Clinical Practice Review

Acute liver failure in dogs and cats

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Abstract

Objective – To define acute liver failure (ALF), review the human and veterinary literature, and discuss the etiologies and current concepts in diagnostic and treatment options for ALF in veterinary and human medicine.
Etiology – In veterinary medicine ALF is most commonly caused by hepatotoxin exposure, infectious agents, inflammatory diseases, trauma, and hypoxic injury.
Diagnosis – A patient may be deemed to be in ALF when there is a progression of acute liver injury with no known previous hepatic disease, the development of hepatic encephalopathy of any grade that occurs within 8 weeks after the onset of hyperbilirubinemia (defined as plasma bilirubin >50 μM/L [>2.9 mg/dL]), and the presence of a coagulopathy. Diagnostic testing to more specifically characterize liver dysfunction or pathology is usually required.
Therapy – Supportive care to aid the failing liver and compensate for the lost functions of the liver remains the cornerstone of care of patients with ALF. Advanced therapeutic options such as extracorporeal liver assist devices and transplantation are currently available in human medicine.
Prognosis – The prognosis for ALF depends upon the etiology, the degree of liver damage, and the response to therapy. In veterinary medicine, the prognosis is generally poor.

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Introduction

A specific definition of acute liver failure (ALF) has not been listed in the International Classification of Diseases framework. Lack of a definition has resulted in ambiguity because numerous definitions for this syndrome are being used throughout the veterinary and human literature.[1] Whereas acute liver injury (ALI) denotes acute hepatocellular damage and necrosis with retained hepatic function, ALF occurs once hepatocellular damage is so extensive that it compromises hepatic synthetic, excretory, and regulatory functions.[2] A recently proposed definition of ALF in the human literature includes the following criteria: (1) the absence of preexisting liver disease; (2) the presence of hepatic encephalopathy (HE) occurring within 8 weeks after onset of hyperbilirubinemia, defined as plasma bilirubin >50 μM/L [>2.9 mg/dL]; and (3) the presence of a coagulopathy, defined by an international normalized ratio (INR) ≥ 1.5.[1] Establishing a standard definition of ALF

Abbreviations

ALF	acute liver failure
ALI	acute liver injury
ALP	alkaline phosphatase
ALT	alanine transaminase
aPTT	activated partial thromboplastin time
AST	aspartate transaminase
DIC	disseminated intravascular coagulation
FNA	fine-needle aspirate
GGT	gamma glutamyl transpeptidase
GSH	glutathione
HE	hepatic encephalopathy
ICP	intracranial pressure
INR	international normalized ratio
NAC	N-acetylcysteine
PT	prothrombin time
ROS	reactive oxygen species
SAMe	S-adenyl-L-methionine
SIRS	systemic inflammatory response syndrome
vWF	von Willebrand factor

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may help clarify optimal therapeutics and prognosis in the future.

Patients with ALF commonly present with nonspecific signs that may progress toward sepsis and multiple

organ dysfunction. Regardless of the etiology, management of ALF in veterinary medicine focuses on supportive care. The prognosis of ALF in veterinary medicine depends upon both the underlying cause as well as the patient's response to treatment. Unfortunately, ALF generally carries a poor prognosis. The following discussion will review the current veterinary and human literature, appropriate patient assessment, standard treatment interventions, and innovative therapeutic strategies.

Etiology

There are numerous causes of ALF in dogs and cats, including toxin ingestion, drug reactions, and infectious agents. A thorough history, including any medications and herbal supplement exposures, should be obtained in order to tailor treatment, including therapy with an antidote when available.[3]

Toxicants implicated in canine ALF

Hepatocellular damage from toxins can be divided into 2 broad categories: direct (destructive) and indirect (disruptive) toxicity. Direct toxins cause nonselective destruction of the structural basis of hepatocyte metabolism, such as the plasma membrane and organelles, leading to total intracellular chaos and cell death. In contrast, indirect toxins cause selective disruption of cell function or structure in a more discriminating fashion, such as by covalently bonding to and distorting individual molecules, secondarily crippling the metabolic organization of the hepatocyte.[4]

Cycad Palms (Sago Palms)

These plants are found throughout the United States, with the highest concentration of toxicities reported in the South. The primary toxin, cycasin, is found in all parts of the plant but the highest concentration is found in the seeds.[5] Nonspecific clinical signs including vomiting, lethargy, diarrhea, or anorexia are seen within 24 hours of ingestion, while hepatic damage is reported to occur within 48–72 hours of ingestion.[6] In one report, approximately 20% of affected dogs had neurologic signs including tremors, ataxia, mentation changes, or seizures at presentation.[5] In this same study, there was a 50% mortality rate; negative prognostic indicators included significantly higher bilirubin and lower albumin concentrations at presentation, as well as lower serum albumin nadir recorded during hospitalization compared to nonsurvivors.[5] There is no specific treatment or antidote for sago palm toxicity.

Blue-green algae (Microcystis aeruginosa)

Toxic algal blooms can occur in shallow and stagnant water during hot, dry weather. Microcystins disrupt the hepatocyte cytoskeleton leading to hepatic necrosis. In one report, a dog developed lethargy, vomiting, and diarrhea within 1 hour of ingestion that then progressed to icterus, blindness, increased transaminase activities, hypoglycemia, hyperammonemia, and prolonged prothrombin (PT) and activated partial thromboplastin (aPTT) within 48 hours.[7] Therapy for algae toxicosis is supportive and there is no known antidote.

