Liver Disease in Birds

Bob Doneley BVSc MACVSc (Avian Health)
West Toowoomba Vet Surgery
194 West St., Toowoomba QLD 4350

Introduction.

Although avian veterinarians frequently diagnose liver disease in their patients, there are few specific therapies recommended for treatment. In part this is due to the often vague nature of the diagnosis, but there is also a lack of peer-reviewed information on proven therapies and remedies.

In this paper, the anatomy and physiology of the liver is reviewed. Common aetiologies of disease and the liver's response to insult are described. Current recommendations for the diagnosis of liver disease are discussed, as are current therapies. New treatments for liver disease in mammals are examined for their applicability to birds.

Anatomy and physiology.

The avian liver consists of the right and left lobes joined cranially in the midline. The right lobe is larger than the left, with each lobe having several small processes. The liver is enclosed in a thin and slightly elastic capsule of connective tissue, allowing its expansion. Blood is supplied to the liver by the right and left hepatic arteries and hepatic portal veins. The hepatic arteries arise from the coeliac artery, while the portal veins drain blood from the proventriculus, ventriculus, duodenum, pancreas, intestines and cloaca. Two hepatic veins join the caudal vena cava cranial to the liver, draining blood away from the liver.[1]

Terminal portal venules and arterioles empty into sinusoids between plates of hepatocytes. The low pressure in these sinusoids allows the hepatocytes to absorb molecules from the blood. Phagocytic Kupffer cells are also present in the sinusoids, collecting particulate matter and micro-organisms. The now "filtered" blood drains into the hepatic veins and onto the heart. The oxygenated arterial blood maintains the viability of the hepatocytes. Bile canaliculi form between three to five hepatocytes, and drain into a bile ductule.

A portal triad of arteriole, portal venule and bile ductule, along with associated hepatocytes, bile canaliculi and sinusoids, forms the basic functional unit of the liver – the hepatic acinus. Hepatocytes close to these portal triads are said to be "periportal". Those further away, near the hepatic venules, are called "periacinar". The intermediate area is termed the "midzone". The hepatocytes in these different areas, although morphologically different, are biochemically different, and react differently to incoming chemicals and metabolites. [2]

Bile is produced by hepatocytes and enters the bile canaliculi and then the ductules in the portal triad, which then empty into the interlobular ducts. These in turn form the right and left hepatic ducts, which join to become the common hepatoenteric duct emptying into the duodenum. A branch of the right hepatic duct either forms the right hepatoenteric duct (emptying into the duodenum) or, in those birds with a gall bladder, the hepatocystic duct entering the gall bladder.

(Pigeons, most psittacines and ostriches do not have gall bladders.) From there the cystoenteric duct runs to the duodenum. Birds thus have two bile ducts emptying into the duodenum. [3]
The liver has several functions in the body:

1. Digestion. Bile contains bile acids, synthesized in the liver from cholesterol. (In birds the primary bile acid is chenodeoxycholic acid. [4]) In the distal duodenum these bile acids emulsify fat, facilitating its digestion.[3, 4] Bile acids are then resorbed in the jejunum and ileum, and recirculated through the liver.[3] Bile also plays a role in the digestion of carbohydrates and protein. It contains amylase, and helps to activate pancreatic amylase and lipase in the duodenum. Because of the lack of biliverdin reductase and glucuronyl transferase in birds, the primary bile pigment is biliverdin, giving avian bile its characteristic green colour.

2. Carbohydrate metabolism. The portal blood supply, carrying nutrient-rich blood from the gastrointestinal tract, supplies the liver with these nutrients before any other major organs. Hepatic enzymes carry out glycogenesis, protein synthesis and lipogenesis in the well-fed bird. The glycogen, protein and triglycerides produced in the liver enter the circulation and are used (or stored) throughout the body. If a bird is fasted (for any reason) the resultant hypoglycaemia stimulates glucagon production, which in turn activates liver enzymatic pathways to produce glucose through glycogeolysis, gluconeogenesis and lipolysis. The liver therefore plays a major role in carbohydrate metabolism.[4]

3. The metabolism of metabolites, drugs and chemicals. The liver, through its microsomal drug-metabolising enzyme system in the periacinar hepatocytes, processes both endogenous metabolites and exogenous chemicals. Hydrophobic, lipid-soluble molecules (which are difficult to eliminate) are converted by the liver to hydrophilic, water-soluble molecules and excreted in bile and urine. This is done in two phases; in the first, enzymes modify the molecules by oxidation or reduction; in the second they are then enzymatically conjugated with other molecules to become sufficiently water-soluble.[2] The best example of this is the synthesis of urea and uric acid from protein in the liver. [1,2]

4. Protein synthesis. The liver is the primary site of synthesis of a range of essential proteins:

a. albumin
b. fibrinogen, prothrombin, and clotting factors I, II, V, VII, VII, IX and XII
. molecules involved in the transport of metals, hormones and lipids eg ceruloplasmin and macroglobulins. [2]

5. Antimicrobial effect. The Kupffer cells in the sinusoids are important in the clearance of micro-organisms entering the portal circulation in cases of intestinal infections or surgery. They also play a role in the detoxification of bacterial endotoxins.[2]

