THE DIAGNOSIS AND MANAGEMENT OF ACUTE LIVER FAILURE IN DOGS AND CATS

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This article reviews the critical care management necessary to optimize outcome in cases of potentially reversible acute liver failure in dogs and cats. Because of the ambiguity of the phrase "acute liver failure," it is useful to initially consider the patient population with which we are dealing. Acute liver failure is the clinical syndrome that results from rapid loss of liver function to the point that there is insufficient hepatic parenchyma to maintain synthetic and excretory homeostasis. The potential for regaining life-sustaining liver function is of paramount importance in deciding whether to continue the intensive, supportive therapy necessary in these cases. A clinically relevant classification of liver failure as potentially reversible or irreversible, regardless of duration of clinical signs, would seem reasonable.

There is no consensus on the duration of what constitutes "acute," and there is not always a correlation between the duration of clinical signs and the reversibility of the underlying pathology. Acute liver failure has been used synonymously with the histopathologic entity of acute hepatic necrosis. Hepatic infiltration by lipid as in feline hepatic lipidosis, inflammatory cells as in feline infectious peritonitis, or neoplastic cells as in lymphoma, however, can also result in acute failure of liver function. The diagnostic evaluation of a patient in liver failure, up to the point of a definitive histopathologic diagnosis, usually takes several days. In practical terms, this means that, regardless of whether the underlying cause is acute or chronic or potentially reversible or
irreversible, supportive care of the patient with liver failure is necessary until a definitive histopathologic diagnosis is available.

Specific clinical criteria for the diagnosis of liver failure, as opposed to dysfunction or injury without clinically apparent dysfunction, should also be considered. In human medicine, the combined presence of coagulopathy and hepatomegaly with an acute hepatic disease is necessary to warrant a diagnosis of liver failure. Similar criteria would seem reasonable in veterinary medicine when used in conjunction with appropriate clinical evidence. Treatment of acute liver failure in dogs and cats is largely supportive and requires specific attention to each functional derangement. With the current advances in veterinary critical care, improved medical and technical management of the patient with acute liver failure should reduce both morbidity and mortality.

ETIOLOGY

Because of the large functional reserve of the liver, loss of more than 70% of the hepatocellular mass is required before clinical signs of acute liver failure become apparent. Rapid and extensive loss occurs with diffuse severe lipidosis, cellular infiltration, and acute hepatocellular necrosis. Underlying etiologies include metabolic, neoplastic, infectious, or toxic processes, and the most commonly reported causes of acute liver failure in dogs or cats are listed in Table 1. More extensive lists of potential causes of acute liver failure are available in the veterinary and human medical literature. Agents that cause hepatocellular necrosis may or may not result in acute liver failure, depending on the severity and extent of the injury. Clinical experience suggests that acute liver failure is more common in cats than in dogs.

Hepatotoxins

Chemical Agents

Although the list of hepatotoxic chemicals is extensive, chemical intoxication is a relatively uncommon cause of acute liver failure in small animals. Ingestion of pine oil, a phenol found in household disinfectants, may cause fatal hepatocellular necrosis in cats. The potential hepatotoxicity of biotoxins is being recognized increasingly. Mycotoxicosis after eating moldy foodstuff or after the ingestion of blue-green algae growing on the surface of standing water may result in hepatocellular necrosis. Ingestion of cycad seeds has also been reported to cause acute liver failure in dogs.

Drugs

The prevalence of drug-related hepatotoxicity is probably higher than is currently recognized because of the difficulty in satisfactorily
establishing a cause and effect relationship. In humans, drug reactions may be responsible for up to 25% of cases of fulminant hepatic failure.93 The majority of drug-related hepatotoxicities reported in veterinary medicine are anecdotal reports involving additional drugs and clinical procedures, as well as the suspected causative agent. Inhalational anesthetics have been implicated as causes of acute liver failure, e.g., methoxyflurane in dogs68, 91 and halothane in a dog34 and a snow leopard.28 Although no clinical studies have been performed in small animals, hepatotoxicity after anesthesia in small animals undoubtedly is extremely rare. Acute hepatic necrosis and liver failure may occur in rare instances after diazepam therapy in cats.47 The authors are aware of seven cats in which diazepam therapy was associated with acute, fatal hepatic necrosis. Because therapeutic use of diazepam is extremely common, it is likely that this is an idiosyncratic reaction rather than a predictable phenomenon. Phenytin has been reported to cause acute hepatic necrosis when used in conjunction with other anticonvulsant medications.14, 65 This highlights the fact that additive or synergistic hepatotoxic effects can occur between medications, which may cause no clinically significant problems when used alone.

Hepatotoxicity is widely recognized after treatment with the heartworm adulticide thiacetarsemide46 and has also been reported with mebendazole.72 Anecdotal reports have implicated trimethoprim/sulfa

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Table 1. CAUSES OF ACUTE LIVER FAILURE IN THE DOG AND CAT