Amanita phalloides

Amanita phalloides, also known as "death cap" or "death angel," is the mushroom species that most frequently leads to human fatalities following ingestion. These mushrooms contain several types of toxins, the most potent of which is amatoxin, which is not destroyed by cooking, freezing, or drying the mushrooms.[8] Following ingestion, the most commonly affected cells are those in contact with the toxin or those that have a rapid rate of turnover, such as the gastrointestinal crypt cells, hepatocytes, and tubular cells within nephrons.[9] The clinical course of disease is divided into 4 phases. The first phase is a latency period, which is followed in 6–24 hours by gastrointestinal signs including nausea, vomiting, hematochezia, and severe abdominal pain. The third phase is a false recovery that lasts anywhere from a few hours to a few days. Phase 4 involves fulminant hepatic, renal, and multiorgan failure occurring 36–84 hours after ingestion of the mushroom. Dogs with amanitin toxicosis often have marked increases in alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP) activities, bilirubin concentration, prolonged PT, and aPTT, as well as severe hypoglycemia that can result from the depletion of hepatic glycogen stores.[10]

The frequency of Amanita phalloides toxicity in small animals is difficult to confirm, as definitive diagnosis requires identification of amanitins in biologic specimens from the affected animal. In one case report, sections of fresh liver from a dog with suspected mushroom ingestion were submitted to the California Animal Health and Food Safety Laboratory where liquid chromatography-mass spectrometry was used to identify the presence of α-amanitin. This technique has also been used to detect α-amanitin in the serum and urine of dogs.[10] It may also be possible to submit pieces of mushroom from the environment or from gastric contents to an experienced mycologist to confirm exposure.[10]

Recommended therapies for the treatment of Amanita phalloides toxicosis include penicillin G and silymarin. In people with ALF due to Amanita mushroom

ingestion, there is a reported mortality rate of 40–100% if liver transplantation is not performed.[8]

Aflatoxins

In 2005, there was an outbreak of aflatoxicosis in dogs secondary to commercial dog food contamination.[11] After ingesting the contaminated food for several weeks, dogs presented with vomiting, depression, anorexia, icterus, ascites, thrombocytopenia, prolonged PT and aPTT, and marked increases in ALT and AST activity. In animals with suspected aflatoxin exposure, hypocholesterolemia, decreased plasma protein C concentration, and decreased antithrombin activity are reliable exposure biomarkers.[11]

Derived from the fungus *Aspergillus*, aflatoxins can contaminate a wide variety of foods both prior to harvest as well as during storage. There are 2 forms of disease caused by aflatoxins, both targeting the liver: acute aflatoxicosis is rapidly fatal, while chronic aflatoxicosis leads to immunodeficiency and hepatic neoplasia.[12] The hepatotoxic effects are dose-dependent and are due to toxic metabolites produced by cytochrome p450 enzymes in the liver. These metabolites cause direct damage to the liver as well as secondary oxidative damage due to depletion of intracellular glutathione.[11] Younger and pregnant animals are most susceptible to aflatoxicosis.[13]

In cases where aflatoxicosis is suspected, the US Food and Drug Administration (FDA) and the product manufacturer should be contacted with both the product name and date code. Premortem diagnostics include measuring urine samples for aflatoxin B1, which is only present in the urine within 48 hours of ingestion of the contaminated food.[13] Other possible diagnostics include submission of frozen sections of liver to determine tissue aflatoxin concentration, or testing the food for the presence of aflatoxin via ELISA or chromatography.[14]

There is no specific treatment or antidote for aflatoxicosis.[11] Reported mortality rates range from 64%[11] to 100%.[14] A reported negative prognostic indicator is the presence of granular cylindruria.[11]

Xylitol

Xylitol is a sugar substitute available in many human food products, including chewing gum and baking products. In dogs, xylitol ingestion may cause an acute hypoglycemia followed in 1–3 days by hepatotoxicity.[15] Xylitol induces an insulin surge 2.5 to 7 times greater than would be stimulated by the equivalent volume of glucose in dogs, resulting in a potentially severe hypoglycemia within 30–60 minutes up to 12 hours following ingestion.[16] Dogs may present with signs of hypoglycemia including lethargy, ataxia, collapse, and seizures. Common clinicopathologic findings due to the insulin surge include hypoglycemia, hyperglycemia due to a Somogyi effect, hypokalemia due to intracellular shifting of potassium, and hypophosphatemia due to increased cellular permeability to phosphate.[15]

There appear to be 2 syndromes associated with xylitol hepatotoxicity: a mild self-limiting, dose-dependent increase in hepatic transaminase activities[17] and idiosyncratic ALF.[18] Xylitol doses associated with hepatic failure range from 0.5 to 16 g/kg and the dose ingested does not appear to correlate with survival.[15,16,18] Hyperphosphatemia has been identified as a poor prognostic indicator.[18] Suggested mechanisms of hepatotoxicity include adenosine triphosphate (ATP) depletion leading to hepatocellular necrosis and production of reactive oxygen species (ROS).[18] Treatment for xylitol toxicosis is supportive and there is no known antidote.[19]

Drug reactions implicated in Canine ALF

Drugs can be classified as intrinsic or idiosyncratic toxins. Intrinsic toxins cause ALF in a dose-dependent and predictable manner, while idiosyncratic reactions are unexpected based on typical metabolism and elimination and are not dose-dependent.[4] Idiosyncratic reactions are often due to the production or accumulation of toxic metabolites or an immune response to the parent drug or metabolite and may show some dose sensitivity if they lead to the accumulation of a toxic intermediate.[20]

Carprofen

Carprofen is a cyclooxygenase-2 (COX-2) preferential nonsteroidal antiflammatory drug (NSAID) used in the treatment of postoperative pain and osteoarthritis. Administration has been associated with idiosyncratic acute hepatotoxicity and death; Labrador Retrievers may be overrepresented in the affected population.[21] There is no specific antidote or treatment.

