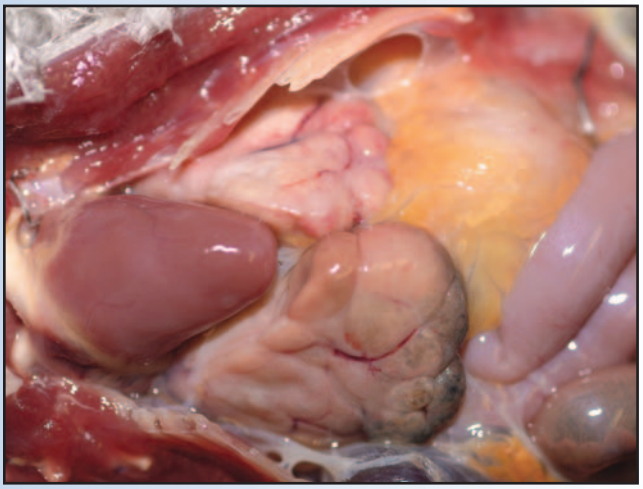
CHAPTER
15

# Evaluating and Treating the Liver

MANFRED HOCHLEITHNER, Dr med vet, Dipl ECAMS;
CLAUDIA HOCHLEITHNER, Dr med vet; LORI DANIELLE HARRISON, DVM



Hepatic dysfunction is among the most common medical problems seen in companion birds.[7,16] In many cases, the involvement of the liver in the overall disease process is not obvious. This chapter reviews the basic pathophysiology, diagnosis, clinical signs and the current therapies for liver disease.

## The Role and Function of the Liver

The liver is the largest organ in the body, but its relative size varies among species. The liver performs many critical functions that maintain homeostasis. Liver functions include synthesis of cholesterol and bile acids and the generation and utilization of glycogen. It also is the site for metabolism of various substances in preparation for their excretion from the body via the bile or urine. It is the site of production of plasma proteins, albumin, fibrinogen, lipoproteins and a variety of alpha and beta globulins. The liver produces all clotting factors. The liver filters from the blood infectious agents and foreign materials that have been absorbed by the intestines. This helps prevent these materials from gaining access to the systemic circulation. Energy is produced by oxidative phosphorylation and beta-oxidation of fatty acids in hepatic mitochondria. This energy is used to sustain the activity of the liver and to provide a reservoir of glycogen for the body.

### HEPATIC DYSFUNCTION

Hepatic dysfunction occurs after severe injury or repeated significant insults. The liver has considerable functional reserve and regenerative capacity. Only lesions that affect the majority of hepatic parenchyma are likely to produce the signs of hepatic failure. Focal lesions rarely destroy sufficient parenchyma to deplete the liver's

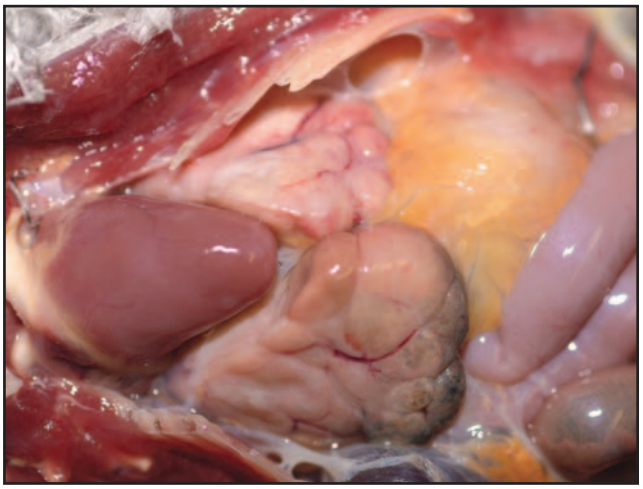


**Fig 15.1** | The marked change in color and liver texture are characteristic of cirrhosis.

reserve. The term hepatic failure implies loss of adequate function from either acute or chronic damage, however, usually not all functions are lost at the same time.

### METABOLIC DISTURBANCES AS A RESULT OF HEPATOPATHY

Decreased hepatic function can be manifested by a variety of metabolic disturbances. The type and duration of the disorder may influence the nature of the metabolic perturbation. Coagulopathies, hypoalbuminemia, cutaneous manifestations and increased resistance in the blood flow through the liver due to fibrosis are common.

### RESPONSE OF THE LIVER

The destruction of hepatic parenchyma results in regeneration, fibrosis and/or biliary hyperplasia. The liver can rapidly and efficiently regenerate lost hepatic mass. Extensive hepatic necrosis is usually followed by parenchymal regeneration without scarring, as long as the normal extra-cellular matrix remains intact. Chronic hepatic injury most commonly manifests as fibrosis. Early fibrosis may respond to treatment or removal of the source of injury, but more advanced fibrosis is generally irreversible with the therapies currently available. Hepatic fibrosis can be produced by a variety of hepatic injuries. The hepatic stellate cells change from the typical lipid-storing cells to cells with a myofibroblastic appearance that subsequently develop the ability to synthesize collagen, leading to hepatic fibrosis. Stellate cells can be activated by various cytokines produced either by inflammatory cells that infiltrate damaged hepatic parenchyma or by constituent cells of the liver (Kupffer cells, endothelial cells, hepatocytes). Damage to the extracellular matrix also stimulates activation of hepatic stellate cells, as do various toxins. End-stage liver disease or cirrhosis as a result of chronic fibrosis is characterized by loss of normal hepatic architecture due to nodular regeneration of parenchyma, fibrosis and, often, biliary duct hyperplasia (Fig 15.1). Often, clinical manifestations of hepatic failure do not occur until the end stage. The cause of the hepatic damage that leads to end stage liver failure frequently cannot be determined by the time signs of hepatic failure are observed.