<table>
<thead>
<tr>
<th>Chemical Agents</th>
<th>Drugs</th>
<th>Infectious Agents</th>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arsenic</td>
<td>Anesthetics/Sedatives</td>
<td>Viral</td>
<td>Neoplastic</td>
</tr>
<tr>
<td>Carbon tetrachloride</td>
<td>Halothane</td>
<td>Feline infectious peritonitis</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>Chlordane</td>
<td>Methoxyflurane</td>
<td>Infectious canine hepatitis</td>
<td>Other</td>
</tr>
<tr>
<td>Chlorinated hydrocarbons, naphthalenes and biphenyls</td>
<td>Diazepam (cats)</td>
<td>Canine herpesvirus</td>
<td>myeloproliferative disorders</td>
</tr>
<tr>
<td>Chloroform</td>
<td>Medications</td>
<td>Bacterial</td>
<td>Other</td>
</tr>
<tr>
<td>Dieldrin</td>
<td>Acetaminophen</td>
<td>Clostridiosis</td>
<td>Acute crisis of copper storage disease</td>
</tr>
<tr>
<td>Dimethylnitrosamine</td>
<td>Apminidine</td>
<td>Leptospirosis</td>
<td>Feline hepatic lipodisosi</td>
</tr>
<tr>
<td>Heavy metals: copper, iron, mercury</td>
<td>Methotrexate</td>
<td>Tyzzer's disease</td>
<td>Massive ischemia</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>Nalidixic acid</td>
<td>Fungal</td>
<td></td>
</tr>
<tr>
<td>Pine oil</td>
<td>Phenytin</td>
<td>Histoplasmosis</td>
<td></td>
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<tr>
<td>Selenium</td>
<td>Primidone</td>
<td>Protozoal</td>
<td></td>
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<tr>
<td>Tannic acid</td>
<td>Tetracycline</td>
<td>Toxoplasmosis</td>
<td></td>
</tr>
<tr>
<td>Biotoxins</td>
<td>Thiacetarsemide</td>
<td>Metazoal</td>
<td></td>
</tr>
<tr>
<td>Mycotoxins</td>
<td>Tolbutamide</td>
<td>Dirofilariasis</td>
<td></td>
</tr>
<tr>
<td>Blue-green algae toxin</td>
<td>Trimethoprim/sulfa</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>Amanita mushroom toxin</td>
<td></td>
<td>Canine acidophil hepatitis</td>
<td></td>
</tr>
<tr>
<td>Zamia floridana seeds (cycads)</td>
<td></td>
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</tr>
</tbody>
</table>

Table content continues with further details on chemical agents, drugs, infectious agents, and miscellaneous categories.
as a cause of hepatocellular damage dogs. Fatal hepatotoxicity has been reported after treatment with nalidixic acid in two pregnant bitches and with tetracycline in another. The antifungal agent ketoconazole is a documented cause of hepatocellular necrosis in humans and has been suggested as a potentially hepatotoxic drug in dogs. As its use for the treatment of canine hyperadrenocorticism becomes more widespread, the potential for hepatotoxicity may become more apparent, especially because these patients may already have subclinical hepatic disease. The authors are aware of one case of icterus and elevated hepatic enzymes after ketoconazole therapy for canine hyperadrenocorticism. The urinary analgesic phenazopyridine can cause Heinz body anemia and hepatocellular necrosis in cats. Acetaminophen has a greater potential for hepatotoxicity in dogs than in cats. Hepatotoxicity has also been reported in dogs receiving antineoplastic chemotherapy.

**Infectious Agents**

Infectious agents are an unusual cause of acute liver failure in veterinary medicine.

**Viral Infections**

Because of the effective vaccines available against Canine Adenovirus I, acute liver failure resulting from infectious canine hepatitis is rare. Feline infectious peritonitis may present as acute liver failure as a result of massive, pyogranulomatous, inflammatory cell infiltration of the liver.

**Bacterial Infections**

Acute liver failure caused by bacterial infection is rare, but it may occur in clostridial hepatitis, Tyzzer’s disease (Bacillus piliformis), and leptospirosis involving the icterohaemorrhagiae and grippotyphosa serovars of Leptospira interrogans.

**Fungal Infections**

Of the systemic fungal infections, histoplasmosis has been suggested to be the most likely to cause serious liver disease. The relative incidence of fungal liver disease obviously varies with geographic location.

**Parasitic Infections**

Dirofilariasis may result in hepatic necrosis caused by hepatic congestion and ischemia in caval syndrome or secondary to thiacetarsemide treatment. Disseminated toxoplasmosis is a potential protozoal cause of acute liver failure.
Canine Acidophil Cell Hepatitis

This entity, which was reported in the United Kingdom in 1985, was suggested to be caused by an infectious organism on the basis of its transmissibility via serum and tissue homogenates from affected dogs. The experimentally induced disease caused a range of clinical signs, varying from acute liver failure to chronic liver disease.

Neoplastic Disease

One of the most common causes of acute liver failure is massive infiltration with neoplastic cells in the multicentric form of feline lymphoma. Although the hematopoietic cell neoplasms have the greatest potential for massive hepatic infiltration, any primary or metastatic tumor may cause liver failure if sufficient hepatic parenchyma is destroyed. Hepatic neoplasia is discussed in detail elsewhere in this issue.

Metabolic Disease

Feline Hepatic Lipidosis

In the authors’ experience, feline hepatic lipidosis is one of the most common causes of acute, potentially reversible liver failure encountered in clinical practice. Intracellular accumulation of lipid results in progressive hepatocyte dysfunction culminating in liver failure. Recent studies have demonstrated the potential reversibility of this condition with long-term, intensive management and persistent, aggressive, nutritional support. Feline hepatic lipidosis is discussed elsewhere in this issue.

Copper Storage Disease

An acute crisis of copper-associated liver disease in Bedlington Terriers can manifest as acute liver failure. Affected dogs are usually young to middle-aged and may have no previous history of liver disease, although long-term hepatic accumulation of copper has been occurring. A small proportion of affected dogs may have concurrent copper-associated hemolytic anemia. Copper hepatopatheses are discussed in a separate article in this issue.

Miscellaneous Causes of Acute Liver Failure

Massive Ischemia

Ischemia resulting from arterial or venous occlusion can cause hepatocellular necrosis and liver failure. Thrombosis, neoplasia, or other mass lesions, right-sided heart failure, and vascular anomalies may all occasionally result in hepatic ischemia.
DIAGNOSIS OF ACUTE HEPATIC FAILURE IN DOGS AND CATS

When a sick dog or cat initially presents to a veterinarian, a diagnosis of liver disease may not be immediately obvious. Owner complaints in animals with liver disease are often vague and commonly similar to findings in disorders of other organ systems, e.g., gastrointestinal or neurologic disorders. Even icterus is not specific to disease of the liver. The clinician, therefore, uses a number of tools (described later) to identify and confirm that failure of hepatic function exists. Because many different disorders of the liver may result in failure, further investigation is necessary to determine the cause of the disease and the potential for treatment and recovery.