Acetaminophen

Acetaminophen is a direct, intrinsic hepatotoxin that can result in liver damage following a single overdose or from repeated subtherapeutic doses. Doses in excess of 100 mg/kg have caused hepatotoxicity in dogs. Clinicopathologic evidence of ALI frequently develops within 24 to 36 hours of ingestion.[22] Acetaminophen can also cause methemoglobinemia in both dogs and cats.[23]

Diagnosis of toxicity relies on the development of signs of ALF as well as known or suspected exposure to acetaminophen. Within 4 hours of exposure, canine plasma can be submitted to a human hospital to measure acetaminophen concentration to confirm exposure.[22] Treatment includes replacement of depleted

glutathione stores using N-acetylcysteine (NAC) or S-adenyl-L-methionine (SAMe).

Phenazopyridine

Phenazopyridine hydrochloride is used as a human genitourinary analgesic and has been reported to cause ALI in a dog after ingestion of 65 mg/kg. Acetaminophen is a toxic metabolite of phenazopyridine and the mechanism of phenazopyridine's hepatotoxicity is thought to be similar to that of acetaminophen.[24]

Sulfonamides

Trimethoprim sulfonamide (TMS) antimicrobials have been associated with hepatic necrosis in 4 dogs. This report was suggestive of an idiosyncratic drug reaction as the duration of therapy, type of TMS combination, and dose administered did not appear related to the ultimate development of hepatotoxicity. All 4 dogs died or were euthanized due to ALI or ALF.[25]

Lomustine

Lomustine (CCNU) is an oral nitrosourea alkylating chemotherapeutic agent that has been reported to cause idiosyncratic increases in liver enzyme activities in up to 86% of dogs receiving therapy. While there is no antidote, Denamarin (SAMe and silybin) has been shown to result in improved ALT, AST, ALP activities, and bilirubin concentration in patients receiving CCNU.[26]

Zonisamide

There has been one case report of Zonisamide, an anticonvulsant medication, causing fatal, idiosyncratic ALF in a dog being treated for idiopathic epilepsy following 10 days of therapy.[20]

Infectious agents

In the developing world, infectious agents such as hepatitis A, B, and E are the most common causes of ALF in people.[27] While canine hepatitis is not caused by homologous agents, there are numerous reported infectious causes of ALF in dogs including bacteria such as Leptospira and viruses such as canine adenovirus-1.[28–30]

Leptospirosis

Leptospira are zoonotic gram-negative, obligate aerobic, spirochete bacteria with worldwide distribution. There are over 250 known serovars; the main serovars causing disease in dogs include *Leptospira interrogans* serovars Icterohaemorrhagiae and Pomona, and *Leptospira kirschneri* serovar Grippotyphosa. Clinical signs and severity of disease will depend upon the infecting serovar and host immune response.[28] Serovars icterohaemorrgiae and Pomona are thought to produce hepatic disease more commonly than other serovars and dogs younger than 6 months of age more frequently develop signs of hepatic dysfunction.[29]

Leptospira are shed in the urine from infected domestic and wild animals. Dogs contract leptospirosis after contact with infected urine or urine-contaminated soil, water, food, or bedding, as well as transmission via bite wounds, ingestion of infected tissues, sexual transmission, and placentral transfer. The incubation period in experimental studies is 7 days, but can be shorter or longer depending on inocula.[28]

Early presenting signs in dogs with acute disease include fever, generalized muscle tenderness, shivering, reluctance to move, abdominal pain on palpation, and polyuria and polydypsia. Dogs may additionally be icteric, azotemic, and have bleeding tendencies due to ALF, disseminated intravascular coagulation (DIC), or direct vascular damage by the bacteria itself. Changes seen on blood work may include thrombocytopenia, increased creatine kinase, azotemia, bilirubinemia, and increased ALT, AST, and ALP activity.[28] The increase in ALP activity is often proportionally greater than the increase in ALT activity. Bilirubin concentrations often peak 6–8 days after onset of disease; the degree of icterus is thought to correspond to the severity of hepatic necrosis.[29]

Diagnosis of leptospirosis is frequently made by antibody testing based on the microscopic agglutination test (MAT). In the first weeks of illness in acute infection, dogs may have false-negative results. Therefore, convalescent titers should be performed 2–4 weeks after the first titer to demonstrate seroconversion.[31,35] A 4-fold increase in the titer is consistent with recent infection.[31] However, a single titer > 1:800 in an unvaccinated dog with classic signs of leptospirosis provides a presumptive diagnosis.[32] Difficulties in interpretation of the MAT include previous antimicrobial therapy, previous vaccination, and exposure.[31] Antimicrobial therapy may blunt the increase in convalescent titer, while natural exposure and vaccination can lead to false-positive results. However, animals with exposure or vaccination will typically not have as rapid an increase in convalescent titers compared to animals with active infection. If antimicrobials have not yet been initiated, culture, and PCR can be used to detect leptospires or their nucleic acid, respectively. Additionally, these tests can confirm active infection in animals with positive antibody test results. For diagnostic purposes, the best fluid to sample depends on the length of time since infection. Within the first 10 days, blood is the best sample as the lesptospire-organisms are in highest concentration. After the first 10 days, urine

has the highest concentration of bacteria and will yield the best results.[28]

Treatment options for canine leptospirosis are aimed at initially clearing the leptospiremic phase and subsequently clearing the carrier phase. For the first 2 weeks after diagnosis, amoxicillin is recommended at 22 mg/kg q 8 h. To clear the carrier state, doxycycline 10 mg/kg for an additional 2 weeks is recommended.[32]