## Diagnosis and Clinical Signs of Liver Disease

Clinical signs of hepatic failure in birds are variable and can range from mild inappetence and inactivity to acute hemorrhage and death. A large percent of liver tissue must be affected before any obvious clinical signs are observed because of the liver's large functional reserve (Table 15.1).

All birds on a poor diet (seeds, poor-quality formulated diets) should be presumed to have decreased functional hepatic mass (see The Improper Diet Cascade in Chapter 4, Nutritional Considerations: Section II, Nutritional Disorders). The liver's ability to regenerate may mask underlying liver disease in its early stages.

There are some clinical signs that are highly suggestive of hepatic failure, however, none are pathognomonic. Hepatic failure is associated with yellow or green discolorations of the urates and/or the feces, which may result from biliverdinuria or bilirubinuria (Fig 15.2). Feathers develop a glossy black color due to the exposure of melanin from total loss of normal green or blue pigment. Hepatomegaly and/or ascites may cause dyspnea. Weight loss, poor feathering, diarrhea, overgrowth and bruising of the beak and nails, bruising or bleeding of the skin

**Table 15.1** | **Clinical Signs of Liver Disease**

| Clinical Sign | Non-specific | More Specific |
|---|---|---|
| Anorexia | ✓ | |
| Lethargy | ✓ | |
| Weight loss | ✓ | |
| Weakness | ✓ | |
| Diarrhea | ✓ | |
| Polyuria | ✓ | |
| Polydipsia | ✓ | |
| Poor feathers | ✓ | |
| Dyspnea | ✓ | |
| Green or yellow urates | | ✓ |
| Abdominal swelling | | ✓ |
| Ascites | | ✓ |
| Coagulopathies | | ✓ |
| Melena | | ✓ |
| Abnormal beak/nails | | ✓ |
| Malcolored feathers | | ✓ |

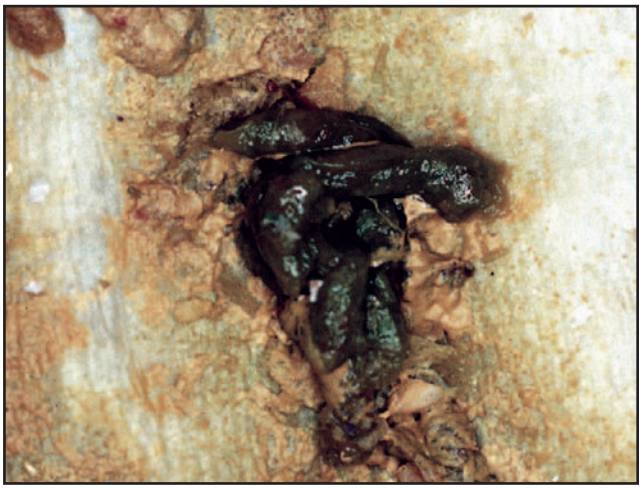


**Fig 15.2** | Yellow urates. See Chapter 23, Diagnostic Value of Biochemistry, for a discussion of biliverdin (green) versus bilirubin (yellow).

and prolonged clotting time may be associated with hepatic failure. Clinical disorders of any type that frequently recur or are resistant to diagnosis and therapy often involve liver malfunction. Diagnostic testing is used to support the diagnosis of liver disease (Table 15.2).

## CLINICAL PATHOLOGY

Analytes such as alanine aminotransferase (ALT), lactate dehydrogenase (LDH) and serum alkaline phosphatase (SAP) are not sensitive or specific for liver disorders in birds[7,11] (see Chapter 23, Diagnostic Value of Biochemistry). Aspartate amino transaminase (AST) is sensitive but not specific for hepatocyte necrosis in birds because AST also is released from damaged muscle tissue. AST levels should be examined in conjunction with creatine phosphokinase (CPK). If only AST is elevated, liver damage is more likely.

Elevations of bile acids are often consistent with hepatic insufficiency and decreased liver function.[16] Therefore, bile acid assays are useful in determining chronic, long-standing and non-inflammatory states of decreased hepatic function that may not be reflected in hepatic enzyme elevation. Since food (protein) does not affect bile acids in psittacines, pre- and postprandial sampling is unnecessary. Species differences may exist. See Chapter 23, Diagnostic Value of Biochemistry.

An elevated white blood cell count (WBC) is common in bacterial and fungal infections, while a depressed WBC is more common in toxic and viral disorders. Lowered serum total solids, hypoalbuminemia, hyperglobulinemia, and hypokalemia also are indicative of hepatic compromise.

