Emerging Diseases - Hepatobiliary
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Canine Cholangitis

Most dogs with neutrophilic cholangitis will have similar presentations to what we commonly associate with the feline form of this disease. This can occur in any breed, age, or gender of cat. Clinical signs are vague and nonspecific with variable duration (vomiting 72%, lethargy 70%, inappetence (65%, diarrhea 32%, fever 30%, icterus 26%, and abdominal pain 22%. In many ways, these cases present and would appear very similar to what we would associate with pancreatitis or acute gastroenteritis.

Table 1. Serum liver enzyme activity and total bilirubin and cholesterol concentrations.

Parameter	Reference Interval (RI)	Median	Range	% above RI
ALT (n = 49)	16–91 U/L	596	25–3,254	87.8
AST (n = 39)	23–65 U/L	162	38–1,123	79.3
ALP (n = 48)	20–155 U/L	1,506.6	59–8,103	97.9
GGT (n = 29)	7–24 U/L	33	0–392	51.7
TBILI (n = 50)	0.1–0.5 mg/dL	2.5	0.1–81	64.0
CHOL (n = 43)	128–317 mg/dL	339	114–1,402	55.8

Summary of biochemical data available at presentation for all 54 cases.

Diagnosis requires histopathologic confirmation on biopsy (cytology is inconsistent and lacks strong agreement – although I would be more inclined to maintain this as a differential is bactibilia is noted on bile cytology) and the other tests that are typically run are used to rule out other differentials and provide supportive evidence. A nonregenerative anemia and inflammatory leukogram (including left shift) may be seen on complete blood count. All liver enzyme activities and cholesterol may be increased, although not always. Bilirubin is commonly increased. Imaging appearance on radiographs and ultrasound can be highly variable and is nonspecific. Gall bladder distention and bile duct distention may be seen in obstructed and non---obstructed cases. Bile cytology may be useful to support NC diagnosis. All cats should have samples submitted for aerobic and anaerobic culture (gall bladder bile is preferable to hepatic parenchyma). Although the emphasis is on obtaining a liver biopsy, this also may not be in the best interest of your patient. You must decide whether they are clinically stable enough to undergo various diagnostics.

Table 2. Hepatobiliary, gastrointestinal, and pancreatic ultrasonographic abnormalities.

Abnormality	# of Dogs and %
Hyperechoic liver	14/45 (31.1)
Mixed echogenicity liver	14/45 (31.1)
Liver enlargement	16/45 (35.6)
Increased gallbladder sediment	27/45 (60.0)
Distended gallbladder	24/45 (53.3)
Dilated bile ducts	24/45 (53.3)
Evidence of pancreatic inflammation	13/43 (30.2)
Evidence of enteritis[a]	6/43 (14.0)
Gastric wall thickening	5/43 (11.6)
Ileus	4/43 (9.3)

On your liver biopsy, neutrophilic inflammation centered in the lumen or epithelial lining of the bile ducts is characteristic of this type of cholangitis. Varying degrees of histopathologic severity are common and a full spectrum of clinical presentations (acute to chronic) may occur. Currently, we are still perplexed as to why this happens in our canine patients, as many of the previously suspected feline mechanisms do not anatomically make sense. The most common historical theory is that it resulted from an ascending infection from the gut due to underlying anatomy or inflammatory disease.

Perfect treatment recommendations are unknown at this time. Antibiotics are the mainstay of most treatment regimens, and ideally chosen on results of culture and sensitivity testing. If cultures are unavailable and there is a high suspicion, I typically use a combination of a penicillin (amoxicillin or clavamox), a flouroquinolone (enrofloxacin) and metronidazole. This treatment will likely continue for 4---6 weeks. These antibiotic decisions are driven by knowledge of the most commonly isolated pathogens (E coli, Entercoccus spp, Clostridium spp, and others).

In addition to antibiotics, supportive care should be implemented including hepatoprotectant medications (SAMe, ursodiol, carnitine, +/--- others) and appropriate nutritional support. Please see guidelines for hepatoprotectants at the end of these notes.

Overall, the prognosis with NC is reasonably good. Median survival time of dogs with this disorder is not been reported and to date no specific clinical variables have been identified to assist in prognosis. For those requiring surgery, the perioperative period is most critical for survival.

Ductal Plate Malformations

Development of the ductal plate is an important component of the biliary epithelium and ultimately the bile ducts. This is an intricate process and when dysregulated for any reason can result in ductal plate malformations (DPM), other structural abnormalities, and functional consequences for the affected animal. These commonly result in varying degrees of extracellular matrix deposition, and in the worst case scenario hepatic fibrosis and portal hypertension. A group led by Dr. Sharon Center at Cornell University has been examining dogs and cats affected with DPM and have proposed the following classification system including 6 DPM subtypes:

1. Simple Biliary Cysts
2. von Meyenberg Complexes
3. Biliary Cystadenoma
4. Choledochal Cysts
5. Caroli's Syndrome (with or without Congenital Hepatic Fibrosis)
6. Proliferative-like DPM (with or without Congenital Hepatic Fibrosis)

There are not new abnormalities in feline (or canine) hepatobiliary disease, and some of these disorders (e.g. biliary cystadenoma) have previously been characterized in the veterinary medical literature. However, these disorders have largely been missed and are now more frequently recognized due to advancements in hepatic histopathology and increased frequency of liver biopsies.