Canine adenovirus-1

Canine adenovirus-1 (CAV-1) causes infectious canine hepatitis worldwide. Most commonly, dogs less than one year of age are affected but unvaccinated dogs of any age are at risk. Following oronasal exposure, the virus causes acute hepatic necrosis. Severely affected dogs may present dead or moribund a few hours after onset of clinical signs. Those that survive the acute viremic period may present with fever, vomiting, abdominal pain, diarrhea, enlarged tonsils, and bleeding diathesis including widespread petechiae or ecchymoses. Liver enzymes will progressively increase for 14 days after infection before starting to normalize. Clinical signs often last 5–7 days before improvement is seen. Diagnosis can be made using serology, virus isolation, and immunofluorescent assays. CAV-1 can also be isolated and cultured from body secretions or body tissues except the liver. There is no specific therapy for canine adenovirus infection, and treatment is supportive.[33]

Cats

Idiopathic hepatic lipidosis

Cats are prone to forming hepatic lipid vacuoles that may be idiopathic or secondary to a number of systemic diseases. Those with idiopathic disease tend to be younger and have a better survival rate that those with secondary hepatic lipidosis (HL). When greater than 50% of hepatocytes are affected, cats develop severe hepatobiliary disease marked by icterus, anorexia, weight loss, and ptyalism. Blood work changes often include increases in ALP, ALT, AST activities, and hyperbilirubinemia with absent to minimal increases in gamma glutamyl transpeptidase (GGT) activity. Reported negative prognostic indicators include anemia, hypokalemia, and older age of the patient.[34]

Trematodes

Platynosomum fastosum is a small fluke that invades the biliary ducts and gallbladder of cats after the cats ingested lizards infected with the fluke. Infected cats may remain asymptomatic or they may present with biliary tract obstruction and liver failure. Diagnosis is by detection of parasite ova in a fecal sample or, less commonly, detection of the parasite on liver biopsy.[35]

Stanozolol

Stanozolol is an anabolic steroid that has been associated with both an acute ALI as well as delayed fatal ALF during a 4 week clinical trial of 21 cats. Cats with gingivitis and stomatitis were more likely to develop delayed ALF.[36]

Oral benzodiazepines

Oral administration of diazepam and zolazepam has been associated with fatal, acute hepatic necrosis 4–13 days following administration.[37,38] It is thought that oral benzodiazepines cause an idiosyncratic hepatotoxicity in cats.

Clinical signs and complications

The liver plays a key role in the production of proteins, such as albumin and coagulation factors: it filters and detoxifies the blood by metabolizing ammonia and lactate, it is one of the first lines of defense against bacterial invaders in blood from the gastrointestinal tract, and it acts as a major glucose reservoir.[2] When the liver fails, the results can be catastrophic. While one of the more distinctive signs of liver disease is icterus, the majority of clinical signs associated with ALF are largely nonspecific, including vomiting, diarrhea, anorexia, lethargy, and abdominal pain. These signs may be due to the underlying etiology or related to the numerous complications that can occur in the more advanced stages of ALF including cerebral edema and sepsis.[39]

Icterus

Although an exact definition of ALF has yet to be firmly established in both veterinary and human medicine, a commonality in many studies is the presence of icterus.[1] Often, the severity of hyperbilirubinemia or the time between the onset of icterus and the development of hepatic encephalopathy (HE) is used both to define ALF and to prognosticate.[1,40] For example, in human medicine there have been several prognostic scoring systems developed and utilized to predict mortality and to identify patients requiring early liver transplantation, including King's College Hospital criteria (KCC), Model for End Stage Liver Disease (MELD) score, and the Acute Liver Failure Study Group (ALFSG) index. Bilirubin is a criteria in each of these systems.[41–43] Additionally, hyperbilirubinemia has been associated with poor outcome in pediatric ALF as well as in adults with nonacetaminophen-induced ALF.[40,44,45] In

veterinary medicine, higher bilirubin concentrations at presentation have been associated with a poor prognosis in dogs with cycad seed toxicosis.[5]

Hyperbilirubinemia in ALF is often caused by intrahepatic cholestasis, which may be due to leakage of the tight junctions that separate bile canaliculi from the blood, swelling of hepatocytes to the extent that canalicular flow is obstructed, or necrosis of hepatocytes. Leakage of tight junctions is associated with toxic or infectious hepatopathies, while hepatocyte swelling is more commonly associated with hepatic lipidosis. Due to the large reserve capacity of the liver, icterus due to intrahepatic cholestasis is only apparent when the liver is severely and diffusely affected.[46]

Coagulopathies

The development of a coagulopathy as measured by clinicopathologic data such as INR is a defining factor in ALF, although the clinical consequences of this can vary. Some patients with ALF may show no evidence of hemorrhage, others may hemorrhage only after invasive procedures including placement of IV catheters, while others may have spontaneous hemorrhage.[47] Alterations in coagulation parameters, such as PT and aPTT, will often manifest early after the development of ALF due to the short half-lives of coagulation factors.[47]

