PVMA Veterinary Conference
Fall 2018
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Feline Triaditis: Fact or Philosophy

Learning Objectives

1. To provide clinicians with an up-to-date assessment of the 3 components of feline triaditis.

2. To provide clinicians with a treatment armamentarium for the 3 components of feline triaditis.

3. To prepare clinicians to critically evaluate current and future treatment strategies for feline triaditis.

Introduction

Occam's Razor has been at the foundation of medical education since the dawn of time. Dr. Hickam first challenged Occam's Razor while on staff at Indiana University Medical School. Although at one level this debate is one of philosophy, for those of us working with cats, the distinction between these two philosophies has a potentially major impact on the clinic floor. Feline "triaditis" serves as an excellent example. Along with a "philosophical" discussion, this presentation will briefly review the pathophysiology of feline IBD, pancreatitis, and cholangitis as it relates to clinically relevant causes and potential treatments of feline triaditis. Furthermore, both evidence-based and anecdotal recommendations and controversies regarding therapy will be discussed.

Definitions

Occam's Razor, expressed in Latin as the *lex parsimoniae* (law of parsimony), is a principle that generally recommends selecting the competing hypothesis that makes the fewest new assumptions, when the hypotheses are equal in other respects. When discussing Occam's razor in contemporary medicine, physicians speak of diagnostic parsimony. **Diagnostic parsimony** advocates that when diagnosing a given injury, ailment, illness, or disease a doctor should strive to look for the fewest possible causes that will account for all the symptoms. **Hickam's dictum** states that it is often statistically more likely that a patient has several common diseases, rather than having a single rarer disease which explains their myriad symptoms. Also, independently of statistical likelihood, some patients do in fact turn out to have multiple diseases, which by common sense nullifies the approach of trying to explain any given collection of symptoms with one disease. The classic examples in Feline Medicine are Chronic Kidney Disease (Occam's Razor) and Diabetic Ketoacidosis (Hickam's Dictum).

Feline Triaditis – Hickam's Dictum or Occam's Razor Applied to the Cat

The origin of the term "triaditis" in feline medicine appears to have been the publication by Weiss DJ et al. (JAVMA 1996) "Relationship between inflammatory hepatic disease and inflammatory bowel disease, pancreatitis, and nephritis in cats." In that report we find the following statement:

> "The prevalence of IBD (83%) and pancreatitis (50%) was greater for cats with cholangiohepatitis, compared with cats without inflammatory hepatic disease. Thirty-nine percent of cats with cholangiohepatitis had IBD and pancreatitis. Evidence of IBD in association with cholangiohepatitis was characterized by infiltration of lymphocytes and plasma cells into the lamina propria; however, neutrophilic infiltrates also were found in 40% of cats with cholangiohepatitis." For the authors the clinical implication of this finding was that cats with a diagnosis of cholangiohepatitis should be evaluated for IBD and pancreatitis.

Unfortunately, our understanding of the term 20 years later remains rudimentary and speculative, as highlighted in the publication by Clark JEC et al. (JFMS 2011) "Feline cholangitis: a necropsy study of 44 cats (1986-2008)."

> "… it is clear that concurrent pancreatitis and IBD occurs in cats with all forms of cholangitis (30%) and that some cats with cholangitis do not have pancreatitis or IBD. It is unknown whether a single pathogenesis relating inflammatory disease of these three organs occurs in cats with all forms of cholangitis. Bacterial and immune-mediated etiologies have been proposed for the various forms of cholangitis. Information regarding etiology of, and predisposing factors for, concurrent cholangitis, pancreatitis and IBD could not be determined in this study. Further investigation is required to better understand the etiopathogenesis of this condition."

Triaditis can be broken down into the component parts; in the original research it was felt that the predominant signs of triaditis were the result of the cholangitis, with pancreatitis and IBD being secondary complications. More recently, with an increased awareness of pancreatitis in cats, and the long-standing popularity of the diagnosis of IBD, rank-ordering the importance of the individual diseases or determining the actual prevalence of the various possible combinations has become problematic.

Feline Cholantitis

A yellow tinge on the inner aspect of the pinna is rarely what signals to a cat owner that it's time to seek veterinary care, but it does serve as a very bright and visible signal to that veterinarian that this is a case that will demand some time and attention, effort and expense.