Pathophysiology of liver disease

The liver can be affected by many agents, but the clinician needs to be aware that in many cases the inciting cause may never be identified. The distribution of the lesions may give some indication as to an aetiology. The periportal hepatocytes, the first to be perfused with blood from the portal system, are most susceptible to hepatotoxins and endotoxins. Periacinar hepatocytes, located further away from the portal blood supply, are more likely to suffer from the effects of hypoxia, toxic metabolites and hypoperfusion (eg passive venous congestion). [7]

The production of cytokines and inflammatory mediators following the initial injury to the hepatocytes and biliary epithelium attracts inflammatory cells. This leads to further hepatocyte necrosis and then fibrosis. If the acinar archi/tecture is maintained, regeneration is frequently feasible. If, however, the acinar structure collapses, regeneration either does not occur, or is very haphazard. Fibrous tissue is deposited in the area of injury, leading to extensive tissue remodelling and changes in the functional capabilities of the hepatocytes. [8]

The liver possesses remarkable powers of regeneration. Because of the relatively low morphological differentiation within the liver, hepatocytes can be replaced as long as 12% remain undamaged.[1] Jaensch et al[2] showed that after surgical removal of 6% of the liver's mass, regeneration occurred within 7 days. If treatment can be instituted to remove the cause of disease promptly, fibrotic changes can be reversed. However, after several weeks, these changes become irreversible. [8]

Aetiology of liver disease.

Reported liver disease in birds can be classified as congenital, traumatic, metabolic/nutritional, toxic, parasitic, infectious, neoplastic or idiopathic. [11]

1. Congenital.

Congenital liver disease is rarely reported in avian literature, possibly because of early death and lack of investigation. Extrahepatic biliary cysts have been reported in an African Grey parrot (*Psittacus erithacus erithacus*).[12] A congenital abdominal hernia involving the liver has been reported in Japanese Quail (*Coturnix japonica*) [13]

2. Trauma

Trauma can cause tearing of the liver parenchyma and/or the capsule. This occurs when the bird is subjected to massive force eg a moving motor vehicle, or when the liver is friable due to other problems eg hepatic lipidosis. The severity of the liver rupture and resultant haemorrhage will determine whether the bird survives the initial trauma.

3. Metabolic/Nutritional

Any condition causing hyperuricaemia can lead to visceral gout – the deposition of uric acid crystals on and in organs. This is typically associated with renal disease, although dehydration and high protein diets can be involved. In the liver, most of this deposition occurs on the capsule, but it can occur within the parenchyma where it is associated with necrosis and heterophilic inflammation. [14]

Amyloidosis is most commonly seen in waterfowl and passerines.[14] Amyloid A is a degradation product of inflammatory proteins, and its deposition is commonly seen in birds with chronic disease.[11]Affected livers are usually enlarged and friable, and can be confused with hepatic lipidosis. Histologically, the amyloid is seen as a pale eosinophilic or amphophilic deposit between the cells, compressing them.[14]

In the normal bird, albumin carries circulating fatty acids to the liver, where they are oxidised for energy or incorporated into triglycerides. If the amount of circulating fatty acids exceeds the liver's ability to process it, the excess lipid is stored in the liver, resulting in lipidosis. Hepatic lipidosis

therefore occurs either when there is excessive fatty acids consumed (in the form of dietary fat), increased lipolysis (eg diabetes mellitus or egg laying activity), decreased fatty acid oxidation in the liver, or decreased ability of the liver to secrete processed fatty acids back into the circulation. Dietary deficiencies of lipotrophic factors such as choline, biotin and methionine may decrease the transport of lipids from the liver.[11, 14, 15] Affected livers are enlarged, pale yellow and friable. Histologically, there is vacuolation of the hepatocytes.[14]

The liver is the main site of iron storage in the body. The iron is stored in two forms. Ferritin is a soluble form of non-haeme iron stored in hepatocytes ready for recirculation into the blood. Old or haemolysed erythrocytes release insoluble haemosiderin, which is phagocytosed by the Kupffer cells. If there is more iron in the circulation than is needed for erythrogenesis, iron will accumulate in the liver, a condition known as haemosiderosis.[8] There is some confusion on the subject of iron storage disease. Many authors refer to the condition as haemochromatosis. In fact this is misleading, as haemochromatosis is a primary form of haemosiderosis, a genetic condition in humans leading to the deposition of iron in organs as a result of a defect in iron metabolism. The term haemochromatosis should therefore not be used in avian medicine. Other forms of primary haemosiderosis result from a usually identifiable source of excess iron intake, either dietary or via excessive blood transfusion.[8] This condition is commonly seen in Sturnidae (mynahs, starlings), Paradisaeidae (birds of paradise), Ptyonorhynchidae (bowerbirds), Bucerotidae (hornbills), and Ramphastidae (toucans and toucanettes). [11] It is also reported in lories and lorikeets. [14] Secondary haemosiderosis also occurs in the liver of birds with a variety of illnesses, or with intravascular haemolysis. Affected livers are enlarged, and are usually golden-brown in colour, often with scattered dark foci. Iron can be seen histologically in the hepatocytes and Kupffer cells. There may be an associated inflammatory process with lymphocytes and occasional heterophils.[14]

Lipofuscin pigment accumulates in hepatocytes secondary to a range of diseases. It is due to excessive biological oxidation at the cellular level. Vitamin E deficiency has been suggested as one possible cause. [14]

4. Toxic

There are many compounds known to be hepatotoxic in birds and many others that are toxic in other animals, and should be assumed to be similar in birds. These include:

a. drugs – alcohol, dimetronidazole, medroxyprogesterone, etc
b. plants – pyrrolizidine alkaloids, oleander, gossypol, avocado fruit, etc
c. aflatoxins, ergot
d. heavy metals – zinc, lead, copper, iron
e. pesticides – metaldehyde, phosphorous, Vit D3 analogs, etc.