Some of the frequently encountered DPM's are clinically silent. These include simple biliary cysts, von Meyenberg complexes, and biliary cystadenomas. In some instances, these can create a space occupying effect that require drainage or removal to resolved associated clinical signs.

The other classifications include choledochal cysts, Caroli's syndrome, and prolferative-like DPM, which all result in a higher incidence of hepatobiliary bacterial infections. So while there is no know specific treatment for the developmental abnormalities, the presence of these abnormalities may alter how we manage patients. For example, the duration antimicrobial courses and the duration of hepatoprotectants required will often be prolonged compared to normal courses used in feline hepatobiliary disease. In the lecture, we will discuss how these specific abnormalities may be managed and approached in clinical practice.

1. Steiner JM. Exocrine pancreatic insufficiency in the cat. *Top Companion Anim Med* 2012;27:113-116.
2. Steiner JM, Medinger TL, Williams DA. Development and validation of a radioimmunoassay for feline trypsin-like immunoreactivity. *Am J Vet Res* 1996;57:1417-1420.
3. Steiner JM, Williams DA, Moeller EM, et al. Development and validation of an enzyme-linked immunosorbent assay for feline trypsin-like immunoreactivity. *Am J Vet Res* 2000;61:620-623.
4. Xenoulis PG, Zoran DL, Fosgate GT, et al. Feline Exocrine Pancreatic Insufficiency: A Retrospective Study of 150 Cases. *J Vet Intern Med* 2016;30:1790-1797.

Hepatoprotectant Medications

As you now have learned, the liver is at the epicenter of the body and as one of the three most important organs in the body (including the pancreas and gut) it is exposed to numerous insults. As a result, the liver has developed both antioxidant mechanisms (enzymatic and nonenzymatic) as well as prosurvival biochemical pathways to help support the liver during periods of oxidative stress. From the clinical standpoint, we are best able to manipulate the enzymatic (catalase, superoxide dismutase, glutathione peroxidase, glutathione transferase) and nonenzymatic (glutathione, vitamin E, beta---carotene, bilirubin) mechanisms of defense. Therefore, you will see the majority of the following drugs used to treat liver disease in some manner affect this area.

You must also remember that the following list of hepatoprotectants are all supportive medications rather than specific cures. The BEST treatment of any liver disease is aimed at the underlying disorder specifically (e.g. PSS shunt correction, antibiotics for leptospiral hepatitis, etc…). These medications are instead use adjunctively with disease specific therapies as well as when there is no specific cure and we as clinicians are limited to supportive care and tincture of time.

S---Adenosylmethionine (SAMe)

SAMe is primarily produced in the liver and is known to be decreased in the majority of experimental models of liver disease. In the liver, SAMe is metabolized in three ways (transmethylation, transsulfuration, and aminopropylation) all of which have hepatoprotective effects. Therefore, we often add this medication to many hepatoprotective therapeutic regimens. It is most commonly available as Denosyl (Nutramax Laboratories) and is dosed at 20 mg/kg/day PO. The

SAMe (S---adenosylmethionine) (Denosyl®SD4)

a. Mechanism
   1). Endogenous molecule essential to metabolism
   2). Indirect glutathione precursor (anti---oxidant)**
   3). Other functions (detoxification, supports membrane function, many others)

b. Indications
   1). Hepatic disorders associated with oxidant injury
      a). heavy metal (Cu) storage
      b). some drug---induced liver injury c). cholestasis/bile duct obstruction
      d). feline hepatic lipidosis
      e). necro---inflammatory liver disorders
      f). ischemia---reperfusion injury
   2). Acetaminophen toxicity
   3). Other RBC oxidant injury

medication should be given on an empty stomach and all tablets should be enterically coated. The drug is poorly bioavailable and these are important to maximize absorption. [Side note – as we discussed in class – there are studies that have examined the relative SAMe amounts in various formulations which showed wide variety and many not meeting label claims! For this reason, remember to always give the formulations that have undergone more testing if at all possible]. When used clinically, this drug has few associated side effects and when they do occur, they most often are gastrointestinal in nature. Overall, current evidence indicates that this is a very safe supplement. Unfortunately, in veterinary medicine we are still lacking high quality studies clearly demonstrating the benefit to this medication and it is often empirical justification.

