REVIEW

Pancreatitis and triaditis in cats: causes and treatment

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Pancreatitis in cats is frequently accompanied by concurrent disease in other organ systems. Co-morbidities include hepatic lipidosis, inflammatory liver disease, bile duct obstruction, diabetes mellitus, inflammatory bowel disease, vitamin deficiency (B12/cobalamin, folate or K), intestinal lymphoma, nephritis, pulmonary thromboembolism and pleural and peritoneal effusions. "Triaditis" is the term used to describe concurrent inflammation of the pancreas, liver and small intestines. Triaditis has been reported in 50 to 56% of cats diagnosed with pancreatitis and 32 to 50% of those with cholangitis/inflammatory liver disease. A definitive diagnosis of triaditis is based on the histopathological evaluation of each organ. However, the specific conditions of each organ that constitute a diagnosis of triaditis remains to be defined. While the aetiopathogenesis of pancreatitis and its relationship to inflammation in other organ systems is unclear, preliminary studies point to a heterogeneous group of conditions with differential involvement of host inflammatory and immune responses and enteric bacteria. Comprehensive, prospective studies that simultaneously evaluate the presence of predefined clinical, clinicopathological and histopathological abnormalities, coupled with high-resolution evaluation of pancreaticobiliary morphology, immunological profiling and screening for bacterial colonisation are required to advance diagnosis and therapy.

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INTRODUCTION

Pancreatitis in cats is frequently accompanied by concurrent disease in other organ systems. Co-morbidities include hepatic lipidosis, inflammatory liver disease (ILD), bile duct obstruction, diabetes mellitus, inflammatory bowel disease (IBD), vitamin deficiency (B12/cobalamin, folate or K), intestinal lymphoma, nephritis, pulmonary thromboembolism and pleural and peritoneal effusions (Hill & Van Winkle 1993, Akol *et al.* 1993, Simpson *et al.* 1994, 2001, Weiss *et al.* 1996, Ferreri *et al.* 2003, Schermerhorn *et al.* 2004). "Triaditis" is the term used to describe concurrent inflammation of the pancreas, liver and small intestines. Triaditis has been reported in 50 to 56% of cats diagnosed with pancreatitis (Swift *et al.* 2000, Forman *et al.* 2004) and 32 to 50% of those with cholangitis/ILD (Table 1) (Weiss *et al.* 1996, Callahan Clark *et al.* 2011, Twedt *et al.* 2014). This paper provides an overview of the causes and treatment of pancreatitis and triaditis in cats, and an in depth consideration of the aetiopathogenesis of triaditis.

THE SPECTRUM OF TRIADITIS

A definitive diagnosis of triaditis is based on the histopathological evaluation of each organ. However, the specific conditions that constitute a diagnosis of triaditis range from any inflammatory process within these organs, to the combination of chronic pancreatitis, chronic cholangitis/cholangiohepatitis and IBD. Care must be exercised when drawing conclusions about the prevalence of specific conditions and triaditis, as studies performed antemortem may select for different subsets of disease and severity *versus* those performed postmortem, e.g. severe conditions such as neutrophilic cholangitis or suppurative pancreatitis may be overrepresented in necropsy studies (Callahan Clark *et al.* 2011, Hill and Van winkle 1993). The situation is further complicated by differences in the histological classification and evaluation of feline pancreatitis, ILD and IBD, which make it difficult to compare studies, and to correlate specific subtypes of hepatic, intestinal and pancreatic disease with triaditis. For example, the development of standardised criteria for evaluating

Table 1. Prevalence of concurrent inflammation of the pancreas, liver and intestines

Study	Primary disease	n	Pancreatitis	ILD	IBD	Triaditis
Weiss *et al.* 1996	Cholangitis/cholangiohepatitis	18	9/18 (50%)	18/18	15/18 (83%)	7/18 (39%)
Callahan Clark *et al.* 2011	Cholangitis	44	22/34 (65%) acute 4 chronic active 6 chronic 7 not specified 5	44/44 CNC=33/44 ANC=7/44	17/37 (46%)	10/31 (32%) 30/37 nephritis
Marolf *et al.* 2013	Cholangitis	10	8/10 acute 1 chronic active 1 chronic 6	10/10	ND	ND
Twedt *et al.* 2014	Inflammatory liver disease	39	15/23 12/15 chronic	39/39	11/24 8/11 LPE 5/24 LSA	7/14 (50%)
Swift *et al.* 2000	Pancreatitis	18	18/18	15/18 (includes lipidosis)	11/18	10/18 (56%)
Forman *et al.* 2004	Pancreatitis	17	17/17	82% 14/17 ILD 3/17 lipidosis	63% 10/16 IBD 3/16 LSA	50%

ILD Inflammatory liver disease and includes reactive hepatopathy in response to pancreatitis, inflammatory bowel disease (IBD) or alimentary lymphoma (LSA), ANC Acute neutrophilic cholangitis, CNC Chronic neutrophilic cholangitis, LPE Lymphocytic-plasmacytic enteritis, Triaditis Concurrent inflammation of the pancreas, liver and intestines

hepatic and intestinal histopathology makes it difficult to reconcile studies performed before and after adoption of these schemes (Van den Ingh *et al.* 2006, Willard *et al.* 2010). Moreover, the reproducibility of these standardised schemes is problematic (Willard *et al.* 2010).