There are many other hepatotoxins described in the literature, and the above list should not be considered complete.[11]

5. Parasitic

A variety of parasites have been identified as causing liver disease in birds.

a. Protozoa

i) *Apicomplexa* (coccidia): Cryptosporidia may occasionally be found attached to biliary epithelium, causing proliferation of the epithelium and a mild chronic mononuclear reaction.[14] Atoxoplasma is primarily reported in passerines, especially canaries. It undergoes schizogony in the liver, causing a generalised inflammatory reaction composed of macrophages, plasma cells and lymphocytes. The organism may be found in macrophages and lymphocytes.[11, 14] Birds infected with Sarcocytis and Toxoplasma are usually intermediate hosts. They produce a similar inflammatory reaction to Atoxoplasma. Organisms can be difficult to locate.[14]

ii) *Haemoprotozoa*: Plasmodium (avian malaria) is a widespread blood parasite. Some species, especially penguins, appear to be more susceptible.[11] Schizogony occurs in the reticuloendothelial cells of many organs, with merozoites released to infect erythrocytes. Affected livers are enlarged, and in falcons often appear grey-black. There is infiltration of the liver with macrophages, plasma cells and lymphocytes, with the organism found in some of the inflammatory cells.[14] Hemoproteus is usually non-pathogenic, with schizonts occasionally found in the endothelial cells of the liver.[14] Leukocytozoon affects many species, with mortalities reported in ducks and geese.[11] Where liver damage does occur it is usually acute and severe, with haemorrhage and necrosis but minimal inflammation. Gametocytes can be found in peripheral blood smears. [11, 14]

iii) *Flagellates*: Histomonas causes the disease known as Blackhead in domestic poultry, especially peafowl and turkeys. It produces classical white-yellow granulomas throughout the liver parenchyma. The organism can be found in the lesions, although it may resemble macrophages and be difficult to detect.[14] Trichomonas is usually a gastrointestinal parasite, but heavy infections can spread to the liver. Necrotic lesions with the parasite found at the periphery are diagnostic.[14]

b. Trematodes: flukes of the family *Dicrocoelidae* inhabit the bile duct of many avian species, including psittacines, anseriformes, ramphastidae and ratites.[11,14,16,17] Wandering flukes may be found in dilated bile ducts, and schistosomes can be found in dilated sinusoids. There is usually minimal inflammation unless there are degenerating eggs present. Fasciola flukes in emus provoke an eosinophilic response, with macrophages and lymphocytes present. Granulomas may form with giant cells and fibrosis.[14]

c. Nematodes – intestinal nematode larvae can migrate through the liver causing extensive fibrosis, bile duct hyperplasia and inflammatory cell infiltrates.[14]

6. Infectious.

Bacterial, viral, fungal, chlamydial and mycobacterial infections can affect the liver.

a. Bacteria. Both Gram positive and Gram negative bacteria can cause liver disease, usually secondary to septicaemia or enteritis. *Salmonella, E. coli, Pseudomonas, Yersinia* and *Camplyobacter* are common isolates. Affected livers are usually swollen, with grey-white foci throughout the parenchyma. Multifocal hepatocyte necrosis with a heterophilic inflammatory response is usually seen. Bacteria are usually seen in macrophages and Kupffer cells.[14] Additionally, endotoxins arising from a bacterial enteritis can enter the portal circulation, damaging the periportal hepatocytes.

b. Viruses.

i) Herpesvirus has been isolated from nearly all species of birds. Ritchie[3] lists the following serotypes as targeting the liver: Pacheco's Disease Virus; Pigeon Herpesvirus; Owl Herpesvirus; Falcon Herpesvirus; Crane Herpesvirus; Stork Herpesvirus; Quail Herpesvirus; and Finch Herpesvirus. Other strains of herpesvirus, while not specifically attacking the liver, may produce some degree of hepatic damage. Affected livers are enlarged, with variable yellow-grey mottling and haemorrhage. Histologically there is acute necrosis with variable inflammation, syncitial cell formation and intranuclear inclusion bodies.[14]

ii) Polyomavirus is primarily recovered from psittacines and finches, but may affect a range of birds.[18] Affected livers are enlarged and friable, with the degree of severity often varying according to species. There is multifocal or mid-zonal necrosis and haemorrhage, with characteristic inclusion bodies in the Kupffer cells.[14]

iii) Adenovirus rarely causes clinical disease unless there are other immunosuppressive factors at work.[18,19] Many species of birds are affected, including psittacines, poultry, pigeons and ostriches. Affected livers are discoloured with scattered yellow-grey areas present. There is multifocal necrosis and haemorrhage, non-suppurative cholangitis and large basophilic intranuclear inclusion bodies in the hepatocytes.[14]