Furthermore, because the liver has great reserve capacity, many animals with liver disease are asymptomatic until extensive destruction of the hepatic parenchyma has occurred. Thus, the duration of clinical signs reported by the owner may be considerably less than the total duration of the disease syndrome. The clinician will evaluate many animals with apparently acute onset of liver disease only to find that the disease has probably been ongoing for a significant period of time.

History

The most common clinical signs in dogs and cats with acute liver failure include weakness, depression, or collapse; gastrointestinal tract signs such as anorexia, vomiting, or diarrhea with or without blood; or neurologic signs attributable to hepatic encephalopathy. Some dogs and cats may also manifest miscellaneous signs such as polydipsia and polyuria or excessive hemorrhage. Observant owners may also recognize the presence of icterus in mucous membranes or sclera. If acute hepatic necrosis is suspected, the clinician should make every attempt to elicit information about possible exposure to drugs such as trimethoprim/sulfa or acetaminophen, infectious agents such as leptospirosis, or toxins such as those produced by blue-green algae. Further, the clinician must make attempts to determine whether chronic illness has been present for some time, such as might be manifested by anorexia and weight loss in the cat with hepatic lipidosis.

Physical Examination

Physical examination findings in animals with hepatic failure are often nonspecific. Icterus caused by acute hepatic failure, for example, must be distinguished from that occurring as a result of an acute hemolytic crisis or post-hepatic obstruction. Neurologic signs are rarely specific, although worsening of neurologic signs after ingestion of a meal can be a useful clue to the presence of hepatoencephalopathy. Palpation
of the abdomen may show the presence of organomegaly, cranial abdominal pain, or a peritoneal effusion, but once again such findings are not specific to liver disease. Cardiovascular collapse or shock may occur as a result of hemorrhage, sepsis, or fluid loss. Animals with severe acute hepatic failure may also be suffering from concurrent failure of other organ systems such as the renal or respiratory system, with clinical signs attributable to those systems.

Thus, a variety of physical examination and historical findings may lead the clinician to suspect acute hepatic failure. Occasionally, the practitioner is presented with a patient suffering from acute onset of icterus, hepatomegaly, hemorrhage, and neurological signs, but such easily diagnosed cases are few and far between. In most cases, further diagnostic evaluation is necessary to determine whether the liver is the culprit and to rule out disease of other organ systems.

**Clinicopathologic Findings**

The next step in evaluation of a patient with suspected liver disease is to establish a clinicopathologic database. This evaluation is discussed in detail by Dr. Sharon Dial (this issue), but is briefly outlined here.

**Complete Blood Cell Counts**

Complete blood cell counts are often nonspecific. Anemia occurs commonly due to hemorrhage or failure of erythropoiesis and must be carefully distinguished from hemolysis in the icteric patient. Regenerative anemia and icterus, in the presence of a normal plasma protein concentration, should lead the clinician to suspect hemolysis rather than liver failure. White blood cell counts may be normal, high if a severe inflammatory process is occurring, or low in the presence of sepsis or neutrophil sequestration. Platelet counts may be low, especially if consumption is occurring via hemorrhage, thrombosis, or disseminated intravascular coagulation, and platelet function is often abnormal in patients in fulminant hepatic failure.69-70, 79

**Serum Chemistry Panel**

Serum chemistry panel results can be extremely helpful in these patients. Cellular leakage enzymes such as alanine aminotransferase, aspartate aminotransferase, and lactate dehydrogenase are elevated if hepatic cell damage or destruction occurs, although they provide no information about liver function. Profound elevation of plasma alanine aminotransferase activity is highly suggestive of severe hepatic destruction, with close correlation between serum enzyme activity and histopathologic changes.96 The half-life of these enzymes is short (approximately 24 hours), with a decrease in serum values occurring rapidly after an insult. It is important to recognize that mild-to-moderate elevation of the leakage enzymes is also a nonspecific finding in many animals with diverse disorders including shock. Elevations in serum activities of
alkaline phosphatase and gamma GT are observed in association with cholestatic disorders that may range from pancreatitis to cholangiohepatitis. Once again, serum activities of these enzymes may also be increased by other, extrahepatic, disease processes or induced by drugs such as corticosteroids. Moderate elevations in cellular leakage or cholestatic enzyme activities are therefore non-specific; they do not indicate the presence of severe liver disease, much less liver failure.

Although liver enzymes do not provide information about liver function, the rest of the serum chemistry panel provides some useful information in this regard. In evaluating the panel, we can obtain information about the synthetic activity of the liver (albumin, cholesterol, glucose, and urea nitrogen), and the ability of the liver to clear toxic or waste substances from the bloodstream (bilirubin and ammonia). If decreases are found in many or all of the substances synthesized by the liver, with concomitant increases in accumulated waste products such as bilirubin and ammonia, clear evidence exists of the presence of liver failure. A word of caution: if the initial serum chemistry panel is obtained when the animal is dehydrated, hemoconcentration may lead to artificial elevation of serum concentrations of albumin, urea nitrogen, and cholesterol. A second chemistry panel obtained after rehydration may demonstrate a different and more realistic picture of hepatic synthetic and waste clearance function.

**Urinalysis**

The urinalysis should be part of the initial database of any animal with serious metabolic disease. Although it provides limited information about the status of the liver, the finding of biurate crystals or calculi is strong evidence for the presence of a portosystemic shunt, and bilirubin crystals may confirm the presence of excessive amounts of urinary bilirubin. In the animal with acute hepatic necrosis, however, the urinalysis is of more importance in evaluating the extent of renal damage as a result of circulatory disturbances and vasoactive amine release. The finding of excessive numbers of cellular or granular casts or isosthenuria should alert the clinician to possible concurrent renal insufficiency or failure, with a resultant grave prognosis.