Biliverdin is the most important bile pigment in birds; therefore, icterus is not a typical clinical sign of hepatic failure. Carotene pigments from the diet may be responsible for yellow skin and plasma color.[14] A study in broilers with gross hepatic bile duct lesions traced the yellow color of the pericardium and carcass to bilirubin.[19] In some cases, bacterial reduction may be responsible for the degradation of avian biliverdin to bilirubin. One practitioner has found elevated bilirubin levels in cockatiels with yellow urine, urates and feathers that were normally white, but turning yellow to gold (G. Harrison, personal communication). Other liver function tests are available, but currently their use in the practical setting is limited. These tests include clearance of indocyanine green and bromsulphalein.

**Table 15.2 | Diagnostic Approach to Assess Liver Disease in Birds**

| History | |
|---|---|
| Baseline testing | Complete blood count/chemistries/urinalysis |
| Non-invasive imaging | Radiology and ultrasound |
| Screening for infectious diseases | See Chapter 21, Preventive Medicine and Screening |
| Liver function testing | Bile acids |
| Abdominocentesis | Culture, cytology, chemistries |
| Coagulation testing | See Chapter 23, Diagnostic Value of Biochemistry |
| Liver biopsy | Culture, cytology, histopathology |

**Table 15.3 | Radiographic Findings**

| Common Radiographic Findings | Interpretation | Comments |
|---|---|---|
| Hepatomegaly | Hepatic lipidosis, cardiac-portal hypertension, infection (viral, bacterial, fungal) | The liver shadow of neonates can appear bigger because the proventriculus in neonates is relatively larger. |
| Normal hepatic size | Early stage of hepatopathies | Normal size may indicate normal liver. |
| Microhepatia | End stage cirrhosis, congenital small liver, emaciation, chronic malnutrition | Species predilection exists: umbrella, Moluccan and palm cockatoos, macaws. |

**Table 15.4 | Hepatomegaly**

| Common Causes in Neonates | Common Causes in Adults |
|---|---|
| Normal neonate | Obesity |
| Hepatic lipidosis | Hepatic lipidosis |
| Hepatic hematoma | Bacterial hepatitis: *Chlamydophila* spp., *Mycobacterium* spp. |
| Viral hepatitis | Lymphoma |
| Lymphoma | Hepatic adenocarcinoma |
| | Fungal hepatitis |
| | Viral hepatitis: herpes |
| | Iron storage disease |
| | Ovarian disorders |

## RADIOLOGY

Hepatomegaly and microhepatia are common findings in birds. Great variations appear among psittacine species but also between individuals. Baseline radiographs of each individual bird should be taken as a part of the routine examination and may be used for comparison in subsequent years (Tables 15.3, 15.4).

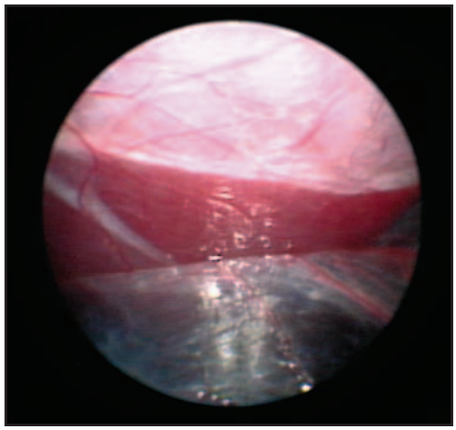


**Fig 15.3** | The normal liver with a sharp border and dark brown mahogany color as seen through the membranes of the air sacs.

### ULTRASOUND

This test provides information concerning the size and structure of the liver. In most cases, it is not stressful. To prevent hypothermia and ensure good contact of the probe with the bird, warmed lubricating jelly should be used.

### ENDOSCOPIC EXAMINATION AND BIOPSY

Liver biopsies are frequently utilized to establish a definitive diagnosis of the pathophysiology of liver disease (Fig 15.3). The risk to the patient in order to gain this information must be considered. Coagulopathies associated with hepatopathies increase the risk of severe bleeding. These authors find very few situations in which liver biopsies are advantageous to the individual avian patient. Many infectious agents responsible for hepatopathy can be diagnosed via serology. Viral infections that are not readily diagnosed via serology are often of short duration. When a diagnosis has been made, treatment for many pathological conditions is purely supportive. Liver biopsy will not change the prognosis in most cases of hepatic dysfunction in parrots. Exceptions would include infection with *Mycobacterium* spp., various neoplasias and conditions unresponsive to therapy. In an aviary situation, hepatic biopsy or submission of necropsy specimens can be a significant means of identifying and eliminating disease. The risk of loss of an individual may benefit the entire flock and to justify the procedure.

A retrospective study of liver biopsies of 71 birds was performed in a zoological collection. Important diagnostic findings included the identification of iron storage disease in mynahs and toucans; presumptive *Atoxoplasma* hepatitis in mynahs; chronic active hepatitis associated with intestinal coccidial infections; and acid-fast organisms or severe amyloidosis in ducks and geese suspected of harboring mycobacteria.[17] The information was useful, but the 4.2% death rate would not be acceptable in pet bird practice (see Chapter 24, Diagnostic Value of Endoscopy and Biopsy).

## Non-infectious Diseases of the Liver

The liver's function as a primary organ of filtration makes it susceptible to a myriad of environmental toxins and irritants (Table 15.5).