iv) Paramyxovirus causes hepatomegaly in isolated cases, but its primary effects are neurological, gastrointestinal and respiratory.[11, 14] Histologically there is a lymphoplasmocytic infiltrate in the periportal area.[14]

v) Circovirus is occasionally seen as an acute disease in young birds. In these birds, and in some adults with severe feather changes, there may be a mild necrosis and a lymphohistiocytic inflammatory reaction in the portal areas. Inclusion bodies can be seen in the Kupffer's cells. [14]

vi) Reovirus has been recovered from psittacines, galliformes, anseriformes, raptors, pigeons and chickens.[11, 14, 18] Affected livers are enlarged with scattered gray-white or yellow foci. Histologically there is hepatocellular necrosis with minimal inflammation.[14]

vii) Hepadnavirus is the cause of duck viral hepatitis, resulting in hepatic necrosis and periportal inflammation. [14]

viii) Togavirus (Eastern Equine Encephalitis) causes enlarged livers with some necrosis in many species of birds.[18]

c Fungi. Fungal infections involving the liver are usually opportunistic spread from other sites within the body. *Aspergillus spp*. affecting nearby air sacs have been reported to locally invade the liver, causing hepatic necrosis.[11, 14]

d. Chlamydia. The obligate intracellular bacterium, *Chlamydophila psittaci*, is a common cause of liver disease in all species of birds. Affected livers are enlarged, discoloured and may show grey-yellow foci of necrosis. There is multifocal to confluent necrosis with a mononuclear inflammatory reaction. Organisms may be found in macrophages and hepatocytes.[14]

e. Mycobacteria. Mycobacterial infection in birds is primarily a gastrointestinal infection, with caseated tubercles occurring in the intestinal mucosa and the liver.[4] Histologically, early lesions are comprised primarily of heterophils and macrophages, with only a few microorganisms. As the lesions progress, large epithelioid macrophages containing mycobacteria appear. These are best seen with an acid fast stain.[14]

f. Rickettsia. *Aegyptianella pullorum* causes hepatitis in many species of birds, especially in the Mediterranean region. Intraerythrocytic inclusion bodies can be seen with Giemsa stain.[11]

7. Neoplastic

Hepatic neoplasia is usually primary, although metastatic neoplasms can occur. Primary bile duct tumours are more common than hepatocellular tumours. In psittacines these may be associated with Internal Papilloma Disease.[14]

8. Idiopathic

Sometimes referred to as "hepatopathy" [21] "chronic active hepatitis" or "hepatic cirrhosis", this is a common condition in many species of birds. No one single cause has been identified, and it is probably multifactorial, possibly involving an immune-mediated component. Affected livers are often shrunken, pale and fibrotic. In the early stages of the disease there is hepatic vacuolization, a pleocellular inflammatory infiltrate in the periportal areas, bile duct proliferation, and mild fibrosis. As the condition progresses, the fibrosis worsens and diffuse biliary hyperplasia develops.[14]

Clinical signs

Liver tissue is unique in that it has the ability to regenerate quickly and has a large functional reserve capacity. This enables a bird to appear clinically normal even though up to 80% of its hepatic function may be lost.[10,22] Nevertheless, liver disease is a common clinical problem.

Clinical signs seen in birds with liver disease can reflect any or all of the following malfunctions:

a. Cholestasis.

Swelling of the hepatocytes and inflammatory infiltrates can cause occlusion of the biliary system. This results in the increased retention of bile, and subsequent rise of serum bile pigment levels. Because of the lack of biliverdin reductase, it is uncommon for birds to produce bilirubin. Icterus is therefore uncommon in birds. However, increased levels of biliverdin in the blood due to

cholestasis will result in ***biliverdin-stained urates and urine***, giving these waste products a green discolouration. Decreased bile secretion into the intestine can result in maldigestion (***weight loss, diarrhoea***).

b. Inadequate conversion of ammonia to uric acid & urea.

Failure to convert ammonia to uric acid and, to a lesser extent, urea leads to increased serum levels of ammonia and the onset of hepatic encephalopathy. Signs include ***weakness, depression, personality changes, behavioural disturbances, seizures*** and ***paresis.*** [22]

c. Protein synthetic deficits.

Inadequate production of clotting factors can lead to coagulopathies. This can be as subtle as ***mild haemorrhages in the rhinotheca***, or as dramatic as sudden death due to ***internal haemorrhaging***. Decreased synthesis of ceruloplasmin can result in decreased iron mobilization and subsequent ***anaemia***. Decreased albumin can be one factor in the development of ***ascites***.

d. Abnormal carbohydrate and fat metabolism.

Hypoglycaemia, weight loss and ***debility*** are frequently seen in birds with severe liver disease. Nutritional deficiencies resulting from liver disease may be the cause of the dermatological signs seen in affected birds. These include ***feather loss, skin changes,*** and ***overgrown beaks and nails.***

e. Failure of Kupffer Cell activity.

Endotoxaemia and ***bacteraemia*** may develop when the Kupffer cells are unable to perform their function correctly.

f. Acquired portosystemic shunting.