**Coagulation Studies**

Coagulation studies are also important, because most of the coagulation factors are synthesized in the liver. Coagulation should always be evaluated, both as a prognostic indicator, and to assess the safety of biopsy techniques. Variable prolongation of both prothrombin time (PT) and activated partial thromboplastin time (PTT) occurs in hepatic failure.\(^{3-4,32}\) Importantly, normal PT and PTT do not eliminate the possibility of hemorrhage at the time of biopsy. Failure of synthesis of coagulation factors is not the only cause of hemorrhage in animals with acute hepatic failure, because concurrent disseminated intravascular coagulation (DIC) may be triggered by massive liver tissue destruction,
endotoxemia, and associated circulatory disturbance. DIC may result in a bleeding diathesis caused by consumption of coagulation factors and platelets. Evaluation of coagulation, therefore, should also include assessment of platelet count, quantitation of serum fibrin degradation products (FDPs), and evaluation of a blood smear for the presence of red blood cell fragments. If the platelet count is decreased, FDPs are elevated, and/or red blood cell fragments are found, DIC may be the cause of prolongation of the coagulation times, rather than failure of synthesis of coagulation factors. A much more grave prognosis is warranted in such patients.

**Liver Function Testing**

Once hepatic failure is suspected based on clinical findings and the presence of abnormalities in the serum chemistry panel, quantitation of the extent of the abnormality may be necessary. A variety of provocative tests of liver function are available, including pre- and postprandial serum bile acid quantitation, bromosulphthalein excretion, indocyanine green excretion, or ammonia tolerance testing. These tests are discussed in detail elsewhere in this issue (see Dial). Of the available methods of assessment of hepatic function, serum bile acid quantitation has become the most widely used, by virtue of its reproducibility, ready availability, and the stability of bile acids in storage. Accurate quantitation of hepatic function is useful from a prognostic standpoint and also as a means of objectively assessing the progression of disease and response to therapy. It is important to recognize, however, that function testing is not useful for the etiologic diagnosis of hepatic failure, but instead only quantitates the extent of disease.

**Imaging Techniques**

The next step in the diagnosis of apparently acute liver failure is to determine whether morphologic abnormalities exist in the liver, by means of noninvasive imaging techniques, which are discussed in more detail elsewhere in this issue (see Partington). Imaging techniques can be extremely useful for distinguishing animals with acute hepatotoxicity from those that have acute manifestation of a chronic disease. It is important to note, however, that the finding of abnormalities by use of these imaging techniques is not diagnostic in itself. Further evaluation by means of histopathology is required to make a definitive diagnosis.

**Plain Abdominal Radiographs**

Dogs and cats with acute hepatic necrosis may have visible hepatomegaly on plain radiographs of the abdomen, or the liver may be within normal size limits. The finding of a small liver is not consistent with acute hepatic necrosis.
Abdominal Ultrasound

A variety of ultrasonographic findings may be noted in animals with acute hepatic toxicity, from normal to diffusely mottled, or most commonly decreased echogenicity. The presence of one or multiple hepatic masses, a very small liver, or a visible portosystemic shunt, may be very useful diagnostic findings that tend to direct away from acute hepatic failure.

Other Imaging Techniques

Several other imaging techniques are available, including nuclear scintigraphy and computed tomography. These techniques may be appropriate for use in some animals with acute hepatic failure, but are only readily available in referral institutions.

Ancillary Diagnostic Testing

Once a clinicopathologic and morphologic database has been obtained, a variety of other diagnostic tests may be indicated in individual patients before biopsies are undertaken. Such ancillary tests may either lead towards a clinical diagnosis of the etiology of the liver disease or may identify and diagnose disease of other organ systems.

Thoracic Radiographs

Thoracic radiographs may be obtained if there is any suspicion of abnormality of the respiratory system. Recumbent or comatose animals are prone to the development of aspiration pneumonia and atelectasis, and documentation of its extent is necessary for accurate prognostication. Animals with severe hypoproteinemia may develop pleural effusion or occasionally pulmonary edema as a result of decreased oncotic pressure. If there is any suspicion that neoplasia may be present, thoracic radiography should be performed early in the course of hospitalization to rule out the presence of metastatic disease.

Abdominal Paracentesis

Abdominal paracentesis is an important diagnostic tool whenever a peritoneal effusion can be palpated, detected on radiographs, or visualized on abdominal ultrasound. A small sample of peritoneal fluid can often be obtained by use of “four quadrant” paracentesis, performed by gentle insertion of a needle through the abdominal wall into the peritoneal cavity and aspiration of fluid using an attached syringe. The fluid thus obtained should be analyzed by measurement of total protein on a refractometer, cell counts, cytologic evaluation, and possibly culture. Fluid analysis can provide useful clues to the etiology of disease. If fluid is present, a modified transudate or hemorrhage would be expected to occur in animals with acute hepatic necrosis. The finding of a pure
transudate suggests the presence of portal hypertension and is more compatible with long-term liver disease. Similarly, the finding of neoplastic cells in an effusion may be diagnostic. If an exudative process is present, the clinician should be concerned about the possible presence of peritonitis associated with pancreatitis, hepatic abscessation, or bile duct rupture.

**Specific Tests**

Specific tests for individual syndromes that might cause acute hepatic necrosis may also be extremely useful. Although assays are not often available for individual toxins, knowledge of the biology of a toxicity may allow the clinician to indirectly infer its presence. For example, the finding of large numbers of Heinz bodies and methemoglobin in an animal with acute hepatic failure is strongly suggestive of acetaminophen toxicity. Serologic testing may be appropriate for some infectious agents such as leptospirosis. If an immune-mediated toxic reaction to trimethoprim/sulfa drugs is suspected, the concurrent finding of swollen joints with a neutrophilic infiltrate in the joint fluid is highly informative. Such tests can be selected according to the index of suspicion in individual patients.

**Ruling Out Disease of Other Organ Systems**

In some cases, even if the diagnosis of primary hepatic disease has been confirmed, further diagnostic testing may be indicated to rule out concurrent disease of other organ systems. For example, gastrointestinal contrast studies or endoscopy may be indicated in animals with gastrointestinal tract hemorrhage. Similarly, if doubt exists that neurologic signs can all be attributed to hepatoencephalopathy, cerebrospinal fluid may be obtained, or specific techniques such as magnetic resonance imaging of the brain may be indicated.

