The Feline Liver

KEY POINTS

- **The cat has a number of anatomic and metabolic peculiarities predisposing this species to some specific liver diseases and posing particular challenges to their dietary management.**
- **Liver disease in cats is quite common, but may be difficult to recognize due to nonspecific signs.**
- **The main hepatic diseases include:**
  —Feline hepatic lipidosis
  —Feline cholangitis/cholangiohepatitis syndrome
- **The nutritional management forms the cornerstone in the management of some feline hepatic diseases.**
  — Dietary treatment is crucial in the management of hepatic lipidosis
  — Dietary management is also essential to ameliorate the signs of hepatic encephalopathy seen with severe liver disease and portosystemic shunts
  — Dietary management can help to support the treatment of cats with cholangitis/cholangiohepatitis

There are a number of specific hepatic disorders seen in the cat, which are based on the unique anatomic and metabolic features of the cat's liver. Hepatic disease is quite common, but may be difficult to recognize initially due to nonspecific clinical signs such as lethargy, inappetence, anorexia, weight loss, and/or gastrointestinal upsets. It is therefore important to include liver disease in the list of differential diagnoses for cats presenting with vague signs. The nutritional management of cats with liver disease may vary depending on the kind of hepatic disorder.

ANATOMY

The liver lies almost entirely within the rib cage, caudal to the diaphragm and consists of different lobes. The gallbladder is attached to the liver via the hepatic, cystic, and common bile ducts. The hepatic ducts convey bile from the liver lobes and may join the cystic duct by one or more stems. The major pancreatic duct joins the common bile duct before its entry into the duodenum. This may explain the frequent coexistence of pancreatic and hepatobiliary disease in the cat.

The liver receives blood from the intestinal tract via the portal vein, which is then delivered to the vena cava through the hepatic vein. The liver therefore receives all materials absorbed from the gastrointestinal tract except for some lipids that passes through the mesenteric lymphatics as chyle. The histologic unit of the liver is the lobule. In cross section, the lobule appears as a hexagon with the central vein (a branch of the hepatic vein) at the center and the portal triad at the corners. The portal triad consists of branches of the portal vein, the hepatic artery, and the bile duct. This lobular pattern is a result of the hydrodynamics of the blood flow through the liver.

FUNCTION

The liver performs many vital functions with respect to nutrient digestion and metabolism, detoxification and excretion, hematology and coagulation, and hormonal balance. Cats have, however, some very specific metabolic features, which are important for the understanding of feline liver disease:

- Cats show a relative deficiency of glucuronyl transferase that affects the liver's ability to metabolize drugs and chemicals.
- The feline species is unable to synthesize arginine (an important part of the hepatic urea cycle), which predisposes cats to the development of hyperammonemia during inadequate food intake or anorexia.

Hormone Metabolism

The liver also plays a crucial role in the metabolism of many hormones and is responsible for the degradation of peptide and steroid hormones.

Vitamin Metabolism

The liver is key in the vitamin metabolism, responsible for the synthesis, storage, and activation of the vitamins A, B, D, E and K.

Carbohydrate Metabolism

Carbohydrates are not essential in the cat's diet, however they are a useful source of energy and certain fibers may also have a beneficial impact on gastrointestinal health. The liver plays a key role in the carbohydrate metabolism including:

- Gluconeogenesis
- Control of glucose levels and glycogen metabolism and storage

Glycogen depletion and inadequate gluconeogenesis may lead to fasting hypoglycemia; this is, however, uncommon due to the large hepatic reserve for maintaining euglycemia. It may be seen with severe acute liver failure, large neoplasms (especially hepatoma), glycogen storage diseases, or congenital portosystemic shunts.

Lipid Metabolism

The liver performs a key role in the fat metabolism of the cat including synthesis of fatty acids, cholesterol and triglycerides, and the excretion of cholesterol and bile acids. The implications of an abnormal lipid metabolism are still largely unknown. However, it is known that the feline liver is unable to handle the rapid mobilization of fat stores during states of caloric restriction or prolonged periods of starvation, and may result in the pathologic deposition of excess lipids within hepatocytes (hepatic lipidosis). Total serum cholesterol may be increased by extrahepatic bile duct obstruction, while it may be decreased in severe hepatocellular failure or portosystemic shunts.

Protein Metabolism

Being an obligate carnivore, protein is one of the key nutrients in the cat's diet. The cat requires a minimum overall protein intake, as well as the supply of certain essential amino acids.