DIAGNOSING PANCREATITIS AND TRIADITIS

The diagnostic approach used to establish a diagnosis of pancreatitis and concurrent inflammation of the liver and small intestines, i.e. "triaditis" in cats is summarised in Table 2. Clinical findings are variable and include anorexia, weight loss, loss of muscle mass, diarrhoea, vomiting, icterus, hepatomegaly, thickened intestines, pancreatic mass, abdominal pain, abdominal effusion, pyrexia, hypothermia, tachypnoea, dyspnoea and shock. Haematological and biochemical abnormalities consistent with liver disease {elevated liver enzyme activities [alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP)], and bilirubin concentration} (Center 1986, Callahan Clark *et al.* 2011), pancreatitis [elevated feline pancreatic lipase (fPL) and feline pancreatic lipase immunoreactivity (fPLI), low calcium concentration] (Kimmel *et al.* 2001, Fererri 2003, Forman *et al.* 2004, Steiner *et al.* 2004) and IBD or alimentary lymphoma (decreased cobalamin, folate and albumin concentrations) (Kiselow *et al.* 2008,

Table 2. Findings used to establish a diagnosis of triaditis

Diagnostic test	Pancreatitis	Inflammatory liver disease	Inflammatory bowel disease
Clinical examination	Abdominal pain, mass or effusion	Jaundice, hepatomegaly, Hypersalivation	Thickened intestines, mesenteric lymphadenopathy
CBC	Neutrophilia, neutropenia, thrombocytopenia	Anaemia, neutrophilia	Neutrophilia
Biochemistry	Low calcium Low albumin Elevated fPLI/fPL	Elevated AST, ALT, ALP, GGT, bilirubin, globulin	Low cobalamin Less commonly low albumin or folate
Radiographs	Loss of serosal detail, focal mass, duodenal distension, ileus, abdominal effusion, pleural effusion	Hepatomegaly, cholelithiasis	Usually not helpful
Ultrasonography	Increased pancreatic size, hypoechoic, hyperechoic rim, pancreatic duct dilatation, abdominal effusion	Hyperechoic liver, hepatomegaly, intrahepatic or extrahepatic bile duct enlargement, choleliths, biliary sludge, gall bladder wall abnormalities	Intestinal wall thickening, muscularis hypertrophy, mesenteric lymphadenopathy
Sonography enabled procedures	Centesis of focal pancreatic masses: necrosis, infection, neoplasia	Centesis: Liver: cytology for lipidosis, inflammation, infection (bacteria, *Toxoplasma*) Gall bladder: culture and cytology Needle biopsy	Centesis: Reactive lymphadenopathy
Endoscopy	Not useful	Not useful	Abnormal colour or texture of mucosa. Biopsy
Laparoscopy	Abnormal size, shape, colour, texture, biopsy	Abnormal size, shape, texture, colour, biopsy, centesis of gall bladder.	Laparoscopy assisted biopsy
Exploratory lapatrotomy	Gross inspection of pancreas and targeted biopsy	Gross inspection of liver, gall bladder and biliary tract. Targeted biopsy, culture of gall bladder	Gross inspection, targeted biopsy, sampling of regional lymph node.

fPL Feline pancreatic lipase, fPLI Feline pancreatic lipase immunoreactivity, AST Aspartate aminotransferase, ALT Alanine aminotransferase, ALP Alkaline phosphatase, GGT Gamma-glutamyl transferase

Janeczko *et al.* 2008, Jergens 2010, Worhunsky *et al.* 2013), may be present. Ultrasonographic abnormalities in the pancreas (size, echogenicity, hyperechoic margins, duct system) (Simpson *et al.* 1994, Saunders *et al.* 2002, Williams *et al.* 2013), liver (changes in size/contour, echogenicity, ducts/biliary system, guided cytology and culture)(Gagne *et al.* 1999, Savary-Bataille *et al.* 2003, Callahan Clark *et al.* 2011) and small intestine (thickness, muscularis hypertrophy) (Daniaux *et al.* 2014) may be detected. The results of clinical evaluation, clinicopathological testing and imaging can provide the clinician with a high index of suspicion for pancreatitis and triaditis, but definitive diagnosis currently requires biopsy and histopathology of each organ.

WHAT CAUSES PANCREATITIS?

The aetiopathogenesis of pancreatits and its sequelae are summarized in Fig 1. While a variety of potential stimuli or "triggers" have been associated with the development of feline pancreatitis (Table 3) an underlying cause is usually not apparent. It is thought that acute pancreatitis can progress to chronic pancreatitis and exocrine pancreatic insufficiency; however it is also plausible that each of these conditions has its own set of triggers and pathomechanisms that lead them to develop independently. Acute pancreatitis ranges from oedematous to necrotising (Macy 1989, Hill & Van Winkle 1993, De Cock *et al.* 2007), with hypoperfusion and thrombosis thought to underpin the progression to necrotising pancreatitis. There are frequently regional differences in the presence and severity of inflammation within the pancreas, and the juxtaposed duodenum can become severely inflamed and immotile (Fig 2). Suppurative pancreatitis carries a particularly poor prognosis (Hill & Van Winkle 1993). Abscesses (sterile or infected) and pseudocysts (created by the accumulation of pancreatic secretions) are relatively infrequent sequelae (Simpson *et al.* 1994). Complicating factors that can modify the situation are bacterial infection and biliary obstruction. Bacterial infection is thought to arise via ascending colonisation of the pancreatic duct or haematogenous seeding of translocated enteric bacteria. A recent study employing fluorescence in situ hybridisation (FISH) detected bacteria in the pancreas of 13/46 cats with pancreatitis (Simpson *et al.* 2011). Bacterial colonisation was more frequent in cats with moderate to severe pancreatitis (11/31) relative to cats with mild pancreatitis (2/15). Bacteria were visualised within connective/periductular regions (n=9), glandular parenchyma (n=6), saponified fat (n=5), areas of necrosis (n=3) and within ducts (n=3). Bile duct obstruction is a potential sequela of pancreatic fibrosis associated with chronic active or chronic pancreatitis and may serve to exacerbate pancreatitis and impair the ability of the liver to clear bacteria.