The alterations in the coagulation system secondary to ALF are multifactorial and complex. These patients can develop defects or deficiencies at numerous points along both the primary and secondary hemostatic pathways. For example, defects in primary hemostasis may be due to thrombocytopenia, thrombocytopathia, or endothelial dysfunction.[48,49] Mild to moderate thrombocytopenia, defined as $< 90.0 \times 10^9 /L$ [$90.0 \times 10^3 /\mu L$], is reported in nearly 40% of patients in the US Acute Liver Failure Study Group.[47] In veterinary medicine, mild to moderate thrombocytopenia has been reported in dogs secondary to toxicosis with xylitol, cycad seeds, or aflatoxin as well as leptospirosis.[5,11,16,18,50-53] Cats with hepatobiliary disease are less likely than dogs to develop thrombocytopenia, but it has been reported in cats with ALF and suspected DIC.[38,54] There are several causes for thrombocytopenia in these patients. The first is decreased hepatic production of thrombopoeitin, which stimulates platelet production from megakaryocytes. The second is through overstimulation of primary hemostasis by continuous, low-grade activation of endothelial cells, and release of von Willebrand factor (vWF). And the third is increased platelet consumption secondary to hemorrhage.[55] Causes of thrombocytopathia due to defective platelet adhesion include increased production of endothelial-derived platelet inhibitors, nitric oxide, and prostacyclin.[48] Thrombocytopenia and thrombocytopathia result in petechiae, ecchymoses, or gastrointestinal hemorrhage.[47]

As the liver is responsible for coagulation factor synthesis, ALF may result in altered production of both procoagulant and anticoagulant factors. Additionally, patients with ALF often have functional defects in the vitamin K-dependent coagulation factors.[47] Vitamin K deficiency may be due to decreased bile flow altering absorption of vitamin K from the intestines, decreased intake of vitamin K due to anorexia, and altered gastrointestinal flora secondary to antimicrobial use decreasing the bacterial production of vitamin K in the gastrointestinal tract.[56] The vitamin K-dependent factors, including factors II, VII, IX, X, protein C, and protein S, require posttranslational modification facilitated by a carboxylase that requires vitamin K as a cofactor.[57] Without adequate levels of vitamin K, these factors cannot be activated, leading to depleted circulating concentration. This type of coagulopathy is more common secondary to cholestatic diseases, such as hepatic lipidosis.[34,56] Typical findings on a coagulation profile for patients with ALF include decreased activity of factors II, V, VII, X, increased activity of factor VIII and vWF, and prolonged PT and aPTT. Additionally, antithrombin and activated protein C activities are often reduced in patients in ALF.[47]

Finally, patients with ALF may have evidence of dysfibrinogenemia or hyperfibrinolysis in the absence of DIC. Hyperfibrinolysis is due to decreased clearance of plasminogen activators by the failing liver.[47] Unfortunately, the presence of hyperfibrinolysis in dogs and cats with ALF is difficult to document as bedside coagulation tests such as PT and aPTT do not account for hyperfibrinolysis, and other available tests such as serum concentration of D-dimers and fibrin degradation products are not sensitive.[56,58]

The end result of these alterations in primary hemostasis, secondary hemostasis, and fibrinolysis is a "rebalanced," but often unstable, system that can result in either hemorrhage or thrombosis.[55] Changes that may occur in liver disease that impair hemostasis include thrombocytopenia, platelet function defects, decreased production of factors II, V, VII, IX, X, XI, vitamin K deficiency, dysfibrinogenemia, and hyperfibrinolysis. In contrast, changes that promote hemostasis include increased activity of vWF and factor VIII, as well as decreased activity of protein C, protein S, and antithrombin.[59] The coagulation abnormalities due to ALF can be difficult to differentiate from DIC as the parameters used for diagnosis of both are similar: prolongation of PT and aPTT, decreased platelet counts, fibrinogen concentration, and antithrombin activity, and increases in D-dimers and fibrin degradation products concentrations.[56] Factor VIII activity may be a useful distinguishing marker as it is often increased in ALF and decreased in DIC.[47]

The severity of the prolongation of PT at presentation, as well as the improvement in the coagulation profile parameters during hospitalization, can be used as dynamic markers of hepatic function and prognostic indicators.[44,60] In veterinary species, lower platelet counts at presentation may be associated with a poor prognosis and may reflect the development of DIC.[5,11,14,18,47] Additionally, prolongation of PT and aPTT as well as decreased activities of protein C and antithrombin have been associated with a poor prognosis in dogs with ALF secondary to ingestion of cycad seed and aflatoxin.[5,11]

Hepatic encephalopathy

Hepatic encephalopathy is a neuropsychiatric disorder that is subdivided into 3 classifications based on chronicity, etiology, and presentation. Type A (acute) is associated with ALF. Type B (bypass) is associated with portal-systemic shunts. Type C (chronic) is associated with cirrhosis and portal hypertension and is further subdivided into episodic, persistent, and minimal.[61] Signs of type A HE often manifest suddenly and progress rapidly.[62] These signs range from minor changes in mentation and motor activity to more significant excitatory neurologic dysfunction including agitation, hyperreflexia, aggression, and seizures, or signs of depressed neurologic function ranging from mental dullness to a comatose state.[63]

The pathophysiology and treatment of each type of HE is distinct. It is believed that ammonia plays a crucial role in the development of type A HE, which is further complicated by cerebral edema, intracranial hypertension, hypoglycemia, hyponatremia, and systemic inflammatory response syndrome (SIRS).[64–67]

Ammonia

Ammonia is produced in the gastrointestinal tract and carried via the portal circulation to the liver where it is metabolized to urea.[68] Ammonia that escapes this urea cycle and enters the systemic circulation can be metabolized to glutamine by extrahepatic cells such as astrocytes. Glutamine is either excreted in urine or metabolized back to ammonia for reentry into the urea cycle.[46]

In ALF, the failing liver is unable to effectively clear ammonia and astrocytes take on a larger detoxification role.[65] Astrocytes contain glutamine synthetase and detoxify ammonia by converting glutamate to glutamine.[68] Glutamine is able to enter the astrocytes' mitochondria where it is metabolized back to ammonia, leading to mitochondrial damage, the production of ROS, and osmotic swelling. Astrocyte swelling is a hallmark histopathologic change observed in acute HE.[65] Ammonia may also lead to upregulation of aquaporin-4 channels in astrocytes and loss of cell volume regulation.[69]