**Histopathologic Diagnosis**

Although hepatic failure can be identified by noninvasive means, determination of the etiology of the disease is only possible by examination of histopathologic specimens. Even though biopsy is required for a definitive diagnosis, liver tissue samples are usually not obtained immediately at the beginning of hospitalization. Many of the diagnostic tests previously described can be obtained before and during stabilization of the critically ill patient with apparent acute hepatic failure. Biopsy, however, can be stressful and potentially dangerous, regardless of the technique used. Because the initial management of most patients is independent of the etiology of hepatic failure, biopsy should be delayed until the patient has been temporarily stabilized, if possible. Thus, biopsies are often obtained on the second, third, or fourth day of hospitalization. A definitive tissue diagnosis is indicated to establish an
accurate prognosis and to identify disorders that might require specific therapy such as hepatic lymphosarcoma or bacterial hepatitis. Hepatic biopsy techniques and their interpretation are discussed in detail elsewhere in this issue. The clinician may elect to simply obtain fine-needle aspirates for cytologic diagnosis, to perform a percutaneous biopsy blind or with ultrasound guidance, or to perform an exploratory laparotomy.

*Fine-needle aspirates* are the least invasive and can be performed safely in most patients, even in the presence of a mild coagulopathy. Such cytologic evaluation may be extremely useful, especially if it is diagnostic of neoplasia or lipid accumulation in hepatic cells. In the case of acute hepatic necrosis, however, fine-needle aspirates are unlikely to yield a specific diagnosis.

*Percutaneous needle biopsy* is a useful way of obtaining small samples for histopathologic examination. Blind insertion of the needle is possible, particularly if palpable hepatomegaly is present. This technique, however, may be associated with hemorrhage, even if a coagulopathy is not identified by screening coagulation tests. Further, blind insertion of the biopsy needle may not allow sampling of tissue from the most severely affected areas of the liver. In light of these drawbacks, needle biopsy guided and observed by use of ultrasound allows safer and more accurate sampling of liver tissue. Hemorrhage may still occur, but it can be minimized by the administration of fresh whole blood or plasma immediately before the biopsy procedure. Temporary pressure wrapping of the abdomen may also be useful for prevention of hemorrhage.

*Exploratory laparotomy* is the procedure most likely to provide a definitive answer regarding diagnosis. Samples may be obtained from visibly abnormal areas of the liver, and the biliary system and other organs can be carefully evaluated and biopsied if necessary. Paradoxically, hemorrhage is easier to control directly during a surgical procedure than during a percutaneous biopsy, and coagulation factors may be supplied by the administration of plasma. Particular care is advised during anesthesia of animals with hepatic failure, because they have a decreased ability to metabolize anesthetic agents, resulting in prolonged anesthesia and hypotension.

**APPROACH TO THE MANAGEMENT OF DOGS OR CATS WITH ACUTE HEPATIC FAILURE**

Once a tentative diagnosis of acute hepatic failure has been made based on clinical findings and initial diagnostic evaluation, aggressive management is often necessary. Many of these patients are critically ill and require intensive support of the liver and other organ systems. As previously noted, general therapy for hepatic failure is often instituted in an attempt to stabilize the animal, before biopsy samples are obtained to make a definitive diagnosis. Once a diagnosis has been reached, specific therapy can be begun if indicated, for example, antibiotic therapy for bacterial hepatitis, or chemotherapy for hepatic lymphosarcoma.

Because specific therapy and liver transplantation are unavailable
for most animals with acute hepatic necrosis, management relies on support of the animal until hepatic regeneration can occur. We therefore seek to support liver function by supplying substances such as glucose, albumin, and coagulation factors that are no longer being synthesized by the liver and by diminishing the production of toxic waste substances such as ammonia. Concurrently, by careful monitoring and attention to fluid, colloid, acid-base, and electrolyte balance, we hope to detect and prevent the occurrence of other major organ failure.

Therapy for such seriously ill patients can be divided into several major categories:

1. Support and monitoring of the major organ systems
2. Fluid therapy
3. General therapy for hepatic failure
4. Nutrition
5. Nursing care

Support of the Major Organ Systems

When caring for any critically ill animal, basic principles can be applied regardless of the cause of the illness. The four major organ systems that are prioritized are the cardiovascular, respiratory, renal, and neurologic systems. The clinician should assess each system, treat any disturbance, and monitor for progression or decompensation.9, 94

Cardiovascular System

Circulatory collapse and shock may occur in dogs and cats with acute hepatic failure because of hemorrhage, hypovolemia caused by fluid loss, and decreased oncotic pressure, or sepsis. Hepatic disease is known to cause increased susceptibility to infection. Impaired humoral1 and cell-mediated5 immunity and decreased Kupffer cell and reticuloendothelial function15 have been documented. Moreover, the animal with acute hepatic failure is exposed to sources of infection from multiple sites. Compromise of the gastrointestinal mucosal barrier may provide access to the body for gram-negative bacteria. Poor airway protective reflexes and recumbency may predispose the patient to bacterial pneumonia. Urinary retention or placement of a urinary catheter can increase the risk of urinary tract infection. Monitoring the cardiovascular system should include frequent assessment of heart rate and rhythm, pulse quality and blood pressure, mucous membrane color, and capillary refill time. Aggressive therapy for shock may be necessary, including judicious use of intravenous fluids, antibiotics, inotropes, and pressors.

Respiratory System

Respiratory failure is also possible and is most often associated with aspiration pneumonia and atelectasis. Other possible causes of respiratory failure in dogs and cats with acute hepatic failure include
pulmonary hemorrhage, acute permeability lung injury associated with sepsis, pulmonary thromboembolism, and pulmonary edema caused by low oncotic pressure or concurrent cardiogenic edema. Respirator function should be monitored by frequent auscultation and observation of the pattern of respiration. Mucous membrane color should also be assessed, but it is a relatively crude indicator of the extent of hypoxemia. Ideally, arterial blood gas analysis or pulse oximetry can be used to sequentially monitor respiratory function. Thoracic radiographs should be obtained early in the course of hospitalization and repeated as necessary.

