxycholic acid treated cats showed a mild improvement in the lymphocytic inflammation in 4 out of 5 cases on corticosteroids but an increase in one case, suggesting unpredictable variability in response to treatment[34] .

Helpful descriptive studies of treatment include an early report of 21 cats with LC in which 11 cats with ascites were treated with paracentesis and diuretics and all ascitic and/or jaundiced cats received high dose prednisolone (up to 4 mg/kg/day) for 3 weeks with gradual tapering over 6-8 weeks [23] . Some cats went into long term remission whereas others relapsed and required long term steroid treatment. At the end of the study, 6 cats were alive with the longest reported follow up of 5 years. One cat which had ascites and treatment with diuretics and prednisolone was killed in a road traffic accident 6 months later when repeat histology of the liver showed a marked reduction in lymphocytes and bile duct proliferation compared with the original liver biopsy, again supporting steroid treatment.

Another older study highlighted the confusion about treatment of cats with all categories of chronic cholangitis. Cats had varying treatments but cases with both LH and CNC were treated with high doses of steroids and antibiotics or no steroids or antibiotics [11] . This study also described assisted feeding in anorexic cats and reported similar survival times in both groups with all treatments. Many cats in each group had serious concurrent diseases including feline infectious peritonitis, chronic renal disease, amyloidosis, and neoplasia which would have affected prognosis.

Given all this confusion, what does the author recommend? Ideally treatment decisions are based on a careful interpretation of histological findings combined with clinical and clinicopathological findings. Important differential diagnoses are feline infectious peritonitis and the emerging feline hepadnavirus (ref chapter in this VCNA), so immunosuppressives should NOT be used without histology. If there is a predominant lymphocytic infiltrate on

histology with no evidence of bacterial infection, the author would use immunosuppressive doses of steroids combined with ursodeoxycholic acid and s-adenosylmethionine and a high-quality diet. Symptomatic treatments of vomiting and abdominal pain are also important. Clinical and clinicopathological response should be carefully monitored and immunosuppression stopped if liver enzyme activities increase – remembering that cats do not have a corticosteroid-induced isoenzyme of ALP. Antibiotics would be reserved for cats with a significant additional neutrophil population and could be started empirically pending bile or tissue culture results. If these are negative but bacterial infection is still suspected, eubacterial FISH could also be requested on tissue blocks.

The reported prognosis is very variable in cats with LC and CNC with some cats having long survival times.

Future directions in chronic biliary tract disease research

The lack of advances in our understanding of the causes and treatment particularly of chronic biliary tract disease (CNC and LC) in cats may be because we have focused on histological studies alone in our attempts to classify the disease. In human medicine, several very different biliary tract diseases look similar on histology and other methods confirm diagnosis. Primary sclerosing cirrhosis (PSC) is most common in younger men and associated in many cases with concurrent large bowel inflammatory bowel disease and a very high risk of cholangiocarcinoma. It is diagnosed on magnetic resonance cholangiopancreatography imaging of strictures of the biliary tree in the absence of other causes [35] . Primary biliary cholangitis (PBC) is a disease commoner in older women associated with a variety of other autoimmune diseases and diagnosed on finding increased serum anti-mitochondrial antibodies (AMA) [36] . IgG4 related disease is a multi-organ immune-mediated disease recently recognized in humans and English cocker spaniel dogs with chronic pancreatitis [37] . IgG4+ cholangitis is part of the human syndrome and is diagnosed from clinical features together with increased serum or tissue IgG4. Neither PSC nor PBC respond to steroids and most cases are gradually progressive until end-stage disease and liver transplant. IgG4+ cholangitis responds well to steroids and to treatment with the anti-B cell antibody rituximab. Dogs have been shown to have four IgG subtypes, like humans, and to produce IgG4 [38] However, cats only appear to produce IgG1 and IgG2 [39] , so specific IgG4 related disease would not occur in this species. However, this does not rule out a similar feline-specific disease involving different immunoglobulins. In conclusion, more studies are needed in cats looking beyond the liver biopsy ideally with advanced imaging and more antibody studies.

In addition, there are no long-term prospective studies of feline chronic cholangitis. Can we currently honestly tell owners if their cat will recover or if its disease will wax and wane life long? How many cats with chronic biliary tract disease die of their disease? How many develop hepatic malignancy? Which treatments are most effective? Such studies are a fundamental part of human clinical research, with patient registries allowing better understanding of clinical course, response to treatment and long-term risk of cancer. It is time we did more of these studies in cats.

Figure legends

Figure 1: diagrammatic representation of the over-lap between histological types of cholangitis as defined by the WSAVA liver standardisation group, indicating potential reasons for overlap

Figure 2: Histological sections of feline liver, provided by Dr Tim Scase, Pathologicus Ltd

Fig 2a Marked chronic lymphocytic/plasmacytic cholangitis/cholangiohepatitis: Very large numbers of lymphocytes along with lesser numbers of plasma cells extend around bile ducts and expand portal triads. Large numbers of intraepithelial lymphocytes and small numbers of intraepithelial neutrophils are present. The main differential diagnosis for this pattern is a small cell lymphoma (21x magnification)

Figure 2b: : Moderate chronic, lymphocytic, plasmacytic and neutrophilic cholangitis: (WSAVA classification chronic neutrophilic cholangitis). Moderate to large numbers of lymphocytes and plasma cells mixed with lesser numbers of neutrophils extend around hyperplastic bile ducts. There is mild to moderate proliferation of hypertrophied endothelial cells and fibroblasts around the bile ducts. Scattered neutrophils extend into the biliary epithelium. (x30)

Figure 2c: Acute mild neutrophilic cholangitis. Small numbers of neutrophils infiltrate within the lumina of bile ducts. There is mild hypertrophy and hyperplasia of biliary. (x25)

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