### HEMATOMA

Hepatic hematoma may present similarly to or in conjunction with pediatric hepatic lipidosis. Hepatic hematoma often occurs in young birds because they have a prominent abdomen, which provides very little keel protection for the underlying organs. In obese birds, the liver is more friable and extends farther into the unprotected region of the caudal abdomen. The hematoma may be visible through the abdominal skin. The extent of anemia and the bird's physical condition will dictate treatment decisions. Parenteral fluids must be given with care. Homologous blood or plasma transfusions can be beneficial using guidelines as in mammals. The ultimate treatment is husbandry and the appropriate amounts of a proper diet.

### HEPATIC LIPIDOSIS

Lipids are normally transported to the liver from the gastrointestinal tract and adipose tissue in the form of chylomicrons and free fatty acids, respectively. Within hepatocytes, free fatty acids are esterified to triglycerides that are complexed with apoproteins to form low-density lipoproteins, which are released into plasma as a readily available energy source. Hepatic lipidosis, or fatty liver, occurs when the rate of triglyceride accumulation within hepatocytes exceeds either their rate of metabolic degradation or their release as lipoproteins. Hepatic lipidosis is not a specific disease entity but can occur as a sequel to a variety of perturbations of normal lipid metabolism. Excessive dietary intake of fat or increased mobilization of triglycerides from adipose tissue subsequent to increased demand, such as in starvation or endocrine abnormalities, may be responsible (see Chapter 4, Nutritional Considerations: Section II, Nutritional Disorders). Abnormal hepatocyte function can lead to an accumulation of triglycerides due to decreased energy for oxidation of fatty acids. Excessive dietary intake of carbohydrates can result in the increased synthesis of fatty acids and excessive triglyceride formation. Hepatotoxins or drugs can impair secretion of lipoprotein from the liver.

**Table 15.5 | Causes of Non-infectious Liver Disease**

- Congenital
- Traumatic: hematoma
- Hepatic lipidosis: pediatric versus adult
- Amyloidosis
- Iron storage disease
- Toxins
- Malnutrition

Decreased apoprotein synthesis can occur subsequent to decreased production and export of lipoprotein from hepatocytes. Deficiencies of the amino acids biotin, choline and methionine have been shown to cause hepatic lipidosis in mammals and some species of birds. More than one defect can occur in any given hepatic disorder. Hepatic lipidosis is most commonly seen in the neonate and the obese, malnourished adult bird. See Chapter 19, Endocrine Considerations.

*Hepatic Lipidosis* (*Pediatric*): The liver in neonates is typically larger relative to the total body weight than in adult birds. Baby birds affected with hepatic lipidosis present with a common history of being handfed with a commercial formula to which the owners have added a high-fat supplement. The higher fat content of macaw hand-feeding formulas is also implicated in this syndrome when these formulas are inappropriately used on other species (especially cockatoos). Affected babies are often grossly overweight for their age and exhibit severe respiratory distress. These birds must be handled gently and minimally to avoid exacerbation of the condition. Cool oxygenation is the best first step. The enlarged liver reduces lung and air sac capacity. These neonates usually present when the stress of feeding and breathing at the same time has exceeded their oxygen reserves. General nutritional changes that are required include reducing the quantity of food per feeding, adjusting the fat type and content and adding lactulose to the formula. Oral or parenteral fluid supplementation, when tolerated, should be added to keep the initially hyperthermic bird hydrated and to detoxify the body. When possible, further diagnostic testing should be pursued to check for concurrent infection or other diseases (Table 15.6).

*Hepatic Lipidosis* (*Adult Bird*): A second group that is predisposed to hepatic lipidosis is the obese adult bird being fed a high-fat diet, which is common in birds with ovarian disorders and hypercholesterolemia. This syndrome can occur in many species, but seems most common in *Amazona* spp. Long-standing malnutrition in an obese bird contributes to the cause of this syndrome. Septicemia can occur secondarily. The most common clinical presentation is an anorectic bird with a quiet demeanor, although other signs of hepatic dysfunction

**Table 15.6 | Treatment for Pediatric Hepatic Lipidosis**

- Cool oxygenation: place the bird in an oxygen chamber at 21° C
- Non-lactated fluids when stable
- Antibiotics that do not require hepatic transformation or elimination if bacterial infection warrants
- Hand-feed small amounts with increased frequency
- Metabolic aids: lactulose[a], milk thistle[b], policosanol[c]

**Table 15.7 | Treatment of Adult Hepatic Lipidosis**

- Fluid therapy guideline: 60-90 ml/kg of non-lactated fluids every 24 hours
- Nutritional support
- Metabolic aids: lactulose[a], milk thistle[b], policosanol[c], psyllium[g], Ayurvedic herbs,[h] SAMe
- Treatment of secondary infections

may be present. Complete blood count and serum biochemistries help confirm the diagnosis and direct treatment. The serum is often very lipemic in spite of fasting. An elevated WBC is often observed. Serum chemistries may be normal or may demonstrate an increase in levels of bile acids, AST, LDH, cholesterol and triglycerides.