First Things First

Bilirubin (or a small child with access to both the cat and finger paints) is the substance that has turned the cat yellow, so the question is why and where did the bilirubin come from? In addition to a complete History and Physical Examination, a KEY diagnostic test in the original work-up of a yellow cat is something as simple as a "crit tube" with its PCV/TP. A marked disparity between a significantly low PCV and normal TP points us down the Pre-hepatic diagnostic road of RBC lysis and brings the Complete Blood Count and a particularly observant Clinical Pathologist to the forefront of our diagnostic efforts.

Clinical Signs Associated with RBC Lysis

Anemia and its associated signs often dominate the clinical picture in these cats, although these signs may be less obvious and less frequently appreciated by cat owners than their canine counterparts; lethargy in a Labrador Retriever is simply not the same as lethargy in a Pixie Bob, and what looks like obvious weakness and exercise intolerance in that same Lab may look like little more than an afternoon nap in a cat. Anorexia is common in anemic cats in our CSU Critical Care service, and any immune-

mediated process can serve as the source of a fever in these patients. The severity and the time course of the anemia are likely to impact the clinical picture, but in general cats appear able to handle lower hematocrits better than dogs. The anemia of RBC lysis in cats is usually regenerative (anisocytosis, polychromasia, elevated reticulocyte count, and nucleated RBCs), although the regenerative response may take 4-6 days to show itself.

Infectious Causes of RBC Lysis in Cats

Although outside the scope of this presentation, the cat has a number of important rule-outs for infectious causes of RBC lysis including FeLV/FIV, *Mycoplasma haemofelis*, *Cytauxzoonosis felis* (regional in the USA), and babesiosis (Africa; not USA). Ehrlichiosis and dirofilariasis are also proposed as differentials for hemolytic anemia in cats and should be considered with appropriate other clinical findings

Non-Infectious Causes of RBC Lysis in Cats

Less common in cats than dogs, non-infectious causes of RBC lysis also need to be considered, and not surprisingly, the cat can be peculiar in its list of problems

IMHA – Primary or Idiopathic

Husbands et al. (ACVIM Abstract 2002) characterized 25 cats with Idiopathic IMHA. Cats (mean age of 6 years) presented for lethargy and anorexia, with pale mucus membranes, a heart murmur and icterus. The hematocrit on admission was 12%, with a regenerative response, and a median serum bilirubin of 0.8 mg/dL, although in some cats, as high as 9.9 mg/dL.

IMHA – Secondary

Osmotic Fragility
Oxidative stress, Heinz body anemia
Hypophosphatemia
Drugs (Acetaminophen, onion powder, lidocaine, antibiotics)
Neonatal isoerythrolysis
Hereditary (pyruvate kinase (PK) deficiency)
Neoplasia

When the Liver Turns a Cat Yellow

If the PCV/TP and CBC suggest that RBC lysis is not the source of bilirubin, our attention is turned towards the liver and gallbladder (Hepatic and Post-hepatic) as the cause of the cats yellow discoloration. This also draws our diagnostic attention to the biochemical profile, where predictably there will be an elevation in total bilirubin (usually greater than 2.5-3.0 mg/dl when the outside of the cat is turning yellow). It might be suggested that the degree of hyperbilirubinemia is indicative of the underlying disorder, with pre-hepatic causes, FIP, and pancreatitis resulting in a mild-to-moderate elevation and hepatic lipidosis and post-hepatic obstruction resulting in much greater elevations. Use caution (of course) when drawing generalities because the timing and severity of the disease will also impact the elevation, and because we are dealing with cats. My colleague at CSU, Dr. David Twedt, reviewed 180 cases of cats with hyperbilirubinemia. Those cats that were clinically icteric (bilirubin> 3.0 mg/dl) without evidence of RBC lysis most often had primary hepatobiliary disease. Cats that were not obviously icteric (bilirubin ranging from 0.5 to 2.9 mg/dl) often had non-hepatic disorders, with the liver being secondarily affected (reactive hepatopathy). Non-hepatic inflammatory disease, such as pyothorax, abscesses or fat necrosis were included in this group. Dr. Twedt also found the higher the

bilirubin, the poorer the survival rate. Those having only mild increases in bilirubin tended to have a better prognosis; however, that prognosis was influenced by the underlying primary liver disease.