The cat’s hepatic protein metabolism shows some peculiarities when compared with other species, such as the dog:

- The cat's **inability to synthesize arginine** predisposes the cat to hyperammonemia, as arginine plays an important part in the urea cycle.

- The cat's **inability to down-regulate hepatic enzyme activity** means that the cat will break down its own body protein tissue when not supplied with adequate levels of exogenous protein.

Further key aspects of the hepatic protein metabolism are:

- **Protein Synthesis**, (e.g., albumin)
  - The reduced synthesis of albumin in chronic liver disease may result in hypoalbuminemia. Other mechanisms of decreased albumin production include anorexia and malnutrition, since protein synthesis strongly relies upon the availability of amino acids, particularly tryptophan. Intestinal or renal protein loss may further lower the serum albumin levels, or levels may appear reduced if the serum volume is increased (e.g., in portal hypertension with ascites). Serum albumin levels are therefore an insensitive index of hepatic function.

  - Monitoring serum albumin levels is, however, important for the dietary management, since it also gives an indication of the patient's overall nutritional status, particularly in states of chronic malnutrition.

- **Regulation of Amino Acid Metabolism**

- **Urea Synthesis**

- **Detoxification of Ammonia**
  - Hyperammonemia is one of the characteristics of hepatic encephalopathy (HE).Ammonia is generated from the catabolism of proteins, nucleic acids, and urea. Most exogenous ammonia is produced in the colon through the degradation of dietary amines and the action of bacterial ureases on urea, after which it is absorbed into the portal blood and converted into urea in the liver by the Krebs-Henseleit urea cycle. In patients with extra- or intrahepatic shunts and thus abnormal blood flow to the liver or, less commonly, with severe parenchymal damage, ammonia is not detoxified and enters the systemic circulation. Ammonia is neurotoxic, but its exact role in the pathogenesis of HE is controversial.

Storage Function

The liver plays a key role in the storage of many nutrients and metabolites including:

- **Vitamins**
- **Lipids**
- **Glycogen**
- **Copper**
- **Iron**
- **Zinc**
- **Blood**

Digestive Function

The liver plays a key role in the synthesis of bile acids and controlling enterohepatic circulation and has therefore important digestive functions.

Detoxification and Excretion

The liver is also crucial for the detoxification and excretion of a number of substances including:

- **Bilirubin**
- **Ammonia**
- **Copper**
- **Cholesterol**
- **Steroid hormones**

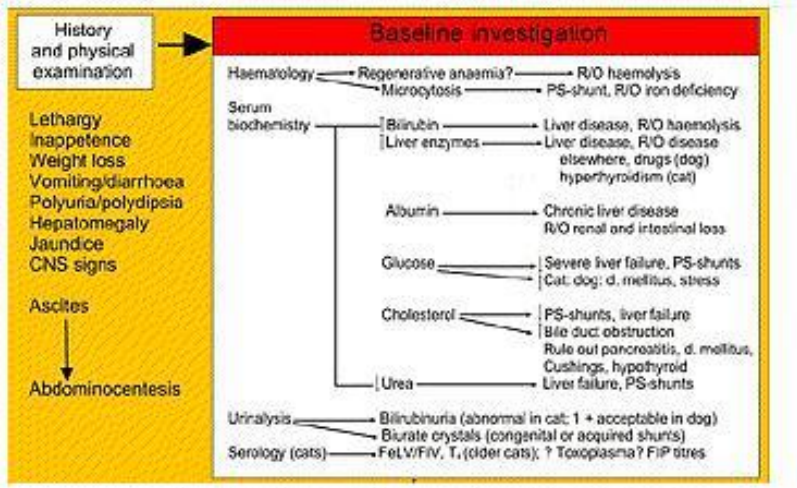
CLINICAL DISORDERS

Chronic hepatitis and hepatotoxicity are seen less commonly in cats than in dogs. More commonly seen primary problems leading to hepatic necrosis include hypoxia, neoplastic disease, and infections. A variety of systemic infectious and metabolic diseases, such as FIP, diabetes mellitus, hyperthyroidism, and septicemia may lead to hepatic changes and result in abnormal liver test

results. The two main disease complexes are feline hepatic lipidosis and the feline cholangitis/cholangiohepatitis complex.

Laboratory Tests

Perform baseline evaluation for diagnostic evaluation and to rule out other metabolic diseases.



Approach to the Diagnostics of Liver Disease in the Dog and Cat.

