

Practical approach to the cat with elevated liver enzymes (including diagnosis and management of feline hepatic lipidosis)

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The feline liver is susceptible to disease as it has limited conjugation capabilities. It can only conjugate to cholic acid with taurine. Also, due to deficiencies in glucuronyl transferase, the feline liver performs limited glucuronide conjugation, the major route for elimination of salicylates, morphine derivatives, diazepam derivatives, phenols, pyrethroids and benzoic acids.

Additionally, the feline liver has high activity of hepatic transaminases and deaminases, requiring a high dietary protein requirement. Cats are unable to down regulate these enzymes in times of limited protein intake (e.g. starvation or reduced appetite), predisposing to the development of diseases such as hepatic lipidosis (HL).

Anatomically, the major pancreatic duct joins the common bile duct from the liver before entering the duodenum, predisposing to ascending infection from the gastrointestinal tract.

Clinical signs of liver disease

Clinical signs associated with liver disease are often vague and include lethargy, weight loss with a reduced appetite (e.g. HL), weight loss with a good appetite (e.g. lymphocytic cholangitis (LC), abdominal pain, vomiting, pyrexia, hepatomegaly, ascites and jaundice. Jaundice in cats can occur due to pre-hepatic causes (e.g. haemolysis), hepatic (e.g. HL) and post-hepatic disease (e.g. pancreatitis, cholelithiasis etc). If there is no evidence of a haemolytic process (e.g. normal red cell count), hepatic or post-hepatic causes of jaundice are investigated. Hepatic causes of jaundice are listed below:

Metabolic

Hepatic Lipidosis*

Neoplastic

Primary or metastatic neoplasia e.g. biliary cystadenoma, hepatocellular carcinoma, lymphoma

Inflammatory

Neutrophilic cholangitis* – acute or chronic

Lymphocytic cholangitis*

Amyloidosis (especially oriental/Siamese cats, often present with sudden onset intrabdominal haemorrhage)

Infectious

Bacterial – Sepsis (mild increases in bilirubin with normal liver enzymes)

Viral – Feline Infectious Peritonitis* (often mild increases in bilirubin with normal liver enzymes)

Parasitic – Toxoplasmosis, liver fluke

Fungal

Toxic

Hepatotoxicity e.g. paracetamol/acetaminophen, diazepam, antithyroid medications, griseofulvin

*Common causes



Other clinical features for consideration are:

Age	<p>Young cats – FIP, lymphocytic cholangitis</p> <p>Young/middle aged – pancreatitis, neutrophilic cholangitis, HL</p> <p>Middle aged/senior – neutrophilic cholangitis, HL, neoplasia</p>
Breed	<p>Siamese/Oriental – FIP, amyloidosis</p> <p>Persian – FIP, lymphocytic cholangitis</p>
History or clinical signs	<p>Overweight with recent weight loss – HL</p> <p>Weight loss & good appetite – lymphocytic cholangitis</p> <p>Any current medications – consider if hepatotoxic</p> <p>Abdominal pain – pancreatitis, neutrophilic cholangitis, cholecystitis</p>
Physical examination findings	<p>Pyrexia – FIP, neutrophilic cholangitis, sepsis</p> <p>Hepatomegaly – lymphocytic cholangitis, HL, neoplasia</p> <p>Ascites – lymphocytic cholangitis, FIP, haemoabdomen (amyloidosis)</p> <p>Respiratory changes – pleural effusion secondary to FIP, neoplasia</p>

Investigation of liver disease

Clinical pathology

Clinical pathology may reveal a mild, non-regenerative anaemia (anaemia of chronic disease). Neutrophilia maybe present, sometimes with toxic neutrophils especially with sepsis or neutrophilic cholangitis (NC). Liver enzymes are commonly increased including hepatocellular markers (ALT and AST) and cholestatic markers (alkaline phosphatase (ALKP) and gamma-glutamyl transferase (GGT)).



ALT is located within the cytoplasm of hepatocytes and damage to liver cells (whether mechanical, toxic or hypoxic) causes leakage into the blood stream. The half-life of ALT is approximately 60 hours.

AST is also present within the cytoplasm of hepatocytes, but is partly bound to mitochondria, thus more damage is required to increase AST than ALT. AST has a shorter half-life (1 hour) and persistent AST elevations are concerning. Although the number of hepatocytes affected relates to the magnitude of increase, there is no correlation between the magnitude of increase and severity or reversibility of disease.

AST and ALT are also present in muscle. If muscle damage is present, it is likely to be accompanied by an increase in creatine kinase concentration. Very severe muscle disease is required to significantly increase ALT, which is uncommon in cats but maybe seen with snake envenomation or other myopathies.