Distortion of the liver's normal architecture can result in blood been diverted around the liver directly to the caudal vena cava. This results in toxic substances bypassing the liver, causing ***hepatic encephalopathy***.

g. Portal hypertension.

Increased blood pressure within the sinusoids can result in the development of ***ascites***, as oedema in the liver results in the movement of a modified transudate out of the liver into the peritoneal cavity.

h. Inadequate or inappropriate metabolism of drugs and chemicals.

Decreased ability of the hepatocytes to modify or metabolise drugs and chemicals can lead to unexpected ***aberrant responses to administered drugs***.

Other clinical signs result from other, less obvious, processes.

* Bile salts deposited in the skin may be the cause of some of the apparent ***pruritus*** seen in birds with liver disease.

* Pain from the stretching of the capsule over an enlarged liver can cause ***featherpicking*** over the torso.

* Occlusion of the space normally occupied by the air sac by either the liver or ascites can result in ***dyspnoea***.

Because of the large functional capacity of the liver, birds suspected of, or shown to have, liver disease should be assessed as having a greater than 80% loss of liver function, an important consideration when assessing prognosis.[22]

Diagnosis of liver disease.

Birds with a history of access to any of the aetiological agents described earlier, and/or showing some or all of the clinical signs listed above should be suspected of having clinical liver disease. Confirmation of liver disease follows the use of diagnostic aids including clinical pathology, diagnostic imaging, and liver biopsy. It should be emphasised at this stage that many diagnostic tests can only confirm the presence of liver disease, not the cause and extent of the problem.

Diagnostic testing should follow a step by step approach, using minimally invasive tests first to direct the focus of more invasive tests as information is gathered. [23] This approach recommends that clinical pathology and diagnostic imaging should be used to confirm liver disease and then endoscopy and/or biopsy can be used to more accurately diagnose the cause and to assess the prognosis.

Clinical pathology

There are five categories of clinical pathology tests that can be used to determine the presence of liver disease:

i) Complete Blood Count
ii) Serum biochemistries
iii) Urinalysis
iv) Abdominocentesis
v) Hepatic function tests

There are other tests eg serology that can be used to further elucidate possible aetiologies once a diagnosis of liver disease has been made.

1. Complete Blood Count (CBC)

A CBC can be used to determine the chronicity of the problem, and the body's response to it. Parameters such as haematocrit, total white cell count, differential white cell count and cellular morphology are important aids to assessing the bird's general health status.[22]

2. Serum biochemistries

The assessment of plasma proteins, enzymes and metabolites is a useful screen for liver disease. However, because of the liver's enormous functional reserve, normal values should not be taken to indicate a normal liver. The biochemistries used in avian medicine differ somewhat from mammalian tests, and the clinician needs to be aware of these differences when requesting an avian profile from a laboratory not used to avian medicine. The following biochemistries are considered most useful for assessing avian liver disease.

a. *Plasma protein*. Plasma electrophoresis (EPH) is used to measure albumin, α_1, α_2, β, and γ proteins This defines the health status of the patient beyond a CBC, measuring the exact blood albumin concentration, determining whether a disease is acute or chronic, and whether an infection is present. [5] Only plasma should be used, as fibrinogen (a β protein) is not present in serum. By observing the pattern of plasma proteins, a clinician can deduce what sort of process is occurring in the body. It does not provide a definitive diagnosis. Possible combinations include:

- low albumin only – chronic degenerative condition or poor husbandry
- elevated β only – acute inflammation
- elevated α and β – acute, severe inflammation/infection; reproductively active female
- elevated γ only – chronic inflammation or infection
- elevated β and γ – chronic-active inflammation (especially chlamydiosis)
- decreased albumen, rest elevated – severe chronic-active inflammation/infection; severe acute infection in a bird with a chronic condition
- decreased albumin, elevated γ – chronic, debilitating disease. [24, 25]

b *Enzymes*. These can be unique to certain cells, or they can occur in a variety of tissues. Elevations occur when a cell membrane is ruptured, allowing enzymes to leak into tissue fluid.[14] The enzymes commonly used in to diagnose liver disease in birds include:

- Aspartate aminotransferase (AST/SGOT). Found in liver and muscle predominantly. Elevations must be interpreted with caution, as muscle injury can cause elevations for several days
- Lactate Dehydrogenase (LDH) – not very liver specific, but persistent elevation with normal CK levels indicates liver disease
- Creatinine Kinase (CK) – elevated with muscle damage, and is used primarily to distinguish between muscle-related and liver-related elevations in AST.
- Glutamate Dehydrogenase (GDH) – very liver specific, but not very sensitive, as severe liver necrosis must be present to cause elevations. [26,27]
- Gamma Glutamyl Transferase (GGT) – also liver specific, but not sensitive. It has been shown to elevate in cases of biliary carcinomas associated with Internal Papilloma Disease.[14, 24, 25]

Enzyme elevations must be interpreted with caution, as there is no single enzyme assay specific for avian liver disease. Bilirubin, ALP and ALT, widely used in mammalian medicine, are of limited usefulness in avian medicine.