From the biochemical profile, in contrast to the dog where ALT is a specific indicator of liver disease, in cats the ALP is an indicator of significant primary liver disease. ALP in cats has a short half-life (6 hours), is in short supply, and is not induced by steroids, so a much smaller elevation of ALP in a cat should raise a much bigger red flag than it would in a dog. Gamma-glutamyl transpeptidase (GGT) is a similarly informative enzyme in cats, particularly in cases of feline inflammatory liver disease, as this enzyme is concentrated in bile ducts. Ironically, in one of the most famous feline liver conditions, idiopathic hepatic lipidosis, there's a marked mismatch between the two enzymes, ALP elevation usually being marked while the change in GGT is minimal. In the cat, elevations in ALT by itself is often indicative of non-hepatic disease. As in dogs, an elevation in bile acids in the non-icteric cat is indicative of a loss of liver function, including but not exclusively portosystemic shunts.

Liver Disease Differentials

The large-category rule-outs for liver disease in cats at CSU include hepatic lipidosis (30%, idiopathic and secondary), cholangitis (29%), neoplasia (23%), and reactive (18%).

Hepatic

- Inflammation
  - Neutrophilic cholangitis (acute or chronic)
  - Lymphocytic cholangitis
- Hepatic Lipidosis (idiopathic or secondary)
- Neoplasia (bile duct adenoma or carcinoma, lymphoma, etc.)
- FIP
- Amyloidosis
- Sepsis
- Hepatotoxicity

Post-Hepatic

- Pancreatitis
- Cholecystitis
- Cholelithiasis
- Intraluminal/extraluminal biliary mass

Feline Cholangitis

Cholangitis is the most common primary hepatic disease of cats (hepatic lipidosis is more common, but secondary to another concurrent condition and anorexia in the vast majority of cases). There are 3 distinct forms of cholangitis in cats: Neutrophilic (bacterial, acute and chronic), Lymphocytic, and Chronic cholangitis associated with liver fluke infection.

Although clinical signs can be non-specific (anorexia, weight loss, lethargy, vomiting, diarrhea, fever), variable, and overlap extensively, Table 1 attempts to summarize the nomenclature and clinical characteristics of Neutrophilic and Lymphocytic cholangitis.

Neutrophilic (N) acute and chronic	Lymphocytic (L)
Younger males	Older, chronic, progressive (European breeds)

Acute, febrile, icteric, lethargic, abd pain	Variable appetite, vomiting, weight loss
+/- Vomiting or Diarrhea	Icteric, ascites
Extra-hepatic biliary obstruction, lipidosis	↑Globulins
↑ALT (although can be normal)	Total bilirubin, ALT, ALP, GGT are all variable
total bilirubin, ALP, GGT are all variable	Bile duct distention, hepatomegaly, mixed echogenicity
CBC shows left shift w/toxic neutrophils	Bile cytology (toxoplasmosis, *Helicobacter*)*
US reveals thickened GB wall	Bile culture (E.coli, other enterics)
Bile cytology (toxoplasmosis, *Helicobacter*)*	Liver touch-prep cytology for bacteria
Bile culture (E.coli, other enterics)	Histopathology for definitive diagnosis

Abd = abdominal; GB = gallbladder; CBC = complete blood count; US = ultrasound
* 22 gauge 1.5 inch spinal needle in a trans-hepatic approach (decreased leakage)