Increases in ALT maybe detected as part of routine screening. If increases are mild (e.g. up to 2-fold) and the patient has no obvious clinical signs, then repeat assessment could be considered at 2 weekly intervals for 4-6 weeks and consideration of treatment with nutraceutical hepatoprotectants (e.g. S-adenosylmethionine (SAME)). Total T4 should be assessed in older cats. If increases are more significant (e.g. 2-5 fold increases) and/or the patient has clinical signs of systemic illness (e.g. inappetance, weight loss) then further investigation would be considered.

ALKP is present on the canalicular and microsomal membranes of hepatocytes and biliary epithelium. Blockage (cholestasis) of the biliary tract increases ALKP via induction of enzyme expression and accumulation within the hepatocyte membranes, which takes approximately 8 hours, explaining why in very early stages of an obstructive event, ALKP may be normal. Bilirubin tends to rise faster in cats with obstruction. The half life of ALKP is also short – about 6 hours in cats. In addition to the liver isoform of ALKP, bone, renal and gut isoenzymes also occur. Of these, only the bone isoform is of any clinical significance, and increases can be seen in cats associated with bone growth (e.g. young patients) and hyperthyroidism. There is no steroid-induced ALKP isoenzyme in cats.

GGT occurs on the biliary epithelium and concentrations also rise with cholestasis, secondary to biliary hyperplasia and induction secondary to bile acid accumulation. Elevations generally mirror ALKP, except in HL, where about 80% of cats have significantly higher ALKP than GGT. As HL often occurs together with other liver diseases though, this may not always be the case.

Bilirubin is made from the uptake and breakdown of haemoglobin by macrophages in the liver and spleen. The major source in cats is from the normal breakdown of red blood cells (RBCs). Bilirubin is released from the macrophage and bound to albumin for transport to the liver. In the hepatocyte, it is conjugated with glucoronide then moved actively into the bile cannalculi – this is the slowest (rate limiting) part of the process. Excretion into bile and movement from the gall bladder into the duodenum results in excretion in the faeces or transformation into urobilinogen and renal excretion. Any conjugated bilirubin that escapes back into circulation becomes attached to albumin with a half life of 10-14 days. This is why persistent icterus can occur, after correction of a cholestatic event. Cats are dependant on hepatocyte conjugation (none occurring in the kidney, as occurs in dogs) This is why bilirubin in feline urine is always abnormal.

The degree of increase in bilirubin can help stratify differential diagnoses. Generally with pre-hepatic jaundice bilirubin will rarely increase above 50-100 umol/l. Diseases such as FIP, pancreatitis, amyloidosis and sepsis rarely increase bilirubin above 100 umol/l. If bilirubin is >200 umol/l, this is most often due to either HL or post-hepatic obstructions. Generally the higher the serum bilirubin, the more likely complete post-hepatic biliary obstruction is present.



Cats with hyperthyroidism often have high serum activities of ALKP and ALT (75%) and approximately 90% of hyperthyroid cats have an elevation in at least one enzyme (i.e. ALKP, ALT, GGT or AST). Assessment of **Total T4** is important in older cats with hepatic enzyme increases and signs suggestive of hyperthyroidism.

The cause of the increase in liver enzymes in hyperthyroid cats is unclear, however it is likely a combination of hepatocyte mitochondrial damage, induction of the bone alkaline phosphatase isoenzyme and lipolysis secondary to increased metabolism. Hepatic biopsies from hyperthyroid cats often reveal only nonspecific and mild changes.

Typically, hyperthyroid cats have mild increases in ALT and ALKP and significant increases should prompt consideration of underlying disease.

In one study of 15 hyperthyroid cats (and 4 control cats), elevated liver enzyme activity was not associated with abnormalities in hepatic parenchyma, regardless of the degree of enzyme increase and serum liver enzyme activities returned to normal after obtaining euthyroidism (radioactive iodine treatment). Additional tests of liver function (e.g. albumin, bile acids) are expected to be normal. Plasma ammonia concentration can be slightly increased.

Investigations of liver enzyme elevations in hyperthyroid cats should be considered if:

- The patient is systemically unwell
- The patient has a disproportionate increase in liver parameters compared with the degree of increase in Total T4 and
- Liver parameters remain significantly elevated despite obtaining a euthyroid status.

Bile acids are formed by the liver and after conjugation are excreted via the biliary system. Gall bladder contraction empties the bile acids into the duodenum where they aid fat absorption and are recycled back into the enterohepatic circulation. If the portal venous system is intact, bile acids are delivered back to the liver where hepatic function is required to reclaim the bile acids from the blood for recycling and re-excretion in bile.

Bile acids are measured fasting and 2 hours after a meal to provoke gall bladder contraction and demonstrate the function of capturing and recycling mass bile acid release following feeding. In cats with increased bilirubin due to hepatic or post hepatic causes, both fasted and post-prandial bile acid concentrations are elevated and no extra information can be derived from bile acid measurement.