- **Hematology**
  - Often normal
  - Occasionally mild to moderate anemia (consistent with anemia of chronic disease)
  - Marked anemia with hemolysis or blood loss
  - Microcytosis (not as common in cats as in dogs)

- **Serum Enzymes Used as Biochemical "Markers"**

  Alanine Aminotransferase (ALT)
  - In the soluble component of the hepatocellular cytoplasm
  - Associated with any type of hepatocellular membrane damage, degeneration, or necrosis
  - Has a much shorter half-life in cats than in dogs and any elevation is indicative of current liver activity
  - Degree of elevation generally reflects the number of hepatocytes damaged in active or acute liver disease

  Aspartate Aminotransferase (AST)
  - Located in both the cytoplasm and mitochondria
  - Increase implies greater hepatic damage than increase in ALT
  - Differentiate from muscular damage with creatine kinase assay

Alkaline Phosphatase (ALP)

- Increased synthesis by epithelial cells lining the bile canaliculi
- Generally following on from reduced bile flow and cholestasis
- Shorter half-life in cats than in dogs (6 to 8 hours versus 48 to 72 hours)

Gamma-Glutamyl Transferase (GGT)

- Increased synthesis by epithelial cells lining the bile canaliculi
- Generally as a result of reduced bile flow and cholestasis
- Not as specific an indicator as ALP in hepatic lipidosis, but may be more sensitive and specific in other hepatic disorders

- **Total Bilirubin**
  - Relatively insensitive test of hepatic function, (i.e., severe hepatic disease may exist with normal serum bilirubin concentrations)
  - Bilirubin may also be increased due to pre-hepatic and post-hepatic causes (hemolysis and biliary obstructions, respectively)

- **Urine**
  - Hyperbilirubinuria is always abnormal in the cat and precedes hyperbilirubinemia

Liver Function Tests

These are used to assess the functional integrity of the liver if serum bilirubin is normal. Liver function tests of value in the assessment of non-hyperbilirubinemic liver disease include:

- **Serum Bile Acid Analysis**
  - Easy to perform, reliable, test of choice
  - Pre- and post-prandial assays required
  - Evaluates enterohepatic circulation and hepatic uptake of bile salts
  - Hyperchylomicronemia may interfere with assay

- **Coagulation Tests**
  - The liver produces the majority of coagulation factors; hence tests may be prolonged when a reduction of factors of over 30% occurs due to insufficient hepatic production. Tests include prothrombin time (PT) and activated partial prothrombin time (APPT)

- Must be differentiated from disseminated intravascular coagulation (DIC) which may also include disturbances in platelet numbers, fibrinogen concentrations, and fibrin degradation products (FDPs)

- **Ammonia Tolerance Test**
  - Not appropriate for encephalopathic patients

- **Sulfobromophthalein Retention Test (BSP)**
  - Influenced by hypoalbuminemia
  - Not widely available; licensed universities only

- **Indocyanine Green (ICG) Clearance**
  - Experimental use only

Liver Imaging

Abdominal radiographs allow an assessment of liver size (hepatomegaly, microhepatia) and liver shape (presence of liver mass). A small liver is often seen in cats with chronic disease and congenital portosystemic shunts. An ultrasonographic assessment of the liver allows visualization of the hepatobiliary system, (e.g., a dilated bile duct due to an extrahepatic obstruction). Ultrasonography is usually far more sensitive than radiography in visualizing choleliths or intrahepatic masses.

Liver Biopsy and Cytology

A liver biopsy with a histologic examination of the tissue is often necessary to diagnose and specify hepatic disease. Liver aspirates for cytology can be obtained relatively easily by needle aspiration, particularly in the presence of hepatomegaly. It is, however, important to assure that the animal has a normal coagulation status prior to biopsy, otherwise factors may be increased or replenished with administration of vitamin K or plasma transfusions.

Feline Hepatic Lipidosis

Hepatic Lipidosis is a common problem in North America, but more rarely diagnosed in other parts of the world. Feline hepatic lipidosis is a life-threatening disease characterized by a complete disruption of the normal hepatic lipid metabolism with an accumulation of triglycerides within the

liver. This can be triggered by hypoxia, the intake of toxins, underlying endocrine disorders, such as diabetes mellitus, or simply acute starvation and weight loss. The etiology is unknown, but obese animals are predisposed.