c *Cholesterol* may be increased or decreased with liver disease. [28]

d *Glucose* levels may decrease with liver disease, as liver glycogen may not be available for glucose synthesis.

iii) Urinalysis

Polyuria is always an indication for urinalysis. Mammalian test strips can be used, but bilirubin is rarely positive, and biliverdin is not detected. Urine can be collected with a microhaematocrit tube, and should not be exposed to direct sunlight, as this can convert bilirubin to biliverdin. Sediment examination for the presence of casts and microorganisms is useful for differentiating renal disease from other causes of polyuria.

iv) Abdominocentesis

Any ascitic fluid should be assessed to determine if it is a transudate or exudate, and it's cellularity determined. Ascites arising from liver disease is usually a modified transudate.[2]

v) Hepatic function tests

Although the tests described above can be used to detect damage to the liver, they are relatively insensitive, and give little indication of the liver's functioning. A variety of tests are available to assess liver function, giving a more sensitive indicator of liver disease. Earlier tests, such as clearance of Indocyanine Green, while providing valuable information, are difficult to perform in a practice setting. Two relatively new function tests are bile acid levels and galactose clearance.

Bile acids are excreted from the liver in bile. They are resorbed in the small intestine, and are cleared from the circulation by the liver for recirculation. In fact, some 90% of bile acids are recirculated, the liver produces the rest.[5] Because of this efficient recycling, only a small amount of bile acids appears in the systemic circulation. Elevated bile acids therefore indicates decreased hepatocellular uptake of bile acids, and is thus a sensitive indicator of decreased liver function.[29,30,31,32] Jaensch[10] showed however that an 18% loss of liver tissue did not cause elevations in bile acids, so a normal bile acid level should not be taken to indicate a healthy liver.

Galactose clearance tests have been used in human medicine for many years, but it is only recently that attention has turned to their use in avian medicine. Galactose single-point concentration at 80 minutes after administration may prove to be a simple test for liver function. Galactose clearance tests have shown the capacity to detect the loss of as little as 13% - 18% of the liver mass.[10]

Diagnostic Imaging.

Radiography and, more recently, ultrasonagraphy are frequently used diagnostic tools employed by avian veterinarians to examine the liver without invading the abdominal cavity.

It is generally agreed that anaesthesia of the patient is advisable for good quality radiography. Two views are usually taken – a lateral and a ventrodorsal view. Positioning is important; on the lateral view the two acetabulae should be superimposed; and on the ventrodorsal view the centre of the

sternum (seen as a dark line) should be superimposed on the vertebrae. Both the size of the liver and the displacement of nearby organs should be examined.

On the lateral view the liver should not extend past the end of the sternum, and the proventriculus should slope down towards the ventriculus at an angle of 30°-45°. There should be little or no space between the heart and the liver. On the ventrodorsal view the liver shadow should not extend past a line joining the shoulder and acetabulum. Care must be taken in interpreting this view that the cardiac shadow or the proventriculus is confused with liver.

Ultrasonography offers several advantages over radiography, in that it allows examination of the internal structure of the liver, as well as examination of the nearby heart and pericardium, spleen and gastrointestinal tract. The avian liver is homogenous, finely granular, and contains transverse and longitudinal blood vessels throughout the parenchyma. The gall bladder, when present, lies to the right of the midline. Changes in echogenicity and size of the liver should be noted. [33,34]

Endoscopy and biopsy.

After using clinical pathology and diagnostic imaging to focus in one the liver as the source of the patient's problem, the next step is to accurately assess the aetiology and pathophysiology of the disease process. To do this requires invasive technology – endoscopy to visually assess the liver, and a biopsy to examine the histological basis of the problem. While many clients may not accept or permit these steps, the clinician needs to be aware that, in many cases, failure to do so can only allow empirical treatment of a "liver problem".

Techniques for endoscopy and biopsy have been described in several papers.[10, 22, 25, 28,35,36] Several approaches have been described; through an incision behind the caudal ribs on either side; [10] an approach through the caudal thoracic air sac; [35, 36] or through a ventral midline incision.[35, 36] Generalised liver conditions may be diagnosed by a biopsy along a hepatic border but more localised lesions should be biopsied directly. Bleeding is rarely reported as a problem, but Jaensch[10] used absorbable gelatin sponge (Gelfoam. The Upjohn Company, Kalamazoo, MI, USA) to successfully control haemorrhage after hepatectomy. Fine-needle aspirate biopsy of the liver has been described, [34] and may be an alternative to biopsy in some cases.

Treatment of liver disease.

Treatment of an avian patient with confirmed liver disease should have three objectives:

a. support the patient and correct abnormalities caused by the liver disease;
b. treat the specific condition; and
c. create an environment within the liver most favourable to regeneration of normal liver tissue.

vi) Patient support

Birds clinically affected with liver disease may be suffering from any combination of the following conditions: dehydration; anorexia, weight loss; hypoglycaemia; hepatic encephalopathy; anaemia; septicaemia; dyspnoea (enlarged liver and/or ascites); bleeding disorders; and diarrhoea. These complications must be dealt with by the clinician if the patient is to recover quickly, or even survive.