HOW IS PANCREATITIS RELATED TO TRIADITIS?

The presence of concurrent inflammation in the pancreas, liver and intestines may be due to separate disease processes at each site or could reflect a common stimulus. The most probable causes of pancreatitis, ILD and IBD are summarised in Table 3. Bacterial infection, immune-mediated and idiopathic mechanisms are considered as the potential causes of inflammation in each organ that may participate in the development of triaditis. When considering the potential roles of these inflammatory stimuli and the temporal development of triaditis, several models emerge.

Acute pancreatitis as the initiating stimulus for triaditis?

Acute inflammation of the pancreas, independent of the initiating trigger, could lead to the development of triaditis through its impact on the intestines and liver (Fig 3A). In this scenario, pancreatitis induces intestinal inflammation through direct contact with the juxtaposed duodenum (Fig 2) and colon and/or

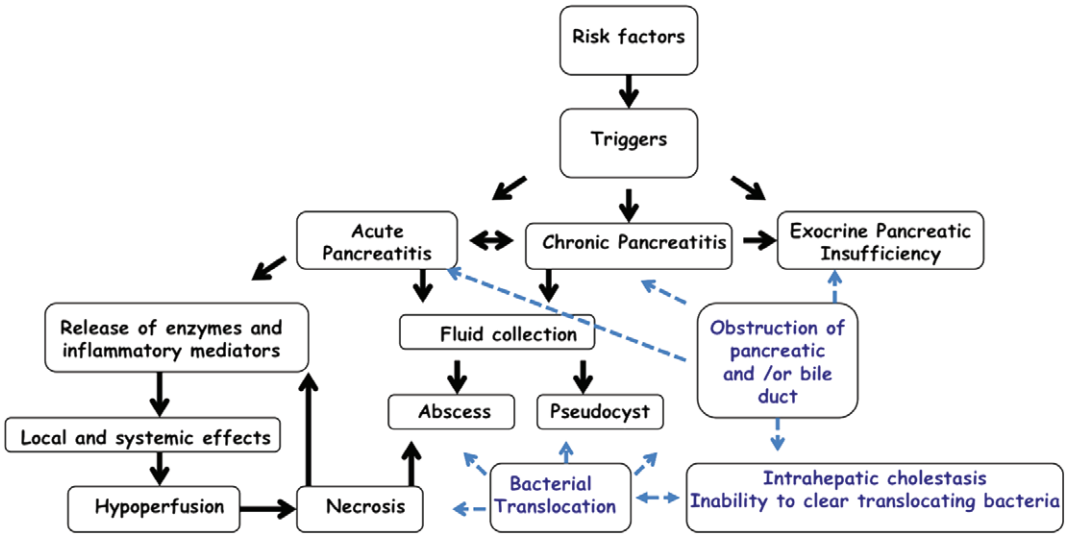

FIG 1. The aetiopathogenesis of pancreatits and its sequelae. Text and arrows in blue indicate confounding variables. Bile duct obstruction is most commonly a direct consequence of pancreatitis, tumours of the pancreas bile duct or liver or choleliths. Translocation of enteric bacteria to the pancreas and liver is thought to be a consequence of impaired intestinal barrier function and/or ascending infection of the pancreatico-biliary duct

Table 3. Suspected causes of feline pancreatitis, inflammatory liver disease and Inflammatory bowel disease

Stimulus	Pancreatitis	Inflammatory liver disease	Inflammatory bowel disease
Fluke Vyhnal *et al.* 2008	Yes; regional sporadic	Yes: regional sporadic	–
Enteric bacteria Simpson *et al.* 2011 Brain *et al.* 2005 Wagner *et al.* 2007, Twedt *et al.* 2014 Greiter-Wilke *et al.* 2006 Otte *et al.* 2012 Janeczko *et al.* 2008	Usually considered secondary to pancreatitis with infection via common pancreatic and bile duct, or hematogenous seeding. Bacteria visualized in 35% of 31 cats with moderate to severe pancreatitis (predominantly *Streptococcus* spp., *E. coli)*	*Escherichia coli, Enterococcus* spp., *Bacteroides spp., Streptococcus* spp., and *Clostridium* spp. cultured from bile or liver of cats Bacteria visualized in 33% of 39 cats. Predominantly Reactive hepatopathy, neutrophilic cholangitis, Acute hepatitis *Streptococcus* spp *E.coli*, *Clostridium* spp? Positive PCR for *Helicobacter* spp DNA in bile and liver but also in controls. Suspected that bacteria are an antigenic/immune stimulus for lymphocytic cholangitis	Dysbiosis (increased *Enterobacteriaceae, Streptococus Enterococcus, and Clostridium* spp). Correlates with severity of mucosal abnormalities and cytokine upregulation. Unclear if cause or consequence.
Bartonella Kordick *et al.* 1999	–	Experimental infection	–
Toxoplasma gondii Dubey & Carpenter 1993 Smart *et al.* 1973	Mild to severe necrotising pancreatitis	Heptaocellular necrosis	Granulomatous inflammation Villus atrophy?
Feline infectious peritonitis Kiss *et al.* 2000 Weiss & Scott 1981	Virus detected, occasional	Pyogranulomatous hepatitis	Focal pyogramulomatous inflammation
Virulent systemic Calicivirus Pesavento *et al.* 2004	Necrotising pancreatitis	Scattered hepatocyte necrosis	–
Immune-mediated Ferreri *et al.* 2003 DeCock *et al.* 2007 Warren *et al.* 2011 Jergens & Simpson 2012	Lymphocytic-plasmacytic	Lymphocytic cholangitis	"Lymphoplasmacytic enteritis"
Diet Guilford *et al.* 2001	–	–	"Lymphoplasmacytic enteritis"
Trauma	*Yes, sporadic*	–	–
Organophosphates	*Yes, but unlikely with current products*	–	–
Acute hypercalcaemia Frick *et al.* 1990	Yes, with experimental hypercalcaemia,	–	–
Lipodystrophy	*Yes*	–	–
Idiosyncratic drug reaction	–	*e.g. oral diazepam, methimazole*	–
Idiopathic	*Yes*	*Yes*	*Yes*