In non-jaundiced patients, elevated bile acids maybe due to:

- A portosystemic shunt
- Cholestatic disorders impairing the enterohepatic circulation
- Any hepatic disease impairing hepatic function or decreasing hepatic mass
- Extrahepatic diseases e.g. pancreatitis, gastrointestinal disease may give mild elevations (usually <40 $\mu\text{mol/l}$).

Clotting factors can be affected by hepatic disease and assessments of coagulation function such as prothrombin time (PT) and activated partial thromboplastin time (APTT)) can be prolonged due to suppression of hepatic production.

In one paper of 45 cats with naturally occurring liver disease, 98% of cats demonstrated an abnormality in at least one parameter (platelet count, PT, APTT, thrombin time, factor II, V, VII, X and XIII, fibrinogen concentration, activities of antithrombin, protein C, plasminogen, a2-plasmin inhibitor and D-dimer concentrations). A more recent paper evaluating bleeding complications in cats (and dogs) following ultrasound guided biopsy found no obvious correlation between abnormalities in coagulation parameters and haemorrhage, although only 11 cats were included.

The author routinely assesses platelet count prior to any biopsy (e.g. fine needle aspirate) and provides supplementation of Vitamin K (0.5 mg/kg subcutaneously, q12 hours) for 24-48 hours prior to considering sampling for histopathology.



Diagnostic Imaging

Abdominal radiography maybe useful in determining liver size but rarely gives a definitive diagnosis, except in cases with radiopaque cholelithiasis. Marked hepatomegaly is often seen with LC and HL. Assessment of liver size is best made on a right lateral recumbent radiograph by assessing the position of the gastric axis. The ventral and caudal edges of the medial liver lobes should form a hepatic angle within the costal arch.

Additionally, the liver length (LL): thoracic 11 vertebrae (T11) ratio has been assessed in normal cats. Liver length was determined by measurement from the point of the diaphragm to the most caudal point of the hepatic angle. A normal reference interval of LL/T11 ratio was 4.22 ± 0.54 was identified, with measurements over this suggestive of hepatomegaly. Further investigations are required in cats with hepatic pathology.

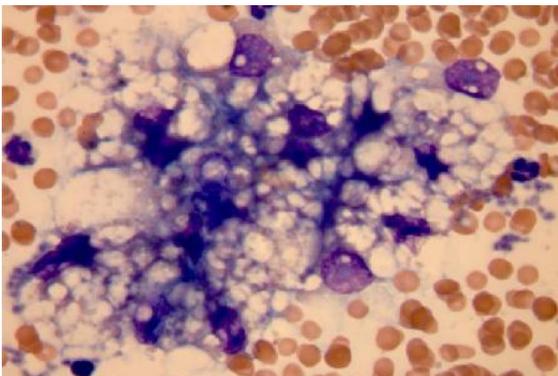
Thoracic radiographs may provide evidence of metastatic disease.



A gall bladder ultrasound demonstrating anechoic bile but a cholelith is present within the gall bladder

Abdominal ultrasonography provides useful information about the hepatic parenchyma and biliary tree but rarely gives a definitive diagnosis. Focal neoplastic lesions may be evident, or diffuse changes in echogenicity identified with diseases such as lymphoma. In HL, the liver typically appears enlarged and bright. NC and LC can result in thickening of the gall bladder wall, sludging or inspissation of bile and a generalised, patchy parenchymal echogenicity. Abdominal ultrasound can be useful to identify signs of obstruction (e.g. post-hepatic disease) such as a grossly distended bile duct and large dilated gall bladder. In contrast to dogs, gall bladder

sludge in cats can be suggestive of increased liver enzymes and increased hyperbilirubinemia.



Fine needle aspirate from a patient with hepatic lipidosis demonstrating marked vacuolar change within the hepatocytes

Ultrasound guided fine needle aspirates (FNA) are useful for identifying lymphoma. Vacuolar hepatopathy is suggestive of HL. FNA are not useful for identification of inflammatory liver diseases or other neoplastic processes. Aspiration of bile can confirm neutrophilic infiltration however this should be performed with caution and by experienced imagers to reduce the risk of bile peritonitis. Cats with a normal gallbladder appearance on ultrasound are unlikely to have a positive bile bacterial culture (negative predictive value 96%). Cats with a thickened gall

bladder wall (>1mm thick) or sludge were more likely to have positive cultures which were typically enteric bacteria in origin.



Hepatic biopsy

The most important tool for definitive diagnosis is liver biopsy. Samples may be obtained for histopathology and bacterial culture via percutaneous ultrasound guided trucut biopsy, laparoscopy (keyhole surgery) or exploratory laparotomy. Advantages and disadvantages are present with each technique.