Sick birds' caloric needs are 2 to 3 times normal. Diets too low in fat cannot provide sufficient calories. Start the patient on a 100% carbohydrate diet[d], add metabolic detoxifier[e] then slowly convert to a sick bird support formula or a hand-feeding mixture[f] with adequate caloric content. Further supportive care includes fluid therapy, metabolic aids (lactulose[a], milk thistle[b], psyllium[g], policosanol[c]) and antibiotics if needed (Table 15.7). Improvement of nutritional status is critical for complete recovery and prevention of recurrence (see Chapter 7, Emergency and Critical Care).

## AMYLOIDOSIS

Amyloidosis is a term used for various diseases that lead to the deposition of proteins in internal organs. The proteins are composed of beta-pleated sheets of non-branching fibrils. The physical properties of amyloid are responsible for its birefringence and apple green appearance in Congo red-stained sections viewed under polarized light. In primary amyloidosis, amyloid light chain protein is derived from immunoglobulin light chains synthesized by plasma cells in affected tissues. Primary amyloidosis may be localized or systemic.[18] In secondary amyloidosis, the most common type seen in veterinary medicine, the liver synthesizes serum amyloid-associated protein, which is the precursor to amyloid-associated fibrils. Secondary amyloidosis occurs as a consequence of prolonged inflammation resulting from chronic infection, tissue destruction, stress or chronic antigenic stimulation.[18] The

third type, inherited or familial amyloidosis, has been described only in some mammalian species.

Regardless of the cause, amyloid accumulates in the intercellular spaces and impairs the normal access of plasma to hepatocytes. Amyloid deposits can produce varying degrees of hepatomegaly, and extensive accumulations cause the liver to appear pale. In severe cases, affected birds may have clinical signs of either hepatic dysfunction or failure. While hepatic amyloidosis is usually fatal, a case was described in a falcon with hepatomegaly, ascites, leucocytosis, elevated AST, bile acids and iron levels. Abdominocentesis was performed and a milk thistle derivative was administered for a month. The bird survived for over 3 years.[18] Resolution of the primary cause is the goal in preventing the progression of this condition.

### IRON STORAGE DISEASE

Pathological storage of iron in the liver (iron storage disease) has to be differentiated from hemosiderosis. Hemosiderosis is defined as the excessive accumulation of iron in hepatocytes without the alteration of normal tissue morphology.[13] High-risk species for iron storage disease include ramphastids (toucans), mynah birds, starlings and birds of paradise. High amounts of dietary iron seem to be the main cause, although complete pathogenesis is unknown. Most of the susceptible species live in a naturally iron-poor nutritional environment.[4,21] The mynah was found to have high intestinal absorption and transfer capacity of iron leading to high retention levels[4] (see Chapter 4, Nutritional Considerations). Dyspnea, hepatomegaly, ascites and sudden death are the most common clinical presentations.

Symptomatic therapy to stabilize the bird's respiratory problems should be followed by long-term therapy based on weekly phlebotomy of 1 to 2% of body weight. Dietary sources of iron such as grapes and raisins should be eliminated, and birds should be maintained on a low-iron (20-50 ppm) formulated diet.[k] Therapy with a chelating agent[i], has been described as useful (Table 15.8).[2] Items that enhance iron uptake, such as vitamin C, should be avoided. Iron uptake interference by dietary chemicals such as tannin may provide natural protection from excessive iron absorption.[25b]

### TOXINS

The liver is the most common site for toxic injuries. The liver receives the major amount of its blood supply from the portal vein, which drains blood from the gastrointestinal tract. Therefore, ingested toxic substances including plants, aflatoxins and bacterial products, as well as metals, minerals, pharmaceuticals and other chemicals absorbed into the portal blood are transported to the liver. The liver possesses enzymes capable of metabolizing a variety of endogenous and exogenous substances for elimination from the body. This metabolic process may alter some substances such that they become more toxic. Toxin production may result in necrosis of hepatocytes, which may be replaced by fibrotic cells or infiltrated with lipids. This process can be self-perpetuating, even if the inciting agent is no longer present.[9]

**Table 15.8 | Treatment for Iron Storage Disease**

| Initial | Ongoing |
|---|---|
| Oxygenation | Phlebotomy |
| Diuretics | Low-iron diet[k] |
| | Defroxamine[2,j] |

**Table 15.9 | Infectious Diseases of the Liver**

| Type | Disease |
|---|---|
| Bacterial | *E. coli*, *Salmonella* spp., *Klebsiella* spp., *Chlamydophila* spp., *Mycobacterium* spp., *Mycoplasma* spp. |
| Viral | Herpesvirus, polyomavirus, adenovirus, reovirus |
| Fungal | *Aspergillus* spp., *Candida* spp. |
| Protozoan | *Atoxoplasma* spp., *Histomonas* spp., *Trichomonas* spp., *Leucocytozoan* spp. |
| Nematodes | |
| Trematodes | |

## Infectious Diseases of the Liver

The pathogenesis, diagnosis and treatment of the individual infectious diseases are beyond the scope of this chapter. See Chapter 28, Implications of Mycobacteria in Clinical Disorders; Chapter 29, Implications of Mycoses in Clinical Disorders; and Chapter 32, Implications of Viruses in Clinical Disorders. The reader is referred to other references for more details on infectious diseases that affect the liver (Table 15.9).