Renal System

Acute oliguric renal failure may follow acute hepatic failure as a result of circulatory disturbances, endotoxemia, and DIC. If shock or hypotension occurs, decreased renal perfusion may lead to acute tubular necrosis and subsequent renal failure or insufficiency. Hepatorenal syndrome is a poorly understood form of functional renal failure seen in some people with fulminant hepatic failure, but has not been reported in small animals to date. Oliguria may also result from increases in intra-abdominal pressure associated with severe ascites. Renal function can best be evaluated by monitoring urine output. If there is any doubt about the adequacy of urine output, an indwelling urinary catheter should be placed in the urethra and connected to a closed collection system for accurate monitoring. Inadequate urine production (<1 mL/kg/hour) should be treated aggressively, with careful attention given to fluid therapy and blood pressure, osmotic diuretics such as mannitol (0.25–1 g/kg slow IV), renal vasodilators such as dopamine (continuous infusion at 2–3 µg/kg/minute), and diuretics such as furosemide. If renal perfusion or function is questionable, aminoglycoside antibiotics should be avoided because of their nephrotoxicity.

Neurologic System

Most dogs and cats with acute hepatic necrosis suffer from some degree of compromise of neurologic function as a result of hepatoencephalopathy (see later for management). Hepatic encephalopathy is a clinical syndrome of neurologic dysfunction resulting from severe loss of hepatic function. Although the multifactorial pathophysiology remains to be fully elucidated, hyperammonemia is probably the most important mediator of hepatic encephalopathy. Furthermore, because ammonia is the only mediator that can be assayed in a clinical setting, it is the only objective way to monitor response to treatment. Other factors thought to play a role in the development of hepatic encephalopathy are toxic substances such as mercaptans, short-chain fatty acids and phenols, altered neurotransmitter concentration or neurotransmitter receptor affinity, and false neurotransmitters. Hypoglycemia caused by diminished glycogenolysis, gluconeogenesis, decreased hepatic insulin metabolism, and sepsis, however, may
affect cerebral function seriously, and it is easily diagnosed and treated. In humans, cerebral edema is the most common cause of death after fulminant hepatic failure. Cerebral edema occurs because of the effect of toxins on neurologic cells (cytotoxic intracellular edema) or on the blood-brain barrier (vasogenic edema). Neurologic function should be monitored by serial neurologic examinations, and deterioration warrants aggressive management of hepatoencephalopathy and cerebral edema. Cerebral edema can be treated by elevation of the head and trunk to a 20-degree angle, avoidance of pressure on the jugular veins, mannitol administration (0.25–1 g/kg slow IV), and hyperventilation to decrease arterial carbon dioxide tension if necessary.

**Other Routine Monitoring**

Monitoring should include frequent measurements of body temperature and heating or cooling as necessary. Packed cell volume and total solids should also be monitored frequently to detect hemorrhage and as an assessment of fluid therapy. Hepatic function should be monitored serially by measurement of blood ammonia and glucose concentrations, and then by chemistry panels and coagulation assays as required.

**Fluid Therapy**

When considering fluid therapy for the patient with acute liver failure, it is important to differentiate between acute fluid therapy for resuscitation from hypotension, as opposed to chronic fluid therapy for water, electrolyte, and acid/base regulation. Hypoperfusion requiring aggressive volume loading is not uncommon in the animal with acute liver failure. Hemorrhage secondary to the hypocoagulable state, loss of intravascular fluid into the peritoneal cavity, osmotic diarrhea and diuresis, reduced colloid osmotic pressure, and sepsis may all contribute to hypoperfusion. When volume loading is necessary, the potential effects of aggressive fluid therapy on intracranial pressure, colloid osmotic pressure, and ascites formation should be considered.

Because fluid resuscitation using isotonic saline has been shown to elevate intracranial pressure, isotonic crystalloid solutions should be used with caution in this patient population. Although fluid resuscitation with hypertonic saline may limit the associated increase in intracranial pressure, sodium loading will predictably and significantly worsen the accumulation of ascitic fluid. Because albumin and hepatogenous globulins provide the majority of the plasma oncotic pressure, liver failure is associated with a hypo-oncotic state. Fluid resuscitation using isotonic crystalloid will further reduce colloid osmotic pressure. Reduced plasma oncotic pressure decreases plasma volume by allowing transudation into the interstitium and peritoneal cavity and potentially reducing renal tubular reabsorption. To avoid the potential complications associated with saline solutions, initial resuscitation with colloid is advisable. Because therapeutic doses of dextran 70 and hydroxyethyl...
starch have been shown to cause hypocoagulability, fresh frozen plasma should be the fluid of choice, if it is available in sufficient quantities. If red blood cells are required to maintain tissue oxygen delivery during volume loading, fresh, rather than stored, blood products should be used because of their lower ammonia content.

Hypokalemia is known to facilitate brain uptake of ammonia, thereby precipitating or worsening, hepatic encephalopathy. One of the most common reasons for the development of hypokalemia is the prolonged use of intravenous crystalloid solutions intended for extracellular fluid replacement, which have high sodium and low potassium concentrations. If mannitol or diuretics are being used, potassium losses will increase greatly. Therefore, it is important to monitor serum potassium concentration regularly and to provide supplementation as necessary. Because potassium supplementation may exacerbate hypoglycemia, serum glucose concentration should be carefully monitored.

In the authors' experience, hypernatremia is a consistent complication of hepatic encephalopathy and of neurologic disease in general in the small animal patient. Lactulose and mannitol therapy increase free-water losses by inducing osmotic diarrhea and osmotic diuresis, respectively. Without the ability to voluntarily increase free-water intake, these patients are at significant risk of developing hypernatremia. Furthermore, any animal that cannot produce concentrated urine will be unable to generate and retain free water from isotonic intravenous fluids and, therefore, will be at additional risk. One clinical study found that 60% of human patients with acute liver failure developed hypernatremia, and mortality was 27% higher in the hypernatremic group than in the eunatremic individuals.