Trucut biopsies are less invasive and require a shorter anaesthesia, however sample size is smaller, representative samples may not be obtained and haemorrhage is a risk. In a recent retrospective study of 30 cats having a percutaneous hepatic trucut sample, all cats had packed cell volume (PCV) decreases. Major bleeding (a decrease in PCV by over 6%) occurred in 56.7% and was more likely in cats with hepatic lipidosis. There was no correlation between changes in PCV or complications and signalment, coagulation parameters, serum parameters, number of biopsies, ultrasound findings or vitamin K administration.

Laparoscopy is a minimally invasive but requires expensive equipment and experience. Exploratory laparotomy requires a longer anaesthetic and is more invasive, but allows evaluation of other organ systems plus intestinal and pancreatic biopsy.

Each procedure requires general anaesthesia and should not be performed until the patient is stabilised. Hepatic biopsies result in bleeding and should be delayed until acceptable coagulation is present (preferably normal APTT, PT and platelet numbers). Impression smears of biopsied tissue can provide more immediate cytological information while histopathology is pending. If the patient is undergoing anaesthesia then consideration for placement of an oesophagostomy tube (O-tube) to facilitate enteral nutrition should be given.

Diagnostic findings that are important to consider include:

Neutrophilia	FIP, sepsis, neutrophilic cholangitis, pancreatitis
Presence of left shift or toxic neutrophils	Neutrophilic cholangitis, sepsis
Mild increase in bilirubin with normal liver enzymes	FIP, pancreatitis, sepsis
More marked increase in ALP compared to ALT	Post-hepatic jaundice, cholangitis, HL
Extremely elevated ALKP with mild increase in GGT	HL
Marked hyperglobulinemia	Lymphocytic cholangitis, FIP, lymphoma
Hypocalcemia	Pancreatitis, sepsis
Radio-opaque area in the gall bladder	Cholelithiasis
Thickened gall bladder/sludge in gall bladder on ultrasound	Cholecystitis / neutrophilic cholangitis Sludge can be normal in some patients, however the gall bladder wall should not be thickened
Diffuse, hyperechoic hepatic parenchyma on ultrasound	HL, lymphoma, amyloidosis
Diffuse, hypoechoic hepatic parenchyma on ultrasound	Diffuse, infiltrative disease e.g. lymphoma, passive congestion
Normal echogenicity, normal architecture	Normal liver, acute hepatitis, toxic hepatopathy, diffuse infiltrative disease
Irregular, hepatic margins on ultrasound	Neoplasia, fibrosis, abscess



Post-hepatic causes of jaundice and investigations



Jaundice may be seen in cats with pre-hepatic, hepatic or post hepatic disease. Marked increases in bilirubin are more commonly seen with hepatic disease such as hepatic lipidosis of post-hepatic bile duct obstruction

Post-hepatic jaundice may be seen in cats of any age and is caused by obstruction (partial or complete) of the common bile duct that is either intra-luminal (within the bile duct) or extra-luminal (outside of the duct). Patients may present with mild to moderate lethargy, inappetence, occasional vomiting, weight loss, abdominal pain and often marked to severe jaundice. Causes of post-hepatic jaundice are listed below:

Anomalous

Hepatic cysts (often in conjunction with polycystic kidney disease cysts)

Neoplasia

Primary pancreatic neoplasia (extra-mural compression)

Primary biliary neoplasia (intra-mural compression)

Primary intestinal neoplasia (extra-mural compression)

Metastatic neoplasia (extra or intra-mural compression)

Inflammatory

Acute or chronic pancreatitis* (extra-mural compression)

Triaditis - inflammatory bowel disease, cholangitis, pancreatitis (extra or intra-mural compression)

Gallbladder mucocoele

Cholelithiasis (most commonly associated with neutrophilic cholangitis)

Infectious

Feline Infectious Peritonitis (secondary to granuloma formation – extra-mural compression)

Trauma

Traumatic rupture of the gall bladder or bile duct

* Common causes

The most common cause of post-hepatic jaundice in cats is pancreatitis, followed by neoplasia. Cholelithiasis and mucocoeles occur but are less common. Cholelithiasis usually occurs in conjunction with NC. Traumatic rupture of the gall bladder or bile duct is rare. Although dogs with pancreatitis frequently present with vomiting, cats often demonstrate mild abdominal discomfort or inappetence. Haematology may demonstrate a mild inflammatory leukogram. Biochemical findings reveal marked increases in cholestatic markers (ALKP, GGT) and mild to moderate increases in hepatocellular markers (ALT and AST). If bilirubin is >100 umol/l, abdominal ultrasound is critical to identify whether extrahepatic biliary obstruction is present.

Serum amylase and lipase are not specific to the pancreas in cats and significant elevations are seen with renal disease. A feline-specific Pancreatic Lipase Immunoreactivity assay (fPLI) is now available commercially and is useful for identifying pancreatitis. Electrolyte abnormalities such as hypocalcaemia may be seen.