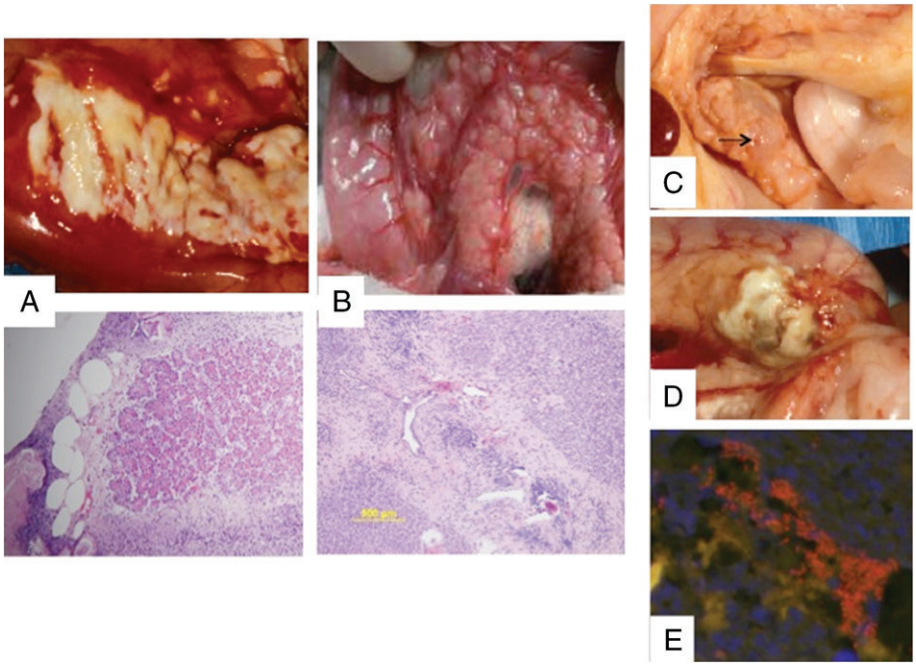

FIG 2. The spectrum of feline pancreatitis. Feline pancreatitis ranges in severity from acute necrotising pancreatitis with peri-pancreatic saponifaction of fat and duodenal inflammation (A), to chronic fibrosing pancreatitis (B). Complicating factors include biliary obstruction (C), pancreatic cyst formation (arrow) (C), abscessation (D) and bacterial colonisation (rod-shaped bacteria visualised using eubacterial fluorescence in situ hybridsation, FISH) (E)