Fluid therapy is often an important part of patient maintenance, especially in cases of acute liver disease. Balanced isotonic solutions can be given by intravenous, subcutaneous or intraosseous routes. Numerous papers[37] give formulae for the calculation of fluid requirements, but in practical terms the clinician should aim to give 10% of the patient's bodyweight daily for at least 3 days, then 5% for each day after until fluid therapy is no longer required. If the patient is hypoglycaemic, 5% dextrose can be added to the fluids.

Anaemic patients may benefit from homologous blood transfusions or colloidal fluids. Iron dextran and Vitamin B are often given to anaemic patients, but care should be taken if the patient is suspected of having iron storage disease.[37]

Anorexic patients need to be fed, but there is some controversy over what should be fed. Low protein diets are usually recommended to minimise the workload on the liver. [37,38] However, work in mammalian medicine suggests that this may not be the case. Low protein levels are of little advantage to debilitated patients in a catabolic state. Inadequate dietary protein will result in catabolism which, through the metabolism of amino acids, can increase ammonia levels in the blood, contributing to hepatic encephalopathy. [8,39] Patients not showing evidence of hepatic encephalopathy should not be restricted in dietary protein; in fact, it may need to be increased slightly. Patients with encephalopathy will need a restricted protein diet until the signs have abated, after which their protein tolerance may be improved by the use of agents such as lactulose and psyllium.[8, 39]

Diets high in simple and complex carbohydrates (such as vegetables, rice and pasta) offer many advantages to patients with liver disease. Vegetable protein appears to lack many encephalopathic components; the higher fibre alters the intestinal flora to minimise ammonia production; carbohydrate metabolism is useful for hypoglycaemic patients; and insoluble fibre (eg psyllium) binds many endotoxins and noxious bile acids.[8] Fat levels in the diet can be left untouched unless cholestasis causes a maldigestion problem with subsequent diarrhoea, or in cases of hepatic lipidosis.

Vitamin supplementation, especially the water-soluble vitamins, may be of some benefit. Vitamin E may have a role as a free radical scavenger. Vitamin K may be useful if a coagulopathy exists. Vitamins A and D should be minimised. Vitamin A is stored in the liver, and excess can lead to hepatotoxicity. Excessive Vitamin D may lead to tissue calcification.[8]

Patients with signs of hepatic encephalopathy need to be handled carefully. Decreased dietary protein and increased dietary fibre can help to reduce the production of ammonia. In mammals, metronidazole and neomycin are used to as reduce the bacterial flora in the intestinal tract, thus decreasing ammonia production. Diluted apple cider vinegar in the drinking water may achieve a similar result. Lactulose can also help by decreasing the pH in the intestinal tract (causing a decrease in bacterial flora) and by causing a cathartic effect, cleansing the intestinal tract of many endotoxins and metabolic byproducts. As the patient's neurological wellbeing improves, lactulose and fibre can be used to increase the tolerance for dietary protein, allowing the increased levels necessary for the liver to regenerate and the catabolic state to be reversed.

Birds with dyspnoea need careful evaluation (eg radiography) to determine if the problem is hepatomegaly or ascites. Birds with ascites can benefit from careful coeliocentesis or the use of furosemide.[37]

The use of Vitamin K and whole blood transfusions should be considered if a coagulopathy exists. This is particularly important if the clinician is considering endoscopy or surgery.

vii) Treat specific condition

Although the clinician should strive to determine the aetiological agent involved in the disease process, it must be recognised that this is not always possible. Where an aetiological agent is identified, every effort should be made to eliminate it.

i) Nutritional/Metabolic

- Amyloidosis. Therapy for amyloidosis is aimed at correcting the underlying problem. Colchicine has been used in dogs to minimise further deposition, and may be of use in birds.[40,41] Other treatments used in humans and dogs have included immunosuppressive therapy, chemotherapy and DMSO (oral or s/c). No reliable treatment has been shown to work in all cases, and success is limited.[41]

- Hepatic lipidosis. Hepatic lipidosis in birds is most commonly due to the feeding of a high fat – low protein diet, where the fat becomes the major source of calories. All seed diets are a typical example of this sort of diet, but hepatic lipidosis occurs in most avian species eg James et al [15] reported lipidosis in a Barred Owl (*Strix var*ia) receiving an excessive number of mice in its diet. Treatment requires a reduction of dietary fat and an increase in dietary protein, as well as the provision of carbohydrates to replace fat as the main source of calories. Anorectic patients may need force feeding with such a diet until their catabolic state is reversed. Protein should not be restricted unless encephalopathy is present. [40, 41] Fluid therapy will be necessary for anorectic patients. Vitamin E (as an anti-oxidant) and B complex vitamins may also be beneficial.

- Iron storage disease. Most cases of iron storage disease are believed to be associated with a high iron diet. Treatment consists of feeding a low iron diet, minimising the absorption of iron from the intestinal tract, and reducing the level of iron in the body. As the ascorbic acid found in citrus fruit reduces the ferric ion (Fe^{3+}) to the more easily absorbed ferrous ion (Fe^{2+}), citrus fruit should be eliminated from the diet. [37] Commercial diets for susceptible species (Ramphastidae and mynahs) are now made with low iron levels (<100 ppm). Tannin added to the diet also binds iron in the intestine, reducing absorption. Iron levels in the body are reduced by weekly phlebotomy (1% bodyweight) and chelation therapy with deferoxamine. [37, 40]

ii) Toxic.