Treatment	Information	Dose
Fluids & Electrolytes	Oral (voluntary), IV, subQ	40-60 Kcal/kg/day
Nutrition	Oral (voluntary), E-tube	40-60 Kcal/kg/day
Maropitant	Antiemetic	1 mg/kg SQ
Cobalamin (vit B_{12})	Taper after 6 weeks	250ug Inj & Oral available
Pain management	Buprenorphine	0.01 mg/kg sublingual
(N) Antibiotics	Ampicillin, Cephalexin, Clavimox*	3-6 months
(L&N) Metronidazole	Immunomodulatory & Antibiotic	7.5 mg/kg BID
(L) Prednisolone	Immunomodulation	1-4 mg/kg/day, taper q2wks
(L) Chlorambucil	Chemotherapeutic	Std dosing or Pulse dosing
Ursodiol	Choleretic, “silver bullet”	10-15 mg/kg q24hr, long term
SAMe	Liver protectant, antioxidant	200 mg q24hr
vit K_1	Dose prior to E-tube placement	5 mg/cat q1-2 days SQ
Lactulose	HE, ptyalism	0.5-1.0 ml/kg PO TID
Neomycin	HE, acts within GI tract	20 mg/kg q8–12hr PO
Methotrexate	Confirmed cases of bridging fibrosis	0.4 mg/day divided, q7-10 days

E-tube = esophagostomy feeding tube; cobalamin = DOSE; BID = twice daily; TID = 3 times daily; HE = hepatic encephalopathy
*May combine with baytril; Avoid chloramphenicol, clindamycin, erythromycin, lincomycin, streptomycin, sulfonamides, trimethoprim- sulfas, tetracyclines

Feline Hepatic Lipidosis

Hepatic lipidosis can develop secondary to any number feline diseases, especially those that involve anorexia and weight-loss. The therapeutic approach is to diagnose and treat the primary disease as well as support the cat nutritionally and metabolically. Feline idiopathic hepatic lipidosis occurs without an (identifiable) underlying cause, so targeted treatment is impossible and supportive care is absolutely crucial. It can be difficult to distinguish between the two forms, but important to remember that the term "idiopathic" means "we don't know", not "we didn't look".

Older and overweight, an episode of stress and a period of anorexia with significant weight-loss, and the cat turns yellow. The combination of a marked elevation in ALP and minimal elevation in GGT is almost pathogneumonic for idiopathic hepatic lipidosis with this case presentation. Hypokalemia is common, as with many sick cats, and clotting times may be abnormal, as in many hepatopathies – hence the recommendation for starting vitamin K therapy prior to placement of an esophageal feeding tube. A CBC may demonstrate an non-regenerative anemia and poikilocytosis. A definitive diagnosis requires a definitive diagnostic – hepatic histopathology. Fine-needle aspiration and cytology should reveal hepatocellular vacuolation, but this is a non-specific finding. At CSU we frequently employ laparoscopy to obtain multiple sizable liver biopsies as well as gall bladder aspiration and cytology, with only very rare complications, rarely of a serious nature. Remember to address the potential for clotting abnormalities prior to the procedure.

Therapy

Immediate supportive care includes IV fluid replacement and electrolyte support, especially potassium (hypokalemia is a poor prognostic indicator for survival). Avoid spiking fluids with glucose (re-feeding syndrome) or fluids that contain lactate, and consider supplementing magnesium.

Nutritional support is the foundation of effective treatment for hepatic lipidosis. At CSU we have become huge fans of esophageal feeding tubes (E-tube) for cats (see www.milainternational.com; Esophagostomy Feeding). Although it requires a brief anesthesia, these can be placed quickly and easily, left in place for months with minimal maintenance, and they provide veterinarians and owners with a large diameter, easily accessible, safe!, route for both nutrition and medication. Combined with an effective antiemetic (Maropitant, 1.0 mg/kg SQ q 24 hr, as it is metabolized in the liver), even vomiting is rarely a contraindication.

At one end of the spectrum is the belief that you simply need to get food into the cat, simple as that. At the other end of the spectrum there is theoretical support for a large number of supplements (Table).

Supplement	Dose
Arginine	1000 mg/day
Thiamine	100 mg/day
Taurine	500 mg/day
Carnitine	250 mg/day
Cobalamin	250 µg SQ once a week
Antioxidants/Liver Protectants	SAMe, Silybin, vit E, Ursodiol
Mirtazapine	1/8th of 15-mg tablet q 24 hr

Cats are able to “eat around” the E-tube when they become so inspired, which is a great tool when trying to avoid premature cessation of support. Done well, done right, and done in a timely manner, when the management of these cases is well done the hope for recovery is much improved. Unfortunately it is often that other gnarly disease that complicates this already complex cat case.