Post-hepatic causes of jaundice are rarely identified on abdominal radiography. Abdominal ultrasound is more useful to identify changes associated with obstruction, such as a markedly dilated gall bladder and tortuous common bile duct. Choleliths can be identified as focal echogenic masses within the duct or result in acoustic shadowing.



Pancreatic and intestinal masses may be identified. Abdominal ultrasonography to detect pancreatitis is poorly sensitive.

Findings consistent with pancreatitis include an enlarged and bulky pancreas of mixed echogenicity and increased echogenicity of the surrounding mesenteric fat, suggestive of inflammation. Some cases of severe or chronic pancreatitis may appear normal on ultrasound.

FNA, trucut biopsy or laparoscopic biopsy maybe attempted if masses are identified, however consideration should be given to the risk of haemorrhage or the development of bile peritonitis. Typically, FNA is attempted first to avoid an invasive procedure should the mass be identified and a guarded prognosis assigned.

Frequently, exploratory laparotomy is indicated to examine the liver and biliary tree and provide corrective surgery for obstructive masses. Corrective procedures should only be performed by experienced surgeons.

It is of note that the more severe the jaundice, the more likely extra-hepatic bile duct obstruction or HL is occurring. The former should be considered a surgical emergency and the latter, a medical one. Both conditions require intensive patient monitoring and possibly invasive diagnostic procedures. Following this diagnostic approach will often lead to a definitive diagnosis, allowing for the development of a tailored and specific treatment plan.

Common Liver Diseases in Cats

Inflammatory liver diseases are described as cholangiohepatitis or cholangitis, however as histopathological changes are centred in or around the bile ducts and portal areas, the term cholangitis is preferred, together with a description of the predominant cellular infiltrate, e.g. neutrophilic, lymphocytic or mixed. Lymphocytic portal hepatitis is classified as a separate pathological process and is generally considered a mild, non-specific reactive change, commonly identified as an incidental finding in older cats.

Neutrophilic Cholangitis

Neutrophilic Cholangitis (NC) is caused by bacterial infection (typically *E.coli*, streptococci, Clostridia spp., or Salmonella) that ascends from the gastrointestinal tract. In cats, the pancreatic and bile ducts join together before entering the duodenum, which predisposes to the development of simultaneous pancreatitis, inflammatory bowel disease (IBD) and NC ("triaditis"). NC is more common in mature to senior cats, but can occur at any age, particularly in patients with predisposing factors such as biliary stasis and IBD. There is no apparent sex or breed predisposition.

Most patients present with acute signs of illness, including jaundice, pyrexia, anorexia and abdominal pain. Laboratory findings include elevated ALT, ALKP, GGT and bilirubin. There may be a neutrophilia with left shift +/- toxic neutrophils. Ultrasound findings may include thickening of the gall bladder wall (> 1 mm), distension of the bile duct (>5mm) and sludge or inspissated bile within the gall bladder. Cholelithiasis may also be identified with radiolucent or radiodense choleliths. Liver parenchyma may appear patchy in echogenicity.

Cytology (e.g. FNA) to differentiate inflammatory liver diseases is rarely helpful and liver biopsy for histopathology is needed for definitive diagnosis. As many cats are acutely unwell, they may represent high anaesthetic risks and stabilisation before anaesthesia maybe required. In these patients empirical treatment (e.g. nutrition, antibiotic therapy)



is often started and liver biopsy performed once the patient is stable.

Coagulation parameters (e.g. APTT and PT) are assessed prior to biopsy and vitamin K is administered pre-operatively (0.5-1 mg/kg SQ q12 hr). Once obtained, liver tissue is submitted for histopathology and bacterial culture.

Additionally, if exploratory laparotomy is performed to obtain samples, the patency of the bile ducts is checked and bile aspirated for cytology and culture. A cholecystectomy maybe required to remove inspissated bile. Cannulation of the duodenal papilla to lavage and check patency of the common bile duct may be needed. Oesophagostomy tube placement (O-tube) should be considered.

Histopathology generally identifies a neutrophilic infiltrate within the bile duct lumen and/or epithelium. In acute NC the inflammatory infiltrate may extend into the portal areas and the hepatic parenchyma.

Periportal necrosis commonly occurs. In more chronic forms, fibrosis and bile duct proliferation together with a mixed inflammatory infiltrate of neutrophils, lymphocytes and plasma cells in portal areas is seen.

Antibiotics are the mainstay of treatment of NC, ideally selected based on culture and sensitivity testing. The ideal antibiotic selected for empiric use is broad spectrum, bactericidal, achieves therapeutic levels within the bile and does not require hepatic metabolism for activation or excretion. Amoxicillin-clavulanate, cephalexin or a fluoroquinolone combined with metronidazole for additional anaerobic activity are good choices. Enrofloxacin is avoided in cats due to the risk of retinal degeneration. Antibiotics are administered parenterally until the patient is eating, then orally for at 4-8 weeks.