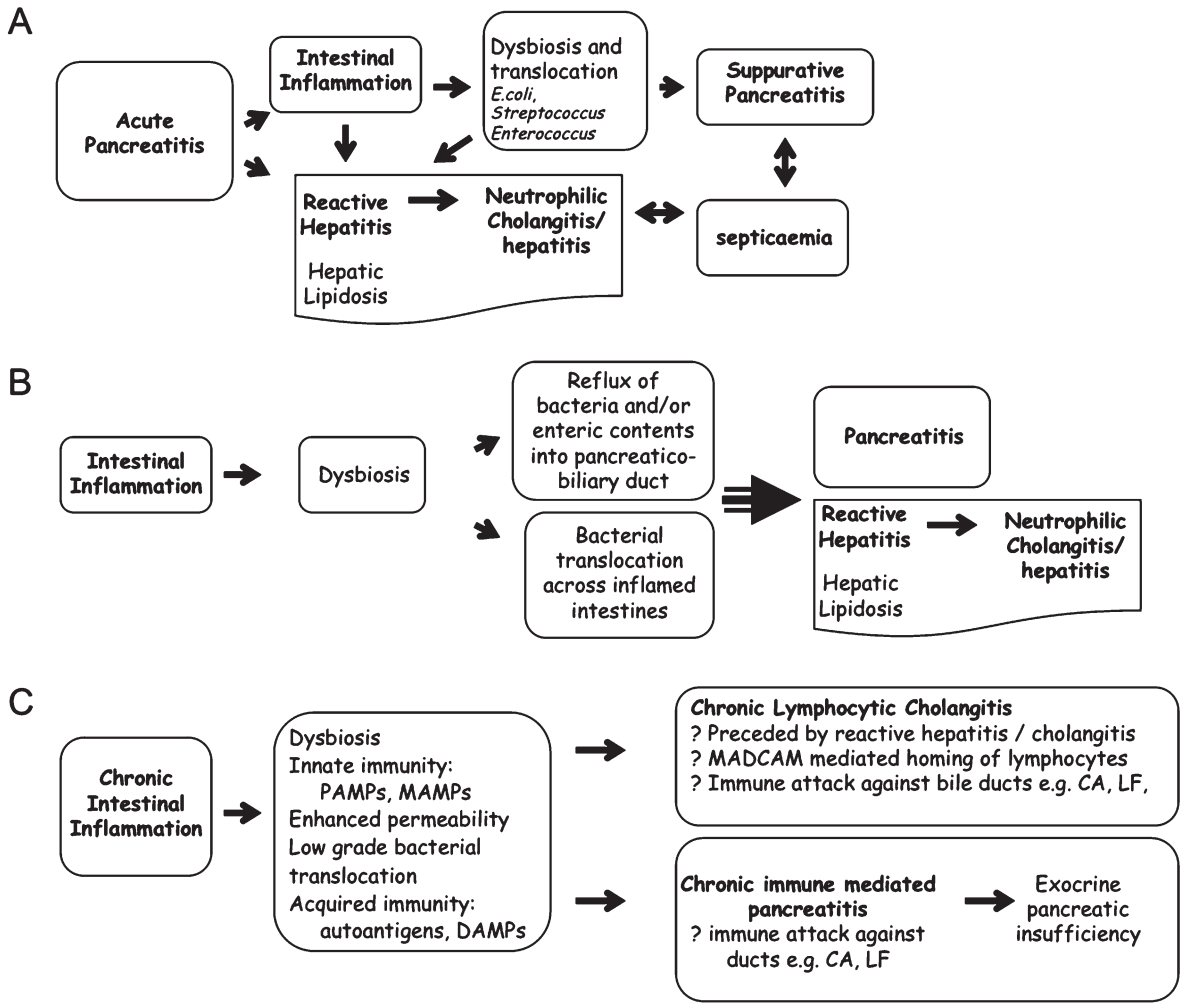

FIG 3. Linking pancreatitis, cholangitis and intestinal inflammation to the development of triaditis. (A) Acute pancreatitis as the initiating stimulus for triaditis? (B) Intestinal inflammation and bacterial translocation initiating triaditis? (C)Intestinal inflammation and autoimmunity as stimuli for triaditis?

associated systemic inflammatory response syndrome, which promotes dysbiosis (Janeczko *et al.* 2008, Cr ven *et al.* 2012) and the translocation of enteric bacteria to the pancreas and liver across the inflamed leaky intestines or via the pancreatico-biliary duct. The combination of pancreatitis, intestinal inflammation and translocation of enteric bacteria drives the development of a reactive hepatopathy, neutrophilic cholangitis or hepatitis and septicaemia. This possibility is supported by culture-based analyses that have identified predominantly enteric bacteria (e.g. *Escherichia coli, Enterococcus* spp., *Bacteroides spp., Streptococcus* spp., *Clostridium* spp. and *Salmonella* spp.) in liver and bile of cats with cholangitis/cholangiohepatitis (Brain *et al.* 2006, Wagner *et al.* 2007, Twedt *et al.* 2014). Recent studies employing FISH have enabled direct visualisation of bacteria (predominantly *E. coli* and *Streptococcus* spp.) in formalin-fixed tissue sections from cats with ILD and pancreatitis. Eighty-six percent of FISH positive cats with ILD and of 79% of FISH positive cats with pancreatitis had concurrent pancreatic, hepatic and intestinal inflammation (Simpson *et al.* 2011, Twedt *et al.* 2014). Moreover, studies of experimental feline pancreatitis have clearly demonstrated that *E. coli* can translocate from the intestines into the acutely inflamed pancreas (Widdison *et al.* 1994a,b,c). It appears plausible that the hypoglycaemia and poor prognosis associated with suppurative pancreatitis (Hill & Van Winkle 1993) could also be attributable to the presence of bacterial infection and septicaemia.

Intestinal inflammation and autoimmunity as stimuli for triaditis?

An alternative scenario that could lead to the development of triaditis places intestinal inflammation as the primary stimulus. In this scenario, intestinal inflammation, most frequently "lymphocytic plasmacytic" or small cell lymphoma, could promote dysbiosis (Janeczko *et al.* 2008, Craven *et al.* 2012) and the translocation of enteric bacteria to the pancreas and liver across the inflamed intestines or pancreatico-biliary papilla. An increase in intra-duodenal pressure during vomiting, a common clinical sign in cats with intestinal inflammation, could also promote reflux of enteric contents into the pancreatico-biliary duct leading to concurrent inflammation and bacterial infection of the liver and pancreas (Fig 3B) (Armstrong & Twedt 2014). With

ascending infection of the pancreatico-biliary duct one would expect to visualise bacteria within or immediately adjacent to bile and pancreatic ducts. However, bacteria in ILD were more frequently ($P<0{\cdot}0001$) localised to portal vessels, venous sinusoids and parenchyma (12/13) than bile ducts (1/13), and only 3/13 cats with pancreatitis and intrapancreatic bacterial colonisation had bacteria visualised within pancreatic ducts (Simpson *et al.* 2011, Twedt *et al.* 2014), suggesting that enteric translocation or haematogenous seeding are more likely routes for infection than ascending infection of the pancreatico-biliary duct.

The models described above, depicted in Fig 3A, B, are most applicable to the subset of cats with triaditis that have moderate to severe pancreatitis and ILD that is categorised as reactive hepatopathy, acute hepatitis, neutrophilic cholangitis or obstructive cholangitis as these cats are more likely to have active bacterial colonisation than those with mild pancreatitis or lymphocytic cholangitis (Simpson *et al.* 2011, Warren *et al.* 2011, Twedt *et al.* 2014).