Pancreatitis

Feline pancreatitis may occur as one of two forms, or an overlap of the two: Acute Necrotizing (ANP) is the more rare presentation, with acute or chronic Lymphoplasmacytic appearing to be more common. There is no age, sex, or breed predisposition, although some reports find Siamese to be over-represented. The clinical signs can be indistinguishable and include lethargy, anorexia, and dehydration, with icterus, abdominal pain, and hypothermia appearing in the more severe ANP form. Abnormalities on the biochemical profile can include elevations in liver enzyme activity, total bilirubin, and blood glucose. The cats are often azotemic with electrolyte abnormalities, including hypokalemia. Low ionized calcium is a poor prognostic indicator. CBC can reveal a nonregenerative anemia and a leukocytosis is more common than leukopenia. The feline PLI (Texas AM GI Lab) or the SpecfPL (IDEXX), run on a serum sample from a fasted cat, are excellent blood tests for the ANP form (100% sensitivity), while they perform with a bit less sensitivity in cases of mild or chronic feline pancreatitis (60-85% sensitivity). At CSU we have removed amylase and lipase from our biochemical profiles entirely. Abdominal radiographs could be normal or show a loss of serosal detail, a mass effect, or dilated fluid or gas-filled duodenum. Abdominal ultrasound could also be normal, or reveal a hypoechoic pancreas, hyperechoic surrounding mesentery, a mass effect, or dilated common bile duct. Definitive diagnosis is histopathology, obtained either through laparotomy or laparoscopy, but with the caveat that pancreatic disease can be focal and non-uniform.

The cause of either form of pancreatitis in cats is unknown or undetermined in the majority of cases. Differentials to consider include parasites (*Toxoplasmosis, Amphimerus pseudofelineus*), viruses (Herpes and FIP), trauma, hypoperfusion and ischemia, and concurrent disease. It seems unlikely that glucocorticoids, obesity, or high fat intake are causes of pancreatitis in cats.

Summary of the treatment options for the various forms of feline pancreatitis

Acute Necrotizing Pancreatitis (ANP)		
Fluids	Crystalloids & Colloids	Consider Hetastarch, Dextran
Nutrition	NE-tube, E-tube	Crucial for the Cat
Antiemetics	Maropitant	1.0 mg/kg q24 hours
	Ondansetron	0.1-1.0 mg/kg q12-24 hours
Pain management	Buprenorphine	0.005–0.01 mg/kg lingual q 4–8 hours
	Meperidine	1–2 mg/kg IM q 2–4 hours
	Butorphanol	0.2–0.4 mg/kg IM q2–4 hours
	Ketamine or Lidocaine	CRI
Acidity	Pantoprazole	0.5–1 mg/kg IV over 15 minutes q12h

Antibiotics	Controversial, Cefotaxime	50 mg/kg IM q8 hours
Plasma	Controversial	20 ml/kg IV
Chronic Pancreatitis		
Fluid support	Oral, subQ, E-tube	Hydration
Nutrition	Highly digestible	Feed the Beast
Cobalamin (vit B_{12})	Taper after 6 weeks	250–500 µg SC once per week
Pain management	Buprenorphine	0.01 mg/kg lingual q4–8 hours
Antiemetic	Maropitant	1.0 mg/kg q24 hours
Choloretic	Ursodiol	10 - 15 mg/kg q24hours
Antioxidant	SAMe	200 mg/day
Probiotic	Proviable, FortiFlora	As directed by package insert
Omega-3 FA	Various formulas	2000 mg/day
Steroids	Human Autoimmune dz	5 mg/cat/day
Antibiotics	Broad spectrum	Cover *E. coli*

Summary

- Feline patients frequently carry more than one significant disease
- Concurrent diseases may be distinct entities or share a common etiology
- Failure to recognize and address concurrent disease often precludes therapeutic success
- Feline cholangitis, pancreatitis, and IBD may be housed within the same cat
- Histopathology remains the gold standard for diagnosis; gallbladder aspiration is an important adjunct

Suggested Reading

Simpson KW. Pancreatitis and triaditis in cats: causes and treatment. J Small Anim Pract 56:40-9, 2015.

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