If a toxin is suspected of causing liver disease, steps should be taken to prevent further access to the toxin, remove any from the gastrointestinal tract and skin, and treating with an antidote if available. The type of toxin will determine the treatment.

iii) Parasitic

Drugs used to treat hepatic protozoan infections are the same as used for intestinal or systemic infections. See Table 1 for suitable drugs and dose rates.

Trematode infections are often difficult to treat. Praziquantel has been shown to reduce egg laying, but may not eliminate the parasite itself. Albendazole has been shown to eliminate *Fasciola hepatica* infections in emus.[37]

iv) Infectious.

Bacterial, fungal, viral, mycobacterial and chlamydial infections all have different treatments, according to the isolate and its sensitivity. Table 1 lists several drugs that may be useful treating an infectious hepatopathy.

v) Neoplastic

Up until recently hepatic neoplasia has been considered untreatable. Recent work [42,43,44] suggests that some neoplasms may well respond to chemotherapy, and drugs such as carboplatin and cisplatin are been trialed for their efficacy.

b. *Allow regeneration of normal liver tissue*

Given the liver's ability to regenerate, treatment to maintain the acinar structure and minimise fibrosis will have a positive effect on patients with liver disease. Several drugs have been trialed in mammals to achieve these aims, and show potential in avian medicine.

Ursodeoxycholic acid (UDCA) is used as an adjunct in the treatment of cholestatic and necroinflammatory liver disorders. Its use as a single agent therapy in mammals is relatively ineffective. Some of its effects include:

- Modifying the spectrum of noxious bile acids accumulating in the liver and blood of liver patients, thus minimising their toxic effect on hepatocytes
- A direct cytoprotective effect
- Minimising the recruitment of hepatocytes and biliary epithelium into an inflammatory process.

Because UDCA is detected in bile acid assays, it will maintain elevated bile acid levels. Although clinical improvement is noted in many patients, histologically little effect is seen.[39] UDCA remains an unproven, but potentially useful, tool in the treatment of avian liver disease.

Colchicine is used as an antifibrotic drug, although it does not appear to restrict the development of fibrosis. It is used concurrently with UDCA. Its effects include:

- induction of collagenase activity
- anti-inflammatory effect
- facilitates excretion of hepatic copper. [39]

Silibinin, the extract from milk thistle, is frequently recommended as a therapy for avian disease. To date, there are no proven benefits in its use, but experimental work in mammals indicates it may have several effects:

- antioxidant
- enhances protein synthesis and hepatocellular regeneration
- protective effect against hepatotoxins
- suppresses fibrogenesis
- promotes fibrolysis

Conclusion

Clinicians should no longer be content to merely diagnose "liver disease" in an avian patient. With improved diagnostics and endoscopic biopsy, it is now possible to more accurately diagnose the aetiology, or at least the process occurring, within the liver. This enables a more specific therapy. Work been done in mammalian and human medicine is showing several drugs that have the potential to improve success rates in treatment.

Drug	Dose	Route	Mode of Action	Comments
Acyclovir	80 mg/kg TID	PO	Herpesvirus (Pacheco's)	Works better on in-contact birds rather than those already affected
Albendazole	10 mg/kg	PO	Trematodes in emus	
Amoxicillin with clavulinic acid	50 mg/kg BID	IM	Antibacterial	
Colchicine	0.04 mg/kf SID	PO	Anti-fibrotic; anti-inflammatory	May cause vomiting
Desferoxamine	100 mg/kg SID	SC	Chelates iron	
Dimetridazole		PO	*Histomonas, trichomonas*	Toxic if overdosed
Doxycycline	100 mg/kg weekly 25 mg/kg	IM PO	Chlamydia	May cause vomiting in macaws
Enrofloxacin	10-15 mg/kg	IM	Antibacterial	
Fluconazole	2-5 mg/kg SID	PO	Antifungal	
Furosemide	0.15-2mg/kg SID-BID	IM, SC, PO	Reduce ascites	
Itraconazole	5-10 mg/kg BID	PO	Antifungal	May cause depression in African greys
Lactulose	0.2 ml/kg BID-TID	PO	Reduces absorption of ammonia from intestine	Can cause diarrhoea
Praziquantel	10-20 mg/kg SID for 10-14 days	PO	For trematode infection	
Piperacillin	100 mg/kg TID	IM	Antibacterial	
Ronidazole	6-10 mg/kg SID 6 days	PO	For protozoal infections	
Silibinin (Milk Thistle)	4-15 mg/kg	PO	Antioxidant; enhances protein synthesis and hepatocellular regeneration; protective effect against hepatotoxins; suppresses fibrogenesis promotes fibrolysis	
Toltrazuril			For *Atoxoplasma* infections	
Ursodeoxycholic acid	10-15 mg/kg SID	PO	Cytoprotective; reduces involvement of hepatocytes and biliary epithelium in inflammatory process; changes mix of bile acids top eliminate toxic bile acids from liver	Toxic to rabbits and Rhesus monkeys; no toxicity trials in birds as yet, but a limited number of cases suggest it may be useful

Table 1. Drugs used in the treatment of liver disease

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