In cats with chronic lymphocytic pancreatitis or lymphocytic cholangitis invasive bacteria are rarely visualised (Simpson *et al.* 2011, Warren *et al.* 2011, Twedt *et al.* 2014), and the presence of DNA for *Helicobacter* species, which have been linked to hepatobiliary and pancreatic disease in other species (e.g. Franklin *et al.* 1996), does not correlate with the presence of disease (Otte *et al.* 2012). Hence the combination of lymphocytic (chronic) pancreatitis, lymphocytic or mixed lymphocytic and neutrophilic cholangitis, and lymphocytic plasmacytic enteritis may be a consequence of an immune-mediated process rather than active bacterial infection (Fig 3C). In humans and experimental animals, autoimmune pancreatitis and cholangitis are recognised as extra-intestinal complications of IBD, with immune attack frequently directed against bile and pancreatic ducts (Navaneethan & Shen 2010, Yanagisawa *et al.* 2011, 2014). Immune-mediated damage is typically considered a consequence of immune responses against bacteria (that may or may not have established an active infection) that cross-react with host tissues with resultant innocent by-stander immune responses in the intestines, liver and pancreas, or immune attack against host antigens unmasked by tissue damage (Haruta *et al.* 2012). Several experimental studies support the possibility that immune responses to enteric bacteria are related to immune-mediated pancreatitis and cholangitis. For example, C57BL/6 mice inoculated intraperitoneally (ip) with heat-killed *E. coli* weekly for 8 weeks, develop marked cellular infiltration and fibrosis of the exocrine pancreas accompanied by a high-serum gamma-globulin concentration and the production of autoantibodies against carbonic anhydrase and lactoferrin (Yanagisawa *et al.* 2011). Subsequent studies have identified a flagellar subunit, FliC, from *E. coli* as an immunogenic stimulus and higher antibody titers to FliC have been detected in serum of patients with immune-mediated pancreatitis (Yanagisawa *et al.* 2014). Expression of host antigens can also shape the immune response. Mucin 1 (MUC1) is overexpressed in an abnormal, hypoglycosylated form on the colonic epithelium in human IBD where it contributes to inflammation. MUC1 is also expressed on pancreatic ductal epithelia. It has recently been shown in mice that MUC1-specific T cells migrate to the colon in mice with IBD and also to the pancreas. This suggests that pancreatitis is an extra-intestinal site of IBD, characterised by proinflammatory abnormal expression of MUC1 (Kadayakkara *et al.* 2010).

The immune targeting of bile ducts in cats with lymphocytic cholangitis is similar to that observed in humans with primary sclerosing cholangitis (PSC) (Day 1998, Warren *et al.* 2011, Eaton *et al.* 2013, Yimam & Bowlus 2014, Otte *et al.* 2014). PSC is typically characterised by progressive inflammation, fibrosis and destruction of the intrahepatic and extrahepatic biliary tree, resulting in the development of biliary fibrosis, cirrhosis and ultimately hepatic failure (Eaton *et al.* 2013, Yimam & Bowlus 2014). PSC is a complex disease that involves host genetics, innate and adaptive immunity and the environment. It is frequently associated with IBD and it has been proposed that immune attack against biliary structures may involve the homing of memory lymphocytes that arise as a consequence of IBD to the liver. The discovery that mucosal vascular addressin adhesion molecule I (MAdCAM-1) and chemokine (C-C motif) ligand 25 (CCL25), previously thought to be restricted to the gut, are up-regulated in the liver during ILDs support the concept that common mechanisms may control lymphocyte recruitment to the inflamed liver and gut (Berlin *et al.* 1993, Eksteen *et al.* 2004, Eaton *et al.* 2013, Yimam & Bowlus 2014). MadCAM-1 expression has also been linked to lymphocytic inflammation of islet cells in diabetes mellitus (Hänninen *et al.* 1998), but has not been directly linked to immune-mediated pancreatitis. A variety of autoantigens have also been implicated in PSC, and the recent identification of b-tubulin isotype 5 (TBB5), which has high homology with bacterial cell division protein FtsZ, as an antineutrophil cytoplasmic autoantibody (ANCA) (Terjung & Spengler 2009) suggests that immune responses to translocated bacteria, perhaps facilitated by a leaky gut, may promote inflammation in a susceptible individual (Eaton *et al.* 2013).

While, PSC has often been linked to autoimmune pancreatitis, it is increasingly thought that intrahepatic and extrahepatic biliary tract abnormalities with strictures are more often attributable to a particular subvariant of PSC, immunoglobulin (Ig) G4-associated cholangitis (Okazaki *et al.* 2011, Zen & Nakanuma 2011). This disease is associated with increased serum IgG4/IgE concentrations, abundant infiltration of IgG4-positive plasma cells and lymphocytes, autoantibodies and steroid responsiveness (Okazaki *et al.* 2011). It is thought that autoantigens, autoantibodies (e.g. to lactoferrin, carbonic anhydrase) and potentially pathogens may drive IgG4-mediated inflammation, but this remains to be determined (Okazaki *et al.* 2011, Zen & Nakanuma 2011). A number of other organs can be involved including the salivary glands (Sjögren's syndrome), bile duct strictures, lung nodules, autoimmune thyroiditis and kidney (interstitial nephritis with an IgG4-positive plasma cell infiltrate and IgG4 deposits in the tubular basement membrane). It is noteworthy that nephritis is commonly reported in cats with cholangitis and/or pancreatitis (Callahan Clarke *et al.* 2011) where it is often considered an age-related co-morbidity.

TREATMENT OF TRIADITIS

Because triaditis is a general term applied to a syndrome that encompasses a spectrum of inflammatory disorders affecting

the liver, pancreas and intestines, its treatment is best guided by in-depth consideration of the overall health of the patient and the specific type and severity of disease present in each of these organs. The treatment plans for each disorder are then evaluated for potential adverse consequences that may result from their concurrent application, and a treatment plan that has been individualised for each patient emerges.