## Therapy for Liver Disease

This section reviews anecdotal and research-based therapy for hepatobiliary disease in birds; the mechanism of action, potential indications, efficacy as reported in humans and side effects. The liver can regenerate lost hepatic mass rapidly and efficiently. The therapy for hepatic dysfunction is directed at regeneration. Potentially hepatotoxic drugs should be avoided. High-quality nutrients are the best source of support for the regeneration of liver cells. The specific etiologic agent of liver disease is often undetermined. Clinical objectives for treatment of liver disease can be divided into supportive care and pharmacologic therapy.

## SUPPORTIVE CARE

Supportive care for birds with hepatic damage includes reducing stress, fluid therapy, nutritional support and treatment of encephalopathy, ascites, coagulopathies and gastrointestinal ulceration. Proper caging options range from a cool, oxygenated incubator in a low-stress area to the bird's normal cage in its household environment. Lowering perches and padding can protect birds with coagulopathies. If infectious disease is suspected, then quarantine would be warranted.

Fluid therapy will flush toxins and toxic by-products through the metabolic pathways and from cells, organs and blood (see Chapter 7, Emergency and Critical Care). The selection of fluids for replacement therapy may be based on serum biochemistry results and physical exam findings and should be devoid of lactate. The volume to be administered will vary, depending on existing fluid deficits and continuing loss. Administration of colloids[j] may be effective in severe non-responsive hypoalbuminemia, however, clotting times should be monitored. Conspecific plasma or whole blood may be a better option.

Nutritional support with gavage-feeding should be provided three to four times daily for the anorectic patient. Calculate the metabolized energy requirements to determine the volume of food to use (see Chapter 4, Nutritional Considerations). A high-quality balanced formula with appropriate levels of vitamins and minerals and devoid of potential hepatotoxic agents, such as pesticides and preservatives, should be provided.

### Hepatic Encephalopathy

The goal of therapy for hepatic encephalopathy is to restore normal neurologic function. In mammalian medicine, this is accomplished by dietary protein restriction, lactulose[a] therapy and antimicrobials. Lactulose[a] is a synthetic non-absorbable disaccharide commonly used in mammalian medicine for the treatment of elevated blood ammonia levels seen in hepatic encephalopathy. It is fermented in the gut by bacteria into acetic acid and lactic acid, which reduces the pH. The acidification causes ammonia ($NH_3$) to migrate from the blood into the colon where it is trapped as an ammonium ion ($NH_4^+$) and expelled with the feces. These acids also increase osmotic pressure drawing water into the bowel, causing a laxative effect. Lactulose[a] has minimal side effects and is therefore considered safe to administer to all birds during gavage-feeding.

### Ascites

Removal of a large volume of coelomic fluid can cause severe protein loss. Removal is indicated if the ascites is associated with respiratory embarrassment or anorexia. Diuretics may be useful in controlling fluid retention. Dietary sodium restriction also is recommended, but the efficacy is unknown.

### Coagulopathies

Cholestasis can cause impaired production of coagulation factors and antithrombin III as well as vitamin K malabsorption. Normal avian values are not available. Coagulopathies may be observed as petechia, hemorrhage or melena. Blood component therapy may be indicated. Vitamin $K_1$ can be administered for hemorrhage associated with vitamin K deficiency.

### Gastrointestinal Ulceration

The empiric indications for the use of H2 blockers include nausea, inappetence and melena. Famotidine or ranitidine are recommended, since cimetidine and omeprazole are involved in cytochrome P450 inhibition and potential drug interactions in mammals.[23] Sucralfate may enhance healing of ulcers in patients with impaired mucosal blood flow, but this agent may bind and prevent absorption of other drugs.

## PHARMACOLOGIC THERAPY

The proper choice of therapy depends on a definitive diagnosis. Technical or financial restrictions often preclude obtaining a definitive diagnosis in avian veterinary medicine. Therapeutic agents used are chosen for their anti-inflammatory, antifibrotic, hepatoprotectant, antimicrobial, diuretic, procoagulant, antacid or bivalent chelating actions. The pharmacologic therapies the authors recommend for hepatic failure in birds have not been validated by controlled studies. The personal experiences of the authors as well as anecdotal reports from colleagues support their use in therapy.

## IMMUNOSUPPRESSANTS

The use of glucocorticoids in avian medicine is controversial. They cause immunosuppression by a variety of pathways. Glucocorticoids may exacerbate an underlying infection, increase hepatic lipid deposition, derange adrenal function and may be contraindicated unless a definitive diagnosis is determined (see Stress in Chapter 19, Endocrine Considerations). They are the treatment of choice in humans with autoimmune hepatitis.

Azathioprine is a thiopurine analogue metabolized in the liver to 6-mercaptopurine. Its metabolites inhibit the proliferation of rapidly dividing cells and modify T-lymphocyte function. Azathioprine is indicated when glucocorticoids are not controlling the immune response or are not tolerated by the patient. No data exist on the efficiency of conversion of azathioprine to its active metabolites in

hepatic insufficiency in birds. Serious side effects include dose-dependent bone marrow suppression, pancreatitis and idiosyncratic hepatotoxicity in mammals.