Although respiratory alkalosis is the most common acid/base abnormality in humans with hepatic failure, this fact has not yet been documented in veterinary medicine. Clinical experience suggests that respiratory alkalosis may not be as common in the small animal patient. Alkalosis can be deleterious by increasing the nonionized and, therefore, freely diffusible, form of ammonia in plasma relative to that of cerebrospinal fluid, leading to elevated concentrations of ammonia in the central nervous system. Because many animals may have metabolic acidosis from tissue hypoperfusion, it is impossible to predict the acid/base status of an individual animal with liver failure.

The fluid of choice for long-term maintenance of the patient with liver failure therefore should be one-third to one-half strength saline, supplemented with potassium and dextrose as necessary. Long-term maintenance of colloid osmotic pressure (ideally >17 mm Hg) and coagulation factor levels with fresh frozen plasma should also be beneficial.

**General Therapy for Hepatic Failure**

**Hepatoencephalopathy**

Therapy for hepatoencephalopathy generally is directed at minimizing the formation of ammonia by enteric bacterial flora. First, oral intake
of food should be avoided until the neurologic status has improved. Warm water enemas may be administered in an attempt to cleanse and empty the colon. Measures should also be taken to minimize the occurrence of gastrointestinal tract hemorrhage (see later), because blood in the lumen of the gut acts as a readily available source of protein for bacterial ammonia production. Most dogs and cats with hepatencephalopathy are managed using a combination of the approaches described in the following sections.

**Lactulose.** Lactulose is a nondigestible synthetic disaccharide that has several beneficial effects in hepatencephalopathy. When administered into the gastrointestinal tract, lactulose is metabolized by enteric bacteria into a variety of small organic acids. As a result of this acidification of the colon, nonabsorbable ammonia ions are present in the lumen, rather than absorbable ammonium. This results in "ion trapping" and excretion of ammonia ions. The presence of an osmotic load in the intestine also causes osmotic diarrhea, which further diminishes ammonium absorption. Finally, acidification of the colon may result in further reduction of ammonia production. Lactulose is given orally (15–60 mL orally QID or until stools become soft), if the animal has normal mentation, but will have the same effect if diluted and given as a retention enema for animals with depressed cerebral function. Retention enemas should be administered every 2 hours until an improvement in mentation is noted or serum ammonia concentrations return to normal. If there is evidence of coagulopathy, enemas should be performed with caution because of the risk of precipitating hemorrhage.

**Oral Antibiotics.** Antibiotics are administered orally to diminish the number of enteric bacteria and, therefore, to minimize intestinal production of ammonia. Oral neomycin sulfate (2.25 mg/kg divided daily) is well tolerated and effective in hepatencephalopathy. It exerts a synergistic effect with lactulose because of its primary action on gram-negative bacteria, sparing *Lactobacillus* and *Clostridia* spp., which are primarily active in metabolism of lactulose. Although neomycin is usually not absorbed from the gastrointestinal tract, the presence of mucosal damage may allow some systemic absorption of this aminoglycoside. Concerns about possible nephrotoxicity and ototoxicity have recently prompted widespread use of metronidazole instead of neomycin for control of the enteric flora. Oral metronidazole (7.5–10 mg/kg TID) seems to be as effective as neomycin against the enteric gram-negative anaerobes that produce ammonia, with minimal risk of toxicity.

**Flumazenil.** Recent studies have suggested that hepatencephalopathy may be associated with increased numbers of GABA receptors in the central nervous system. A benzodiazepine binding site exists on GABA receptors; therefore, the increased numbers of receptors result in heightened sensitivity to benzodiazepines such as diazepam. Increased concentrations of endogenous benzodiazepine agonists have also been demonstrated in the brains of people and rats in fulminant hepatic failure. Studies in humans have demonstrated some response to the administration of flumazenil, a benzodiazepine receptor antagonist, in
humans with hepatoencephalopathic coma.\textsuperscript{29,35} Subjective clinical experience in a small number of dogs and cats with hepatoencephalopathy at the Veterinary Hospital of the University of Pennsylvania suggests that variable improvement in neurologic status can be obtained with administration of flumazenil. Because some animals seem to respond well, with marked improvement in neurologic status, and because the drug seems to be well tolerated and safe, a trial administration of flumazenil (0.02 mg/kg IV) may be considered in severely affected animals. If a response is likely to occur, our experience suggests that it will be evident immediately after administration of the drug.

**Hemorrhage**

Reduced hepatic synthesis of coagulation factors results in a clinically significant, hypocoagulable state. This may be exacerbated by concurrent platelet dysfunction, disseminated intravascular coagulation, and possibly vitamin K deficiency caused by reduced bile-salt facilitated fat absorption. Ulceration of the upper gastrointestinal tract potentiated by portal hypertension is the most common reason for hemorrhage, often manifesting as melena and hemorrhagic diarrhea. Blood in the lumen of the gut provides an increase in protein substrate for intestinal flora, leading to increased production of ammonia and other encephalopathogenic substances, which is often associated with severe exacerbation of encephalopathy. The control of hemorrhage, therefore, is a priority in animals with fulminant hepatic failure. Several options are available.