Cerebral edema and intracranial hypertension

Cerebral edema and increased intracranial pressure (ICP) can lead to brain herniation or anoxic brain injury. In people with ALF, intracranial hypertension has been associated with 20–25% of deaths from ALF.[70] Clinical signs of increased ICP include an acute worsening of mental status, fixed, and mydriatic pupils, a change in respiratory pattern, and the Cushing reflex, which is characterized by acute systemic hypertension with concurrent bradycardia.[62] The etiology of cerebral edema and increased ICP in ALF is multifactorial and is likely related to hyperammonemia, astrocyte swelling and loss of cell volume regulation, increased cerebral blood flow, and increased production of inflammatory mediators.[71–74]

Patients with ALF often have a disruption of cerebral blood flow autoregulation due to cerebral vasodilation, which leads to increased ICP through the resulting increase in cerebral blood flow, increased hydrostatic pressure in brain capillaries, and increased delivery of ammonia to the brain.[75] Studies in people with ALF have shown that there is a close relationship between ICP and cerebral blood flow, suggesting that cerebral hyperemia may be important in the surges of ICP seen in this patient population.[72]

A neuroinflammatory response characterized by microglial activation and increased cerebral production of proinflammatory cytokines is thought to contribute to the pathogenesis of cerebral edema and intracranial hypertension seen in ALF.[72,76] Proposed mechanisms of this neuroinflammatory response include direct effects of systemic proinflammatory cytokines and release of proinflammatory cytokines from activated microglia due to cerebral lactate accumulation. In a study of people with ALF, patients with increased ICP had a more marked inflammatory response, as measured by a higher SIRS score, increased C-reactive protein activity, and increased concentrations of proinflammatory cytokines TNF-alpha, IL-6, and IL-1 beta.[72] It is hypothesized that these proinflammatory substances are released from the necrotic liver since human ALF patients who undergo hepatectomy while awaiting liver transplantation show improvement in systemic and cerebral hemodynamic stability.[73] These proinflammatory cytokines, in addition to altering the blood brain barrier, appear to have a synergistic effect with ammonia in oxidative and nitrosative stress. Current experimental therapies for ALF that focus on controlling the neuroinflammation include controlled hypothermia, NAC, and the anti-inflammatory antimicrobial minocycline.[76–78]

Hypoglycemia

The liver plays a central role in blood glucose regulation as it is involved in both gluconeogenesis as well as glucose storage in the form of glycogen. While euglycemia can be maintained with the loss of up to 75% of liver parenchyma, ALF can result in hypoglycemia due to impaired glycogen storage and gluconeogenesis.[2,79] When glycogen stores are depleted, body proteins are catabolized to supply amino acids for gluconeogenesis, resulting in a negative nitrogen balance and loss of muscle mass.[80]

Sepsis

In health, the liver plays a key role in the body's innate and acquired immune systems; when the liver fails, sepsis is a common sequela.[81] Through the portal circulation, the liver is exposed to bacteria from the gastrointestinal tract. The nonparenchymal cells of the liver, including Kupffer cells and liver-associated lymphocytes, monitor the hepatic environment.[82] In addition, the liver synthesizes factors involved in the complement cascade.[83] In ALF, the liver is unable to effectively remove or neutralize pathogens prior to the blood passing into systemic circulation, resulting in bacteremia or septicemia. In people with ALF, bacteremia has been reported in up to 80% of the patient population, most commonly with gram-negative enteric organisms, staphylococci species, and fungal organisms, such as *Candida albicans*. Iatrogenic sources of bacteremia are common and include indwelling intravenous and urinary catheters, as well as skin contamination.[84]

Diagnosis

While there is no single test utilized in veterinary practice to evaluate dynamic liver function, blood work, imaging, and tissue sampling can be combined to assess the hepatic function and degree of hepatic damage and also to monitor progression of disease. In acute hepatic necrosis, the leakage enzymes ALT and AST are typically the first values on standard blood work to increase. This may then be followed by hyperbilirubinemia, prolonged PT, and hypoglycemia. Hypoalbuminemia is typically a finding of end-stage liver failure.[85]

Transaminases

Increase in both ALT and AST activities are sensitive indicators of acute liver damage, but the degree of increase in these values above the reference interval does not necessarily correlate with the degree of hepatocellular damage.[85] Transaminases are stored in hepatocyte cytosol and are released into circulation immediately following damage to the hepatocyte membrane. Within 24–48 hours of acute, severe hepatocellular necrosis ALT activity can increase up to 100-fold. This increase often peaks approximately 5 days following hepatocellular injury and then gradually declines once the inciting cause is removed.[86,87] In general, acute toxic hepatopathies will cause ALT to more rapidly peak and then normalize as compared to viral hepatopathies.[88] However, this is not universally true; some toxins, such as microcystins and aflatoxin, inhibit transaminase gene transcription and so the increase in ALT activity is not seen.[88,89] In general, changes in AST activity parallel those in ALT; however, AST is found in both the cytosol and the mitochondria of the hepatocytes and may indicate more severe hepatocellar necrosis. Increases in AST activity in the absence of an increase in ALT activity should point the clinician toward an extrahepatic source, such as muscle injury.[88]

The reported half-lives of transaminases are controversial, with estimates ranging between 3 hours and 17 days in the dog and approximately 77 minutes in the cat. As the liver is responsible for plasma clearance of the transaminases, ALF may result in sustained increase in transaminase activity. Declining ALT activity back toward normal values may be associated with hepatocellular recovery or, conversely, declining serum ALT activity may also be associated with such severe hepatocellular damage that hepatocytes are no longer able to generate transaminases as seen in end-stage hepatic failure.[88]