Silymarin

The milk thistle plant contains an active ingredient called Silymarin. This is a group of flavonoid compounds with antioxidant properties among other hepatoprotective properties. Specifically, it is also known to inhibit the uptake of Amanita mushrooms in the liver and therefore is indicated as an antidote for toxic hepatopathies secondary to Amanita mushroom ingestion. In clinical use this is a safe and well---tolerated supplement. However, it does affect P450 drug metabolism and therefore, other drugs in your patients that typically undergo that type of metabolism should be monitored closely for changes. As you will see is a common theme, there is very limited data in veterinary medicine to support the use of this supplement. Its clinical recommendation comes from empirical evidence, high safety profile, as well as theoretical benefit based on drug mechanism. It is typically dosed at 10---15 mg/kg/day divided into either BID or TID dosing. The most commonly used formulation of silymarin include a combination product with SAMe (Denamarin) or combination product with vitamin E and zinc (Marin). Both of these are produced by Nutramax Laboratories. Additionally, due to the poor bioavailability of this supplement, there is a less commonly used but higher bioavailable complexed form called Siliphos.

Milk Thistle (silymarin)

a. Flavonoid mixture
b. Derived from seeds of Silybum marianum
c. Ancient liver remedy
d. Hepatoprotective properties
    1). Antioxidant
    2). Anti---fibrotic Anti-
    3). --inflammatory
    4). □ uptake of amanita mushroom toxin
e. Variable potency and absorption
f. Absorption improved when complexed with phosphatidlycholine (Marin®, Sil---Phos®)

Vitamin E

Vitamin E is a variety of antioxidant compounds occasionally used in a hepatoprotectant manner, with alpha---tocopherol being the most active of the family of compounds. Murine and human studies of hepatic diseases have shown a significant benefit with administration. However, direct evidence in our companion animals is still lacking. When used, the alpha---tocopherol acetate form is dosed at 10---15 IU/kg PO SID. Emulsified formulations also exist for chronic cholestatic patients (vitamin E is a fat soluble vitamin).

N---acetylcysteine

This medication is used as an intravenous supplement of cysteine, which serves as a precursor to increase glutathione levels. It is used in two different clinical situations. It has proven to be very effective in acetaminophen hepatotoxicity specifically. However, the more common use is with hospitalized patients where oral antioxidants listed above are difficult to administer. It is dosed at 140 mg/kg IV initially, then 70 mg/kg QID for a total of seven treatments. This medication is not given orally due to the high incidence of gastrointestinal side effects.

Colchicine

This drug is most commonly used for its potential anti---fibrotic effects. You will see it used for this purpose latter in this unit. However, it also has anti---inflammatory effects. It is NOT used for its anti---inflammatory effects specifically. This is an added bonus when used for fibrotic hepatopathies. It has significant side effects including gastrointestinal dysfunction (hemorrhagic diarrhea), bone marrow injury, and neuropathies. Typical dose range is between 0.01---0.3 mg/kg/day PO.

Zinc

Zinc is an important co---factor in many important anti---inflammatory, antiapoptotic and antifibrotic processes in the liver. Zinc is used because it inhibits the uptake of hepatic copper (as is discussed below) and also as it is known to be low in some inflammatory hepatopathies.

Carnitine

This is an important factor in lipid metabolism in the body. It also plays a vital role in the maintenance of antioxidant systems. The most common use is in cats with hepatic lipidosis. It has been shown to increase lipid mobilization in fat cats. As a result supplementation at 250 mg/cat/day PO has been recommended in hepatic lipidosis cats.

Ursodeoxycholate (Ursodiol)

Ursodeoxycholate is the major bile acid in the bile of the chinese black bear and is know for its minimal hepatotoxicity. All bile acids have some hepatotoxic nature and it has to do with their hydrophobicity. Toxic bile acids disrupt cell membranes and stimulate apoptosis.

Ursodiol, when supplemented, augments the bile acid pool to a friendly gang. This has several cytoprotective effects include less hepatotoxicity, apoptosis inhibition and induction of choleresis. The choloretic properties of ursodiol are from direct stimulation of a bicarbonate rich bile flow in the ducts and also membrane transport mechanisms are upregulated which promote flow.

When used clinically, absorption is enhanced when this medication is given with food. Little information is available on the effectiveness of this medication but we commonly use it for its potential benefits and high safety profile. It is dosed at 10--- 15 mg/kg/day PO

Ursodiol (Actigall®)

a. Primary bile acid of Chinese black bear; now synthetic
b. Hydrophilic bile acid
c. Ancient healing powers
d. Marketed for dissolution of cholesterol gallstones in humans; but found other effects on liver
e. Hepatoprotective effect
   1). Anti---inflammatory
   2). Anti---fibrotic
   3). Immunomodulatory
   4). Choleresis
f. Mechanism: replace hepatotoxic hydrophobic bile acids; others
g. Used in chronic cholestatic disorders; contraindicated in biliary obstruction (□'s watery bile secretion)