Additional supportive treatments include:

- Intravenous fluid therapy e.g. 0.9% NaCl or Hartmanns with potassium chloride supplementation
- Assisted enteral feeding e.g. naso-oesophageal tube (NO) for short term feeding or placement of a O-tube for longer term feeding
- Analgesia e.g. buprenorphine (0.01-0.02 mg/kg IV, IM, SC or sublingually q 6-8 hr)
- Anti-emetics if vomiting or nausea are present e.g. maropitant (1 mg/kg SQ q24hr) +/- metoclopramide (constant rate infusion 1-2 mg/kg q24hr)
- Ursodeoxycholic acid (UDCA 10-15 mg/kg PO q24hr) is administered if there is no evidence of biliary tree obstruction (e.g. markedly dilated biliary tree) for its immunomodulatory and antifibrotic effects and to reduce the concentration of hydrophobic bile acids that are toxic to hepatobiliary cell membranes
- S-adenosylmethionine (SAME) can be provided (20 mg/kg PO q24hr) for hepatic support. Normally the liver produces ample SAME but in liver disease endogenous conversion to glutathione maybe deficient and SAME supplementation will increase liver and RBC glutathione levels.

Mixed Inflammatory Cholangitis

Liver histopathology occasionally yields mixed inflammatory cell infiltrates, which are considered to be a chronic form of NC. History may include an episode of acute illness followed by gradual weight loss, inappetance and lethargy. Management is similar to NC with broad-spectrum antibiotic administration preferably based on culture and sensitivity for 4-6 weeks. If clinical improvement does not occur within 1-2 weeks, anti-inflammatory prednisolone (0.5 mg/kg PO q 12 hr) can be given.



Lymphocytic cholangitis

Lymphocytic cholangitis (LC) is likely an immune-mediated disease and is most commonly seen in younger cats between 1-5 years. Persians and male cats maybe over-represented. Patients are often systemically well with weight loss despite a normal to increased appetite, hepatomegaly and sometimes generalised lymphadenomegaly and ascites. Pyrexia is not a feature.

Helicobacter spp. are associated with liver and biliary tract inflammation and neoplasia in humans, however in cats *Helicobacter* DNA or other bacteria are rarely isolated. It appears that the altered immune response targets bile ducts and can result in ductopenia and peribiliary fibrosis.

Laboratory features include raised ALT, ALKP, GGT and bilirubin. Neutrophilia is less common and there is rarely a left shift or toxic neutrophils. A mild non- or poorly regenerative anaemia (anaemia of chronic disease) can occur as can hyperglobulinemia. Lymphopenia maybe seen. Ultrasound often identifies marked hepatomegaly with patchy echogenicity.

If extensive cirrhosis occurs, the liver maybe hyperechoic. Mesenteric lymphadenomegaly and ascites may occur. If ascites is present, the fluid is usually high in protein with a low mixed inflammatory cellular infiltrate (e.g. similar to Feline Infectious Peritonitis). Some clinical features to help to differentiate between FIP and LC are detailed below:

	Lymphocytic Cholangitis	Feline Infectious Peritonitis
Clinical feature	Jaundice, weight loss, often marked hepatomegaly +/- ascites. Pyrexia not a feature	Jaundice, weight loss +/- ascites. Pyrexia may occur. Uveitis, chorioretinitis, pleural effusion, neurological signs
Demeanour	Usually bright	Dull and lethargic
Appetite	Normal to increased	Decreased
Clinicopathological findings	Increased liver enzymes, often hyperbilirubinemia, lymphopenia, anaemia of chronic disease	Bilirubin mildly increased +/- liver enzyme elevation. Lymphopenia +/- anaemia of chronic disease occurs
Ascites	If present fluid is typically proteinaceous and the albumin:globulin ratio is >0.45	If present, fluid is proteinaceous and albumin: globulin ratio is <0.45
Imaging features	Marked hepatomegaly. Mesenteric lymphadenopathy. Pleural effusion absent	Marked hepatomegaly is rare. Mesenteric lymphadenopathy is common. Other organ abnormalities occur e.g. renal changes. Pleural fluid may occur

Ultrasound cannot differentiate between types of diffuse hepatic infiltrative disease. Liver histopathology is required for definitive diagnosis. LC is characterised by a lymphocytic infiltrate restricted to the portal areas and often associated with portal fibrosis and biliary duct proliferation. Epithelial degeneration and/or inflammation within the lumen of the bile ducts is usually absent. It can sometimes be difficult to differentiate between LC and lymphoma, however findings of bile duct targeting, ductopenia, peribiliary fibrosis, portal B cell aggregates and portal lipogranulomas are features of LC. Sometimes clonality PCR and immunophenotyping maybe helpful. Most infiltrates are T cell predominant.