Inducible enzymes

Alkaline phosphatase is a metalloprotein enzyme and GGT is a glycoprotein. They are both anchored to the hepatocyte membrane by glucosyl phosphatidylinositol linkages that must be cleaved by endogenous phospholipases before the soluble form of the enzymes can be distributed into circulation.[90]

Following acute, severe hepatic necrosis in the dog and cat, ALP activity increases 2- to 5-fold and then gradually declines.[88] In dogs and cats with experimental acute, severe, diffuse hepatocellular necrosis, GGT activity remain unchanged or only mildly increased.[91] However, extrahepatic biliary obstruction in both dogs and cats will result in moderate to significant elevations in GGT over a period of days to weeks.[88]

Electrolyte and acid-base derangements

There are several electrolyte and acid-base derangements that occur either as a result of ALF or complicate management of ALF patients. These abnormalities include hypokalemia, hypophosphatemia, hyperphosphatemia, hyponatremia, hyperlactatemia, and refractory metabolic acidosis. Hypokalemia can precipitate HE by stimulating renal ammoniagenesis, leading to hyperammonemic states in the body.[92,93] It is thought that

hypokalemia induces increased production of ammonia in the proximal tubules of the nephron.[94] Additionally, during periods of hypokalemia, the hydrogen-potassium exchangers in the intercalated cells of the distal nephron preferentially secrete hydrogen ions into the lumen in exchange for potassium.[95,96] Hypokalemia may also increase the expression of hydrogen-potassium-ATPase pumps in the collecting duct that facilitate reabsorption of potassium in exchange for hydrogen ions.[95,97] Both of these changes result in a more acidic luminal environment and are believed to alter ammonia transport in the nephron, favoring increased ammonia absorption.[95,96] Conversely, higher concentrations of potassium suppress renal ammoniagenesis and increase urinary excretion of ammonium.[98] Hypokalemia is a common sequel to ALF secondary to decreased caloric intake, vomiting, and diarrhea commonly present in these patients.[95]

Hypophosphatemia in ALF results from an intracellular shift of phosphate due to hepatocyte regeneration and may be a positive prognostic indicator.[99] Conversely, hyperphosphatemia in people with acetaminophen-induced hepatotoxicity is a poor prognostic indicator.[100] In a report of 8 dogs with ALF secondary to xylitol ingestion, 4 of the 5 that died or were euthanized were hyperphosphatemic.[18] Severe hypophosphatemia can result in weakness, vomiting, platelet dysfunction, hemolysis, and neurologic signs that may be confused with HE when serum phosphorous concentrations are < 1.5 mg/dL (0.48 μmol/L).[95] It is therefore important to monitor serum phosphorus concentration daily and correct deficiencies as necessary. Patients with ALF often develop hyperlactatemia and an associated metabolic acidosis. Causes of hyperlactatemia include hypotension, poor tissue perfusion, and tissue hypoxia with subsequent anaerobic metabolism and lactate production at the level of the tissues. These can be due to fluid loss and hypovolemia secondary to vomiting and diarrhea, as well as microcirculatory changes associated with ALF including low systemic vascular resistance and compensatory increase in cardiac output. Circulating endotoxin and inflammatory mediators from the failing liver can cause patients to decompensate and lose autoregulation at the level of the microcirculation resulting in tissue hypoxia and increased lactate production.[101] Hyperlactatemia has been associated with a poor prognosis in human patients with ALF and HE as well as people with ALF secondary to acetaminophen toxicity.[102,103]

Ammonia

Plasma ammonia concentrations can be measured from venous, arterial, or capillary blood.[104,105] In a healthy patient, ammonia concentrations from venous and arterial blood should be similar. However, in animals with liver dysfunction more ammonia enters systemic circulation and there is a resultant differential between arterial and venous blood, with arterial ammonia concentration being significantly higher than in venous samples.[104] This is why, historically, arterial blood samples were the recommended sample for measurement of blood ammonia concentration. However, obtaining an arterial sample from patients with ALF can be problematic as these patients may be hypotensive or coagulopathic. Recent studies indicate that venous blood may still be useful in determining ammonia concentrations.[88] Regardless of the source of the sample, plasma ammonia concentrations remain difficult to interpret as it is the actual exposure of the brain to ammonia, not the concentration of ammonia in circulation, that leads to the development of HE. Therefore, the health of the blood–brain barrier, an immeasurable quantity, plays a significant role in the clinical interpretation of ammonia concentration and the development of HE.[104] However, serum ammonia concentration may be useful for prognosis as hyperammonemia at presentation as well as persistent hyperammonemia in spite of treatment has been associated with both increased rates of cerebral herniation as well as an increased mortality rate.[106,107]

To measure serum ammonia, the serum should be separated and placed in a melting ice bath immediately after collection and the analysis run within one hour of collection. However, the sample can be stored for up to 4 hours in a melting ice bath with minimal exposure to air. Exposure to air will result in a falsely low value, while samples left at room temperature or not spun down quickly will result in falsely increased ammonia concentrations.[108]

Imaging

Survey radiographs may be used for evaluation of liver size, although this is subjective and nonspecific, as well as for detection of ancillary conditions such as choleliths. Sonography is a more useful and sensitive tool for evaluating hepatic parenchyma, the biliary system, and vascular structures. It is also used to guide sampling of hepatic tissues and peritoneal effusion. However, sonography has limited usefulness at detecting diffuse parenchymal disease such as round cell neoplasia, diffuse fatty infiltration, and toxic hepatopathy.[109] Possible ultrasonographic findings in patients with ALF include rounded liver borders associated with hepatomegaly, diffuse hypoechogenicity, or increased contrast between a hypoechoic hepatic parenchyma and hyperechogenic periportal tissue.[110] The overall accuracy of sonography to differentiate causes of diffuse hepatic disease is less than 40% in dogs and less than 60% in cats.[109] Therefore, when diagnosing ALF, sonography is a useful, but not

definitive, tool and must be paired with appropriate history, physical examination findings, biochemistry results, and histopathology.[110]