### ANTIFIBROTICS

Colchicine is indicated when there is evidence of fibroplasia or bridging fibrosis. Colchicine helps prevent fibrosis by a variety of inhibitory actions. It also may protect the liver via stabilization of hepatocytes' plasma membranes. Most common side effects are associated with gastrointestinal upset, but in humans a peripheral neuropathy and bone marrow suppression have been reported. Formulations of colchicine containing probenecid can inhibit biliary and renal excretion of many drugs. Elemental zinc and glucocorticoids also have antifibrotic properties, but should be used with caution.

### CHELATING AGENTS

Chelating agents are used to chelate bivalent metals such as zinc, lead, copper and sometimes iron. Copper induced liver disease is not a common problem in avian medicine.

### HEPATOPROTECTANTS

Hepatoprotectants comprise a varied group of compounds that may protect hepatocytes from injury caused by free radicals, bile salts, drugs, environmental toxins and other insults.

Ursodiol, ursodeoxycholic acid, is a hydrophilic bile acid that competes with other bile acids for absorption in the ileum, and shifts the bile acid profile in favor of less toxic hydrophilic forms. It is suspected to reduce hepatocellular injury and fibrosis, modulate immune response and act indirectly as an antioxidant by preventing bile acid-induced peroxidation. Ursodiol is indicated in mammals for chronic active hepatitis, cholangiohepatitis, and disorders involving cholestasis or elevated bile acids. No efficacy studies have been performed with birds. GI upset has been reported rarely in humans. Ursodiol is contraindicated in bile duct obstruction because it is choleretic.

Vitamin E is a potent antioxidant. Studies indicate that it protects against bile salt-induced oxidant injury in-vitro.[29] It is indicated as an empirical therapy for inflammatory hepatopathies. The side effects are minimal unless there is a massive overdose or if it used with selenium (see Chapter 4, Nutritional Considerations).

S-adenosylmethionine (SAMe) is an indirect precursor of the antioxidant glutathione[20] (see Chapter 4, Nutritional Considerations: Section II, Nutritional Disorders). There are no side effects reported in veterinary medicine. Neurological side effects were reported in humans taking tricyclic antidepressants.[12] Early empirical results of SAMe use in birds with elevated cholesterol and fatty disorders are encouraging.

Milk thistle[b] (*Silybum marianum:* silymarin) is an extract from the seeds of milk thistle. It is thought to have antioxidant effects via scavenging of reactive oxygen radicals, and to have anti-inflammatory effects via inhibition of 5-lipoxygenase.[3] Side effects of GI upset and allergic rashes are rare in humans. It is a nutritional supplement, not a pharmaceutical. See Chapter 10, Integrative Therapies for more information.

Policosanol[c] is a blend of compounds isolated from natural plant waxes. It decreases blood triglyceride and reduces low-density lipoprotein cholesterol, inhibits abnormal platelet aggregation, protects against low-density lipoprotein oxidation, suppresses arterial inflammatory factors and increases beneficial high-density lipoprotein cholesterol.

## Monitoring Parameters

The best test for monitoring the treatment of liver disease is the test(s) that was used to confirm the diagnosis in the first place. If hepatic lipidosis was diagnosed in an obese Amazon by history and clinical signs, hepatomegaly noted on radiographs and an elevated serum bile acid assay, then repeat radiographs and serum bile acid assay would be indicated. Repeat biopsies would give the most definitive answer, but are not always best for the individual patient.

#### Products Mentioned in the Text

a. Lactulose, Cephulac, Marion Merrell Doug, Kansas City, MO, USA
b. Milk Thistle, *Silybum marianum*, Nature's Answer, Hauppauge, NY, USA
c. Policosanol, Mountain States Health Products, Inc, Lyons Co, USA, 1-800-647-0074
d. Ultrafuel, Malt dextran and fructose, Twin Laboratories, Inc, Ronkonkoma, NY 11779, USA
e. Ultra Clear Plus, Ultra Balance Medical Foods, 5800 Soundview Dr, Gig Harbor, WA, 98335, USA, www.ultrabalance.com
f. Juvenile Hand-Feeding Formula, HBD International, Inc, 7108 Crossroads Blvd., Suite 325, Brentwood, TN 37127, USA, 1-800-346-0269, www.harrisonsbirdfoods.com
g. Metamucil, Proctor and Gamble Pharmaceuticals, Cincinnati, OH, USA
h. Ayurvedic herbs, Hepasan, Indian Herbs Research and Supply Co Ltd, Institut fur Veterinarpharanakologic und — toxikologie, Winterhurstrasse 260, 80547 Zurich, Schueiz, http:/www.vetpharm.unezh.ch
i. Desferal, Novartis Pharmaceuticals Corp, East Hanover, NJ, USA
j. Hetastarch, DuPont Pharmaceuticals, Wilmington, DE, USA
k. Harrison's Bird Foods, HBD International, Inc, 7108 Crossroads Blvd., Suite 325, Brentwood, TN 37127, USA, 1-800-346-0269 www.harrisons-birdfoods.com