Prioritising therapy in cats with triaditis

The initial treatment of cats with triaditis is guided by the results of clinical evaluation, clinicopathological testing, imaging and targeted aspiration where indicated (e.g cytology of liver, pancreas, mesenteric lymph node, gall bladder and culture). In cats with persistent vomiting, abdominal pain, jaundice, anorexia, hypovolaemia, shock, sepsis, hypothermia or pyrexia, the initial objective is to provide supportive care while rapidly determining the most likely cause for these signs. Symptomatic care typically involves parenteral fluids, analgesia, antiemetics and antibiotics (suspected sepsis, neutrophilia with left shift) (Table 4). Assisted alimentation is initiated in anorexic patients (e.g. initially via a liquid enteral diet via a naso-oesophageal tube). In cats with evidence of triaditis treatment is dictated by the most significant

Table 4 Treament of triaditis: pancreatitis, inflammatory liver disease and inflammatory bowel disease

Treatment	Pancreatitis	Inflammatory liver disease	Inflammatory bowel disease
Analgesia	Buprenorphine (0·005 to 0·01 mg/kg SC q6-12 hours) Fentanyl (25 µg/hour patch q 118 hours) Maropitant?	Not usually	Not usually
Antiemetics	Maropitant (1 mg/kg SID) Ondansetron (0·5 mg/kg PO/IV BID) Chlopromazine (0·2 to 0·4 mg/kg)	Maropitant Ondansetron	if acute and severe
Fluid therapy	Parenteral cystalloids Colloid support Plasma: DIC, oncotic support	Parenteral crystalloids	If acute and severe
Antibiotics	Should be considered in cats with increased probability of bacterial infection, i.e. clinical signs of sepsis, moderate to severe pancreatitis,neutrophilia, left shift. Infection confirmed by aspirate, biopsy or culture. Bacterial species are similar to those associated with ILD; e.g. Amoxicilin-clavulanic acid Cephalosporin Fluorquinolone Metronidazole	Active bacterial infection in ILD is most prevalent in cats with neutrophilic and mixed cholangitis,reactive hepatitis and bile duct obstruction.Therapy is ideally based on culture of bile / liver. e.g. Amoxicilin-clavulanic acid Cephalosporin Fluorquinolone Metronidazole	LPE: tylosin (15 mg/kg PO BID), metronidazole (7·5 mg/kg PO BID) to abrogate dysbiosis, limit translocation. e.g fluroquinolone + cephalosporin
Immunomodulatory drugs	Not at this time	Culture negative lymphocytic dominant cholangitis : Prednisolone (1–2 mg/kg/day) Chlorambucil: 2 mg PO every other day Methotrexate (0·4 mg, with treatments given at 0, 12 and 24 hours of 0·13 mg PO) + folate (0·25 mg/kg) ?Ursodiol (15 mg/kg divided BID with meals)	Moderate to severe LPE: Prednisolone: 2 to 4 mg/kg initially, tapered to 1 mg/kg in tolerant cats. If severe and unresponsive : Chlorambucil: 2 mg PO every other day
Assisted alimentation	Naso-oesophageal Oesophagostomy	Naso-oesophageal Oesophagostomy	Occasionally
Dietary modification	Liquid enteral diet via tube	Liquid enteral diet via tube	LPE: Restricted antigen or hyrolysate Colitis: added psyllium
Vitamins	Not usually	Vitamin K (0·5 to 1·5 mg/kg SC, IM, q12h)	Cobalamin: 0·25 to 5 mL cynaocobalamin SC Q14days Folate (0·25 mg/kg) Vitamin K if fat malabsorption
Neutraceuticals	Not usually	SAMe (40 to 50 mg/kg bioavailable product)	Not usually
Surgery	Biopsy Non-responsive pancreatitis Bile duct obstruction Abscess Infected necrosis	Biopsy Bile duct obstruction: stent or cholecystojejunostomy Cholecystectomy	Biopsy: Not usual for IBD alone unless focal mass or suspicion of mural lymphoma

DIC Disseminated intravascular coagulation, SC Subcutaneously, PO Orally, IV Intravenously, ILD Inflammatory liver disease, IM Intramuscularly, LPE Lymphocytic plasmacytic enteritis

component, e.g. acute pancreatitis, suspected cholangitis, cholecystitis, biliary obstruction, potential intestinal perforation. Whether the cat requires immediate surgical intervention or continued medical management should be determined. As the definitive diagnosis and characterisation of triaditis currently require histopathology of each organ and the detection of bacterial infections (culture of liver and bile and and FISH analysis of liver and pancreas), a decision has to be made when to perform an exploratory laparotomy. This is also a good opportunity to place an oesophagostomy tube in persistently anorectic patients. If an exploratory laparotomy is not possible, or advisable, minimally invasive sampling of the intestines by endoscopy and the pancreas, liver and gall bladder via ultrasound guided needle aspiration may inform treatment. Subsequent therapy is governed by the presence, or strong suspicion, of bacterial infection in the hepatobiliary tree, pancreas or intestines (e.g. neutrophilic or granulomatous enteritis) with antimicrobial selection based on susceptibility testing or best guess (Table 4). Corticosteroids are frequently used to treat specific components of triaditis such as lymphocytic cholangitis or lymphocytic plasmacytic enteritis that is refractory to diet and antimicrobials. In these situations, treatment with corticosteroids or other immunosuppressive drugs (e.g. chlorambucil) is not initiated until active bacterial infections have been excluded or treated, and the specific type and severity of disease comprising triaditis have been determined.

Treament considerations for pancreatitis, inflammatory liver disease and inflammatory bowel disease