**Blood Products.** Because hemorrhage associated with fulminant liver failure is associated with depletion of coagulation factors due to both failure of production and consumption, provision of such factors is an important aspect of therapy of an ongoing bleed. Coagulation factors may be provided by administration of fresh whole blood if anemia exists, or fresh plasma in animals that are not anemic. Blood products that have been stored for more than 24 hours should be avoided in patients with hepatic failure, because ammonia concentrations in such products may be high.\textsuperscript{43} Plasma should not generally be relied on as a source of protein for animals with hypoalbuminemia. Unless the animal is small, very large volumes of plasma will be required to treat hypoproteinemia effectively, and such large volumes are generally unavailable in clinical practice.\textsuperscript{27,84}

**Vitamin K.** Some animals with biliary obstruction develop a vitamin K responsive coagulopathy as a result of failure of gastrointestinal absorption of fat soluble vitamins. Because vitamin K is relatively innocuous, a therapeutic trial is warranted in animals with coagulopathy associated with hepatic disease. Intravenous injection of vitamin K can cause anaphylaxis; therefore, it should be administered parenterally (1–2 mg/kg) by subcutaneous injection. Oral administration will be ineffective because of the absence of enteric bile acids in animals with biliary obstruction. Most animals with a vitamin K responsive coagulopathy demonstrate improved coagulation in 24 hours. If no response is noted, administration of vitamin K should be discontinued.
Gastrointestinal Protective Agents. Several therapeutic agents are available for management and prevention of ulceration in the gastrointestinal tract. Sucralfate (250 mg/15kg orally QID) is an orally administered salt of sucrose sulfate and aluminum hydroxide, which polymerizes to form a protective coat over ulcerated gastric mucosa. It can be safely combined with agents that act to reduce gastric acid secretion, of which the most widely used are the H₂ receptor blockers cimetidine (5 mg/kg orally or IV QID) and ranitidine (2 mg/kg orally or IV BID to TID). Cimetidine may be administered as an adjunct to therapy of some toxicities such as acetaminophen, because of its inhibition of hepatic-mixed function oxidases, thereby minimizing the production of toxic metabolites. Ranitidine does not inhibit hepatic microsomal enzymes. Because cimetidine requires hepatic metabolism, variable dose reductions may be advisable in animals with hepatic failure. For this reason, and by virtue of its less frequent dosing regimen, ranitidine may be preferable for such patients.

Nutritional Support

Like all patients with critical illness, dogs and cats in acute hepatic failure undergo a number of changes in metabolism that are designed to maintain vital tissues through a crisis. Body glycogen stores are depleted rapidly, and metabolism of fat and protein stores begins. Because ketoadaptation is limited, body protein stores are a significant energy source for these patients. Studies have documented profoundly negative nitrogen balance in critically ill dogs, resulting in rapid depletion and redistribution of labile protein stores. Such depletion may be manifested not only in loss of skeletal muscle tissue mass, but also in myocardial and diaphragmatic muscle weakness, depletion of labile proteins such as albumin, globulins, and acute phase proteins from plasma, and also eventual loss of structural proteins such as collagen. Depletion of protein stores may lead to delayed healing and regeneration of hepatic tissue. Immunosuppression also results, which can further increase the risk of sepsis. Early provision of nutritional support, therefore, is vital in all critical patients to prevent excessive tissue catabolism, to promote healing, and to support the immune system.

It is now well recognized that nutritional support is a vital part of long-term management of patients with many types of hepatic disease. Cats with hepatic lipidosis, for example, are totally dependent on the provision of adequate nutritional support for reversal of their hepatic disease, and for ultimate survival. In the patient with acute hepatic necrosis, however, the provision of nutritional support at an early stage of hospitalization is likely to be fraught with difficulty. The presence of hepatorenal failure mandates cleansing of the gastrointestinal tract and, therefore, maintenance without oral feeding. The simultaneous occurrence of gastrointestinal hemorrhage, vomiting, and diarrhea are further limitations to the use of the oral route. Therefore, if immediate nutritional support is deemed necessary in these critically ill patients,
total parenteral nutrition remains the only effective and safe route available. Although intravenous infusions of branched chain amino acids have been used experimentally in an attempt to ameliorate hepatencephalopathy, mixed results have been obtained, and such solutions are not routinely used in veterinary clinical practice. Discussion and recommendations for parenteral nutrition in dogs and cats with acute hepatic necrosis are beyond the scope of this article.

If animals with acute hepatic necrosis are in good body condition before the onset of illness, immediate nutritional support is less important than initial stabilization of neurologic and gastrointestinal function. Adequate tissue reserves are probably available for short-term use, and enteral intake of food may be anticipated within a short period of time. In a patient that was previously healthy, nutritional support may be safely delayed up to 3 days, if necessary. This will be enough time for recovery of adequate neurologic and gastrointestinal function in most dogs and cats with acute hepatic necrosis, and oral nutritional support should be initiated at that point. Oral nutrition is the optimal route for all critically ill animals because of its trophic role for gastrointestinal epithelial cells. Maintenance of enteral nutrition therefore helps to minimize the risk of gut-origin sepsis. Diets and rationale for enteral nutrition of the dog or cat with hepatic failure are discussed elsewhere in this issue (see Dial).

Nursing Care

Because many of these patients are recumbent or comatose, intensive nursing care is a vital part of their recovery process. As much as possible, animals should be maintained in sternal recumbency, but if in lateral recumbency, the animal should be turned from side to side 4 to 6 times a day. Patients should be provided with soft bedding that further prevents the development of decubitus ulcers, particularly in the case of large breed dogs. Animals that are demented or seizuring should be placed in an environment in which they cannot injure themselves. Comatose animals that are not blinking or properly closing their eyes require the application of artificial tears a minimum of 4 to 6 times a day. Recumbent animals should be kept clean and dry to prevent the development of moist dermatitis. They should be monitored for urinary retention, and all urine and feces should be cleaned away quickly (particularly if enemas are administered). Long-haired dogs and cats may require clipping. If the animal shows any tendency to vomit, the head should be placed below body level to allow adequate drainage of vomitus and to minimize the chance of the development of aspiration pneumonia.

SUMMARY

Management of the small animal patient with a presumptive diagnosis of acute liver failure should aim to provide high quality supportive
care aimed at the functional derangements that occur. A definitive histopathologic diagnosis should be pursued to allow evaluation of the reversibility of the underlying condition. With the current advances in veterinary critical care, improved medical and technical management should reduce both morbidity and mortality in the patient with potentially reversible liver failure.

References


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