Common clinical signs include anorexia, progressive weight loss, vomiting, jaundice, hepatomegaly, and more rarely, hepatic encephalopathy. The history often indicates a sudden stop of food intake, either due to an inability to eat (e.g., due to tooth root abscess) or loss of appetite (e.g., due to an unrelated systemic illness or stress) or a very rapid weight loss program. Because of the increased risk in overweight cats, it is crucial that cats are never allowed to fast and that all weight reduction diets are balanced and highly palatable. Nutritional management is the cornerstone in the treatment of hepatic lipidosis.

Feline Cholangitis/Cholangiohepatitis Syndrome

The Cholangitis/Cholangiohepatitis Syndrome (CCHS) is probably the most common liver disease complex in cats, including cholangitis, cholangiohepatitis, and biliary cirrhosis. It is best considered a syndrome, as there are several histologic subcategories including a suppurative and a nonsuppurative form that require biopsy for differentiation. The syndrome can be acute or, more commonly, chronic with usually only very subtle clinical signs. Often there are other concurrent organ disorders, an illness of the pancreas or the large intestine, for example.

Suppurative Cholangitis/Cholangiohepatitis (CCHS)

Suppurative CCHS is usually seen in conjunction with an underlying disorder of the biliary system, promoting the development of hepatic bacterial infection. The most common associated problems are inflammatory bowel disease (IBD), duodenitis, pancreatitis, or acute extrahepatic bile duct obstruction. Some patients may develop hepatic lipidosis secondary to anorexia seen with CCHS and require aggressive nutritional management for this complication. Further nutritional considerations may depend on the presence of other concurrent disorders.

Nonsuppurative Cholangitis/Cholangiohepatitis (CCHS)

Patients with nonsuppurative cholangitis/cholangiohepatitis may initially display nonspecific clinical symptoms, such as vomiting, diarrhea, and lethargy, and then progress to jaundice and severe malaise. Possible concurrent disorders include pancreatitis, extrahepatic bile duct

obstruction, and most frequently, inflammatory bowel disease (IBD). Nutritional management may depend on the presence of other concurrent disorders.

Congenital Portosystemic Shunts

Congenital portosystemic shunts are becoming more frequently diagnosed in cats. Most patients show abnormal neurobehavioral signs associated with hepatic encephalopathy from the early age of two months. A very prominent sign in cats is hypersalivation. Further common findings include small body size, prominent kidneys, and copper-colored irises. Surgical correction may be curative. Dietary management is a crucial aspect of conservative treatment postoperatively or in those cats in which surgery is not an option due to financial or other considerations.

Hepatic Encephalopathy

Hepatic encephalopathy (HE) comprises a series of neurologic signs, which develop as a result of portosystemic shunting or a significant loss of liver function (60% to 70%) in acute or chronic liver disease. The clinical signs vary and can be clinical or subclinical. The exact pathogenesis remains controversial, and it is believed that a number of factors are involved.

There are a number of nitrogenous waste products including ammonia, possibly aromatic amino acids (leucine, isoleucine, valine), and methionine, as well as gamma-aminobutyric acid (GABA) and fatty acids, which can act as toxins. These substances are derived from the gastrointestinal tract, either consumed in the diet or synthesized by the gastrointestinal flora, and are normally detoxified in the liver. In animals with portosystemic shunts and/or a significant loss of liver function, these toxins can enter the peripheral circulation and subsequently pass the blood-brain barrier. Once past the blood-brain barrier, they may then alter the central nervous function through a range of different mechanisms including the modulation of neurotransmitters or receptors.

Dietary management is the cornerstone in treating patients with HE and a particularly difficult task in the growing cat due to their high protein requirements.

Clinical Signs of Hepatic Encephalopathy

Subclinical	Clinical
Anorexia	**Personality change (irritable, aggressive, dull)**
Drowsiness	**Ataxia**
Lethargy	**Weakness**
Ptyalism	**Disorientation**
Vomiting	**Coma**
	Seizures

MANAGEMENT

The objectives of therapy are the elimination of causative agents (if known), the reduction of inflammation and minimization of fibrosis, the provision of optimum conditions for hepatic regeneration, and the control of complications such as secondary bacterial infection, hepatic lipidosis, or hepatic encephalopathy. Dietary management varies depending on the type of liver disease, as well as the presence of other concurrent disorders.

Dietary Management

The dietary approach in cats with liver disease varies according to the type of liver disorder present, as well as to the presence of any other concurrent illnesses. Cats are obligate carnivores, which means that feline diets must provide adequate levels of highly digestible good quality protein to meet the cat's unique requirements for protein and essential amino acids.