Prednisolone is the mainstay of therapy for LC administered at immunosuppressive doses (1-2 mg/kg PO q12hr), tapering over a 6-12 week period if a good response is seen. If the patient does not respond, additional immunosuppressive medications include chlorambucil, methotrexate and cyclosporine however if there is an inadequate response it is important to be certain of the clinical diagnosis before pursuing other immunosuppressive

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therapies. If additional immunosuppressive medications are indicated, chlorambucil (0.25 mg/kg PO q 48 hr) is a good first choice.

Additional supportive treatments include:

- UDCA as above. In one retrospective study, prednisolone treatment resulted in longer survival times when compared to UDCA alone.
- SAMe as above
- Colchicine (0.03 mg/kg PO q24 hr) may be of benefit to reduce fibrosis where present but may cause gastrointestinal side effects.

Prognostic information for inflammatory liver diseases is limited. NC can be severe and the outcome depends on how early aggressive management is instigated. Concurrent pancreatitis and IBD ("triaditis") carries a more guarded prognosis. The response of LC to treatment can be difficult to monitor as clinical signs may wax and wane and cats may be bright and eating despite severe histopathology changes. Some cats require repeated courses of prednisolone or long-term therapy.

Hepatic Lipidosis

Hepatic lipidosis (HL) development is a risk for any anorexic or inappetent cat, but particularly obese cats. It occurs as a primary disease but is more common secondary to underlying diseases causing inappetence such as diabetes mellitus, pancreatitis, IBD, cholangitis and neoplasia.

Cats accumulate lipids in their hepatocytes, however why cats develop HL is not clear. Possible mechanisms include metabolic changes associated with anorexia and obesity, androgenic release during illness and stress, protein and nutrient (e.g. taurine) deficiency, relative carnitine deficiency and insulin deficiency. Cats with HL have higher serum concentrations of non-esterified fatty acids (NEFA) compared to normal cats. Increased release of NEFAs from large peripheral fat stores may overwhelm the capacity of the liver for lipid deposition in hepatocytes. Additionally, impaired metabolism of very low density lipoproteins (VLDL) necessary for triglyceride mobilisation and increased leptin (a pro-inflammatory adipokine) concentrations likely contribute.

HL is suspected based on a history of progressive inappetence, weight loss, depression and vomiting. Physical examination findings may include signs of hepatic encephalopathy (HE), weakness, jaundice, ptialism and hepatomegaly. Laboratory findings may include poikilocytosis due to altered RBC membrane lipids or oxidative stress. Serum biochemistry commonly reveals markedly elevated bilirubin (although a normal bilirubin doesn't exclude HL), ALT, ALKP, AST and GGT. The ALKP increase is often much higher than ALT or AST increases (often 5 times greater). GGT is often normal or only mildly increased, unless there is concurrent cholangitis or pancreatitis. Hyperglycaemia may occur due to concurrent DM or stress.

Hypokalaemia is common secondary to reduced intake and weakness occurs. Hypophosphatemia following feeding (refeeding syndrome) can be severe enough to result in haemolysis (<0.3 mmol/L). As with any hepatic disease, coagulation abnormalities can occur and must be tested prior to invasive procedures. Hepatomegaly is identified radiographically and on ultrasound and the liver may appear diffusely bright and enlarged. Liver FNA yields additional evidence of HL with documentation of hepatocellular vacuolation but cannot differentiate between primary or secondary HL. Definitive diagnosis requires histopathology, which may be contraindicated depending on patient stability.

The cornerstone of treatment for HL and an important consideration for all inappetent cats regardless of underlying disease is ensuring adequate nutrition. **It is vital to initiate enteral feeding immediately in cats with HL.** Malnutrition promotes lipolysis and glycogenolysis and contributes to imbalanced triglyceride mobilisation. Management of anorexia decreases hospitalization time and improves survival.



Providing enteral nutrition should be considered in any patient consuming less than their resting energy requirements (RER (Kcal/day = 70 x (body weight (kg)^{0.75}) for three days. Energy requirements are equivalent to the RER to limit weight loss and provide energy for metabolic processes. Illness energy factors are no longer used as this results in over-feeding. A balanced diet prescribed for hospitalized, recovering or critical care patients is recommended.

Forced feeding is avoided at all times. Food aversion is common in hospital, particularly in cats force-fed (e.g. syringe feeding) or offered food during periods of nausea or pain. It is imperative that nausea and pain are controlled prior to feeding. Cats may be tempted to eat by offering different food types, textures and temperatures. Favourite foods should be identified at hospital admission. Providing physical contact and attention (coaxing) may encourage eating. Removing the cat from the hospital cage and placing them in a quiet, safe environment (e.g. consultation room) may help. Food shouldn't be left for long periods within the cage as this contributes further to food aversion. Barriers to feeding (e.g. Elizabethan collars, litter tray close to food bowls) and stressors within the hospital (e.g. barking dogs) should be addressed prior to offering food.