## References and Suggested Reading


1. Conn HO, Leevy CM: Comparison of lactulose and neomycin in the treatment of chronic portal-systemic encephalopathy. Gastroenterology 72:573-583, 1977.
2. Cornelissen H, Ducatella R, Roels R: Successful treatment of a channel-billed toucan with iron storage disease by chelation therapy: Sequential monitoring of the iron content of the liver during treatment period by quantitative chemical and image analysis. J Avian Med Surg 9:131-137, 1995.
3. Dehmlow C, Murawski N, de Groot H: Scavenging of reactive oxygen species and inhibition of arachidonic acid metabolism by silibinin in human cells. Life Sci 58:1591-1600, 1996.
4. Dorrenstein GM, et al: Hemochromatosis/iron storage: New developments. Proc Assoc Avian Vet, 2000, pp 233-237.
5. Flinchum GB: Potential use of policosanol in the treatment of hyperlipidemia in pet birds. Exotic DVM 5(3): 19-23.
6. Flora K, et al: Milk thistle (*Silybum marianum*) for the therapy of liver disease. Amer J Gastroenterology 93(2):139-142, 1998.
7. Fudge A: Avian liver and gastrointestinal testing. *In* Fudge A (ed): Laboratory Medicine: Avian and Exotic Pets. Philadelphia, WB Saunders Co, 2000, pp 47-55.
8. Garner MM, et al: Three psittacine fatalities due to an unidentified sporozoan parasite infection in a closed psittacine aviary. Proc Assoc Avian Vet, 2001, p 56.
9. Hardy RM: Diseases of the liver and their treatment. *In* Ettinger SJ (ed): Textbook of Veterinary Internal Medicine Vol. II, Philadelphia, WB Saunders Co, 1989, pp 1479-1527.
10. Hess L: Possible complications associated with topical corticosteroid use in birds. Proc Assoc Avian Vet, 2001, pp 29-32.
11. Hochleithner M: Biochemistries. *In* Ritchie BW, Harrison GJ, Harrison LR (eds): Avian Medicine: Principles and Application. Brentwood, TN, HBD International, Inc., 1999, pp 223-245.
12. Irulea LM, et al: Toxic interaction of S-adenosylmethionine and clomipramine. Amer J Psychiatr 150:522, 1993.
13. Jacobs A.: Iron metabolism, deficiency and overload. *In* Scott BR (ed): Price's Textbook of the Practice of Medicine. Oxford, Oxford University Press, 1978, pp 1118-1129.
14. Lin GL, Cornelius CE: Bilirubin and biliverdin excretion by the chicken. Amer J Phys 226:881-885, 1974.
15. Lothrop C, et al: Miscellaneous Diseases. *In* Harrison GJ, Harrison LR (eds): Clinical Avian Medicine and Surgery. Philadelphia, WB Saunders Co, 1986, p 526.
16. Lumeij S: Hepatology. *In* Ritchie BW, Harrison GJ, Harrison LR, (eds): Avian Medicine: Principles and Application. Brentwood, TN, HBD International, Inc., 1999, pp 522-536.
17. McGavin MD, Carton WW, Zachary JF (eds): Thomson's Special Veterinary Pathology 3rd ed. St. Louis, Mosby, 2001, pp 81-124.
18. McKinney PA: Amyloidosis in Falconiformes. Proc Assoc Avian Vet Australian Com, 2002, pp 257-264.
19. Mizobe M, et al: High performance liquid chromatographic analysis of bilirubin and biliverdin from jaundiced broilers. J Vet Med Sci, 59(8):677-680, 1997.
20. Osman E, Owen JS, Burroughs AK: Review article: S-Adenosyl-L-Methionine — A new therapeutic agent in liver disease? Aliment Pharmacol Ther 7:21-28, 1993.
21. Otten BA, et al: Mineral content of food items commonly ingested by keel-billed toucans (*Ramphastos sulfuratus*). J Avian Med Surg 15(3):194-196, 2001.
22. Pepping J: Milk thistle: *Silybum marianum*. Amer J Health Syst Pharm, 56:1195-97, 1999.
23. Reynolds JC: The clinical importance of drug interactions with antiulcer therapy. J Clin Gastroenterol Suppl 2:S54-S63, 1990.
24. Ritchie BW: Diagnosis and management of common problems in companion birds. Proc Assoc Avian Vet, 2001, pp 99-119.
25a. Ritchie BW, Harrison GJ: Formulary. *In* Ritchie BW, Harrison GJ, Harrison LR (eds): Avian Medicine: Principles and Application. Brentwood, TN, HBD International, Inc., 1999, p 465.
25b. Seibels B, et al: Effective use of tea to limit dietary iron available to starlings (*Sturnus vulgaris*). J Zoo Wildl Med 2003; 34:314-316.
26. Spalding MG, et al: Hepatic encephalopathy associated with hemochromatosis in a toco toucan. J Am Vet Assoc 189(9):1122-23, 1986.
27. Stanford M: Effect of dietary change on fecal Gram's stains in the African grey parrot. Exotic DVM, 4(6):12, 2003.
28. Stone EG, Redig PT: Preliminary evaluation of hetastarch for the management of hypoproteinemia and hypovolemia. Proc Assoc Avian Vet, 1994, pp 197-199.
29. Twedt D, et al: Vitamin E protects against oxidative damage of bile acids in isolated hepatocytes (abstract). Proc 16th ACVIM Forum, 1998, p 705.
30. Weber MA, et al: Benefits and complications of liver biopsy in birds. Proc Assoc Avian Vet, 2001, pp 211-213.