Diets should be highly palatable containing adequate levels of arginine and taurine and be supplemented with B vitamins, since these become rapidly depleted in feline liver disease. Hepatic lipidosis may develop as a complication of all liver insults, (e.g., as a complication of severe cholangitis/cholangiohepatitis). Furthermore, hepatic encephalopathy is commonly seen in cats with congenital portosystemic shunts, but may equally develop when a significant part (60% to 70%) of liver function is lost.

Nutritional Management of Hepatic Lipidosis

Feline hepatic lipidosis is a life-threatening disease, in which the restoration of nutrient intake is essential for the patient's survival. Aggressive nutritional management is the cornerstone in the

treatment of cats with hepatic lipidosis. Nutritional therapy should aim to provide a readily digestible source of energy, which is adequate in protein content, yet does not accentuate hepatic encephalopathy. Nutrient intake needs to be ensured by tube feeding the patient in order to stop the break-down of body fat resources and the accumulation of triglycerides in the liver.

Further considerations are:

- Overall food intake should be at 1.5 to 2 times maintenance energy requirement levels.
- Chosen diet should be highly energy dense in order to feed small volumes and avoid stress through frequent feeding of large amounts.
- Chosen diet should be highly digestible to reduce “digestive stress.”
- Chosen diet must have increased levels of protein and the essential amino acids arginine, glutamine, and taurine. The best nutritional profile is given with diets specifically designed for cats. If human products are used, supplementation with these amino acids is essential and it is important to remember that arginine must be supplied on a daily basis, as the cat cannot synthesize arginine and a deficiency can lead to hyperammonemia.
- Carnitine is an important intermediary in the hepatic fatty acid metabolism and carnitine supplementation may be beneficial in the management of hepatic lipidosis.
- Highly digestible carbohydrates, such as simple sugars, may worsen the effects of glucose intolerance which may be seen with hepatic lipidosis.

Nutritional Management of Cholangitis/Cholangiohepatitis

The dietary management in cats with CCHS is based on providing a highly digestible, well-balanced diet to support liver function, as well as to take into account any nutritional demands for other concurrent disorders that may affect the patient.

Nutritional Demands for Concurrent Disorders

Concurrent Disorders	Dietary Requirements
History of diarrhea & vomiting	**Highly palatable, highly digestible diet**
Underlying pancreatitis	**Restricted fat intake**
IBD - immune mediated mechanisms	**"Hypoallergenic" diet containing single novel protein source**
Chronic liver damage	**Adequate intake of B complex vitamins, fat soluble vitamins K and E, and good quality protein for hepatocyte repair**

Hepatic Encephalopathy

The nutritional management of hepatic encephalopathy is based on restricting protein intake and supplying good quality protein of high biologic value. However, care must be taken to ensure adequate exogenous protein intake to avoid protein malnutrition. Cats are unable to down-regulate their hepatic enzyme activity, and thus are particularly at risk of mobilizing protein with the breakdown of body tissues. A minimum of 3.3 to 3.8 g protein/kg/day should be fed to adult cats.

The difficulty is to find the right balance of protein restriction and protein supply in young, growing kittens with congenital portosystemic shunts and each case needs to be treated with great care in order to find the maximum tolerated level of protein for each individual patient.

SUMMARY

The cat shows a number of specific hepatic disorders based on some anatomic and metabolic peculiarities seen in this species. Hepatic disease in cats is quite common, but may be difficult to recognize due to nonspecific clinical signs. The two main disease complexes are feline hepatic lipidosis and the feline cholangitis/cholangiohepatitis syndrome. Severe forms of these diseases can further lead to hepatic encephalopathy, which is also seen in conjunction with portosystemic shunts. Dietary management forms a cornerstone in the management of many feline liver diseases. It may, however, vary significantly according to the type of liver disorder present. Protein restriction, (e.g., to ameliorate the signs of hepatic encephalopathy), is a considerable challenge in the cat, as it is crucial to find the right balance between restricted intake and meeting the individual's requirements. There is a wide choice of commercially available diets for cats with liver disease, ranging from protein restricted diets for the management of hepatic encephalopathy, to diets with selected protein

sources in support of the management of cholangitis/cholangiohepatitis, to highly digestible, energy dense diets for the nutritional support of patients with hepatic lipidosis.