If these efforts don't result in sufficient intake to maintain RER then assisted enteral nutrition is required and is generally necessary in every cat with HL. Common routes are NO or O tubes. NO tubes are often attempted earlier as anaesthesia is not required, however only liquid diets can be administered. Cats with HL often require enteral nutrition for weeks, thus O tube placement when the patient is stable is preferred and is recommended for all cats with HL.

To reduce re-feeding syndrome risk anorexic patients are weaned onto their full RER requirement, with 1/3 RER administered on Day 1, 2/3 RER on Day 2 and the entire RER requirement on Day 3 of feeding. Typically, four or more feeds are administered per day. For patients anorexic for over 3 days, feeding volume on Day 1 should not exceed 5 ml/kg bodyweight per feed as gastric distension may cause nausea. Feeds of 5-10 ml/kg bodyweight per feed are typically well tolerated thereafter. Diets are warmed to body temperature using a water bath. Microwave heating results in uneven temperatures and should be avoided. The patient should be monitored during feeding for nausea (gulping, ptialism, retching) and feeding temporarily discontinued if this occurs. Food is administered slowly over 20-25 minutes. Rapid administration causes vomiting. Maintenance water requirements (1 ml water/kcal or 4 ml/kg/24 hours) for patients not on intravenous fluids are administered in the same number of feeds, with care taken to avoid gastric distension. This volume maybe administered before and after food to flush the tube and decrease the risk of blockage.

Refeeding syndrome typically occurs within 24-48 hours of commencing enteral nutrition. Increased insulin levels in response to food result in movement of potassium, phosphate and magnesium intracellularly, resulting in marked hypophosphataemia and hypokalaemia. It has been reported with DM and HL. Monitoring phosphate and potassium concentrations (daily during the first three days of feeding) is ideal.

Additional complications following enteral nutrition may include aspiration pneumonia secondary to incorrect feeding-tube placement or aspiration of food secondary to vomiting or regurgitation or stoma site infections. If vomiting is controlled, there is rarely a contraindication to providing adequate nutrition.

Appetite stimulants are useful for short-term appetite increases or to overcome food aversion, however underlying causes of anorexia must still be addressed. Mirtazapine (1.88 – 3.75 mg per cat, PO, every 1-3 days), a serotonin re-uptake inhibitor with significant appetite stimulant, anti-emetic and anti-nausea effects is useful in inappetant but otherwise well cats. It is rarely effective in significantly unwell patients. Potential dose-dependent adverse effects include vocalisation and hyperactivity.



Renal and hepatic impairment decreases drug clearance and dosage reduction (e.g. 25%) maybe required. Cyproheptadine (0.2-0.5 mg/kg PO, every 12 hours) can be useful but excitability, aggression and vomiting may occur. Oral diazepam is avoided due to the possibility of acute hepatic necrosis. Intravenous diazepam (0.2 mg/kg) results in sedation and effects are unpredictable.

Some drugs should be used with caution in patients HL, particularly, those that may promote hepatic fat mobilization including stanozolol, glucocorticoids and any hepatotoxic drugs.

Additional supportive management for HL includes:

- Intravenous fluid therapy with potassium chloride added to fluids depending on serum potassium concentration. Half the serum potassium deficit can be replaced as potassium phosphate to help prevent hypophosphataemia.
- Antiemetics e.g. maropitant, metoclopramide as above
- Vitamin K supplementation (0.5-1 mg/kg q 12 hr for 3 doses) for prevention/treatment of coagulopathy
- Vitamin B12 supplementation (250 ug SQ weekly or twice weekly until levels are normal)
- Thiamine deficiency can result in neurological signs (e.g. vestibular signs, seizures) and thiamine supplementation is useful (Vitamin B1 100 mg/cat SQ q24hr)
- L-carnitine deficiency can occur causing decreased mitochondrial function. Supplementation (250-500 mg/cat/day PO) may improve mitochondrial fatty acid oxidation and glucose utilization.
- Taurine supplementation (250 mg/day) can be useful as low plasma taurine levels are often documented and substantial quantities of taurine conjugated bile acids are lost in the urine.
- SAME (20 mg/kg PO q 24hr)
- Hepatic encephalopathy if present is treated using lactulose and amoxicillin to lower ammonia concentrations. HE if present may suggest other primary hepatic pathology in addition to HL.

HL is a severe, often rapidly fatal disorder. Immediate aggressive treatment utilising the provision of enteral nutrition is required, however despite this, not all cats will survive the episode. The prognosis is dependant on the metabolic status of the cat and the presence of absence of concurrent disease. Prognosis is fair with early aggressive management, but nutritional management is frequently required for at least 3-6 weeks. Survival rates of 50-80% are reported, but only 20% if there is concurrent pancreatitis.