Pancreatitis: Treatment of pancreatitis is symptomatic and supportive (Table 4). Fluid therapy is directed at maintaining pancreatic perfusion and restoring acid base and electrolyte abnormalities, and colloid oncotic pressure. While many cats with pancreatitis do not show overt signs of abdominal pain analgesics such as buprenorphine or fentanyl are commonly administered. Antiemetics (e.g. maropitant, ondansetron) are used to combat vomiting or perceived nausea. The antiemetic maropitant may also provide analgesia through inhibition of visceral NK_1 receptors. A mainstay of therapy is assisted alimentation with a commercial liquid diet via a naso-oesophageal or oesophagostomy tube (Klaus *et al.* 2009). Antimicrobial therapy is warranted in patients with left shift, shock or suspected bacterial complications. Many cats respond well to supportive care (Klaus *et al.* 2009). Failure to respond adequately to supportive care should prompt consideration of complications such as pancreatic necrosis and disseminated intravascular coagulation (DIC), septicaemia or bacterial colonisation of the pancreas, an alternate diagnosis such as pancreatic neoplasia, and concurrent disease in other organ systems. Ultrasound-guided aspiration of the pancreatic parenchyma or focal pancreatic abnormalities for cytology and culture and culture of bile and blood may help to detect these complications (Simpson *et al.* 1994). An exploratory laparotomy with pancreatic biopsy, culture, histopathology and FISH analysis is required to more fully characterise the type of pancreatic inflammation that is present. Persistent biliary obstruction secondary to pancreatitis is another indication for surgery and may be amenable to stenting or cholecystojejunostomy (Buote *et al.* 2006, Mayhew & Weisse 2008). It should be noted that corticosteroids or immunosuppressive drugs are not typically employed in the treatment of pancreatitis in cats. Their use may be indicated in cats with suspected immune-mediated pancreatitis such as biopsy proven chronic lymphocytic pancreatitis, or if cats are discovered to have an IgG4 like syndrome. However, their use must be weighed carefully by considering the potential benefits of treating a cat with subclinical chronic lymphocytic pancreatitis and whether these outweigh the adverse effects of long-term corticosteroid therapy.

inflammatory liver disease: Cats with concurrent pancreatitis and ILD typically receive initial care that is similar to cats with pancreatitis. Additional therapeutics targeting Vitamin K responsive coagulopathies and oxidative stress are frequently administered to these patients. Treatment with Vitamin K is based on the high prevalence of vitamin K responsive coagulopathies in cats with intestinal and hapatobiliary disease (Center *et al.* 2000). Antioxidants such as acetyl cysteine and *S*-adenosyl methionine (SAMe) are used to combat oxidative stress associated with abnormal red cell morphology, anaemia and depletion of hepatic glutathione in cats with hepatobiliary disease (Center *et al.* 2002, 2005) (Table 4). More specific therapy is guided by the results of hepatic biopsy (aspiration cytology if the cat is too unstable for biopsy) and cultures of bile and liver. Because of the association of enteric bacteria with many forms of ILD and biliary obstruction empirical therapy with broad-spectrum antibiotics is frequently employed and modified on the basis of culture results (Brain *et al.* 2006, Wagner *et al.* 2007, Twedt *et al.* 2014). Culture negative lymphocytic cholangitis should be distinguished from hepatic lymphoma and may respond to corticosteroids or other immunosuppressive drugs (Warren *et al.* 2011, Otte *et al.* 2013). Ursodiol has not been shown to be an effective agent in cats with lymphocytic cholangitis (Otte *et al.* 2013).

Inflammatory bowel disease: The treatment of IBD (Table 4) is best guided by intestinal biopsy to determine the type of cellular infiltrate (lymphoplasmacytic, eosinophilic, neutrophilic, granulomatous) and the severity of architectural changes (predominantly villus blunting, fusion), and to distinguish it from small cell lymphoma. Low-grade lymphocytic plasmacytic enteritis (lacks significant architectural changes) frequently responds to dietary modification alone, e.g. an antigen restricted or hydrolysed diet (Guilford *et al.* 2001). Patients that do not respond to diet alone and those with moderate to severe lymphocytic plasmacytic enteritis (villus blunting and fusion are common) are usually treated with diet plus antimicrobial therapy, e.g. tylosin, escalating to diet plus tylosin plus prednisolone if they are unresponsive. Cats with moderate to severe lymphocytic plasmacytic enteritis that do not respond to prednisolone may have low-grade lymphoma rather than IBD [clonality polymerase chain reaction (PCR) and immunocytochemistry of mucosal biopsies can help to distinguish these conditions] and are frequently treated with chlorambucil (Table 4). In cats with neutrophilic and granulomatous infiltrates it is imperative to consider infectious

aetiologies, e.g. feline infectious peritonitis (FIP), bacteria and fungi, and to avoid empirical immunosuppression until these agents have been actively excluded by thorough re-evaluation of the patient, faecal evaluation for enteropathogens, and additional analyses of mucosal biopsies and regional lymph nodes, e.g. histochemical staining (e.g. acid fast, silver, Gram, PAS), culture, PCR (e.g. FIP), eubacterial FISH analysis. Deficiencies in vitamin B12 are common in cats with chronic gastrointestinal disease and require treatment with parental cobalamin (Simpson *et al.* 2001, Ruaux *et al.* 2005, Worhunsky *et al.* 2013). Malabsorption of folate and Vitamin K are less common and should be addressed with supplementation when present. Concurrent low-grade small T-cell intestinal lymphoma can respond well to therapy with chlorambucil, prednisolone and supplementation of vitamins B12 and folate (Fondacaro *et al.* 1999, Kiselow *et al.* 2008).

Conclusions and future directions

Since the recognition of acute pancreatitis in cats (Macy 1989) a broad spectrum of feline pancreatic pathology has been described that is often associated with inflammation in other organ systems, not only the intestine and liver (triaditis), but also the kidney. While the aetiopathogenesis of pancreatitis and its relationship to inflammation in other organ systems is unclear, preliminary studies point to a heterogeneous group of conditions with differential involvement of host inflammatory and immune responses and enteric bacteria. Comprehensive, prospective studies that simultaneously evaluate the presence of predefined clinical, clinicopathological and histopathological abnormalities, coupled with high-resolution evaluation of pancreaticobiliary morphology [e.g. magnetic resonance imaging (MRI)], Marolf *et al.* 2013), immunological profiling (e.g. IgG4, autoantibodies), and screening for bacterial colonisation (e.g. culture and culture independent analysis) of a large cohort of cats undergoing surgical biopsy or necropsy are required to gain further insights to guide diagnosis and therapy.

Conflict of interest

The author of this article has no financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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