Computed tomography (CT) and magnetic resonance imaging (MRI) are frequently used in human medicine to evaluate liver morphology and the anatomic relationships between the liver and adjacent organs.[111] These modalities are used less frequently in veterinary medicine due in part to the need for sedation or anesthesia, increased cost, and lack of experience in interpreting the data.[110] However, further experience with advanced imaging may enhance its diagnostic usefulness. For instance, CT may be used to diagnose autoimmune ALF and MRI can detect moderate cerebral edema.[112,113]

Tissue sampling and histopathology

Hepatic histopathology allows for evaluation of parenchymal and vascular structures, tissue distribution of disease, and may help determine chronicity of the disease process.[114] Techniques for obtaining hepatic tissue include ultrasound-guided fine-needle aspirate (FNA) and percutaneous, laparoscopic, or surgical biopsy. Prior to any sampling procedure, a coagulation screening (PT, aPTT, and platelet count) should be performed.[110] However, the values at which abnormal coagulation indices become contraindications for percutaneous liver biopsy are controversial.[115] In one study of ultrasound-guided intraabdominal organ aspirates in dogs and cats, increased risk of hemorrhage was associated with thrombocytopenia $<80.0 \times 10^9/L$ [$<80.0 \times 10^3/\mu L$], aPTT $>$ 1.5 times the upper end of the reference range in cats, and a prolonged PT $>$ the upper limit of the reference range in dogs.[116]

Ultrasound-guided FNA is the least invasive and most economical way to obtain a diagnostic sample. However, this technique has several important limitations: the sample size obtained is small and may limit the accuracy of diagnosis, only a small portion of the liver is sampled, the sample may be distorted during fixation, and post-sample visualization to monitor for hemorrhage is limited.[85] FNA is most useful in a certain subset of hepatic diseases such as hepatic parasite infestations, diffuse neoplasia, and suppurative hepatitis.[117–120] FNA cytology, however, may not agree with histopathology results.[114,121,122]

In cases where there is concern for hemorrhage, laparoscopic biopsies are favored over percutaneous biopsies as they allow direct visualization and control of hemorrhage.[123,124] Another technique used in human medicine to obtain a diagnostic hepatic sample in coagulopathic patients is transjugular hepatic biopsy, which avoids traversing the liver capsule and therefore minimizes the risk of bleeding.[125]

Therapy

Aggressive treatment for ALF should be initiated as soon as possible. If the underlying cause is known, it should be removed and an antidote, if available, administered. Unfortunately, the inciting cause of ALF is often unknown and thus the cornerstone of therapy in veterinary patients remains supportive care while the liver is allowed time to recover.[81] Generalized supportive care includes intravenous fluid therapy, liver supplemental medications, nutritional management, and management of any complications that may arise.

Supportive care

Fluid resuscitation

Intravenous fluid therapy is of vital importance as patients are typically hypovolemic and hypotensive secondary to microcirculatory disturbances, decreased fluid intake, and increased fluid losses from vomiting and diarrhea.[81,126] Balanced replacement crystalloid solutions such as 0.9% NaCl[a] or Plasmalyte-A[b] are recommended. Lactated Ringer's solution[c] should be avoided as it contains lactate as a buffer, which requires a functioning liver for proper metabolism.[81] Colloidal solutions, such as hetastarch,[d] are often required in animals with hypoalbuminemia in order to maintain adequate colloid osmotic pressure and intravascular volume.[127] The goal of fluid therapy is to replace intravascular volume while avoiding excessive fluid administration, as this can result in pulmonary edema, worsening of portal hypertension, and exacerbation of cerebral edema.[101] In patients who remain hypotensive (systolic blood pressure < 90 mm Hg, MAP < 65 mm Hg) despite correction of intravascular volume depletion with fluid therapy, vasopressor therapy may be required.[128] Norepinephrine is preferred due to its consistent and predictable increase in cerebral perfusion pressure in severely hypotensive patients.[129] Vasopressin and its analogs are not recommended as they can directly cause cerebral vasodilation and therefore increased ICP.[130] In patients who are persistently hypotensive despite volume resuscitation and the use of vasopressors, relative adrenal insufficiency, and a trial of a supraphysiologic dose of a corticosteroid could be considered.[131]

Maintenance of normoglycemia and normal electrolyte status

Patients with ALF should have their blood glucose monitored every 2–4 hours and they should be supplemented with dextrose as needed. Additionally, these patients are frequently hypophosphatemic, hypokalemic, and hypomagnesemic and these values should be monitored at least once daily during the hospital stay and

supplemented as needed.[127] Hyponatremia should be strictly avoided as it can result in cerebral edema. Treatment is dependent on the duration of hyponatremia, volume status of the patient, or presence of neurological signs. Hypovolemic hyponatremia should be treated with volume expansion with isotonic saline. In acute hyponatremia with severe neurologic signs such as obtundation, seizures, or coma, treatment with hypertonic saline should be pursued to rapidly improve cerebral edema. Newer drugs available in human medicine to treat hypervolemic hyponatremia include the vasopressin receptor antagonists vaptans talvaptan and conivaptan.[132] Vaptans antagonize vasopressin, which induces free water diuresis without natriuresis or kaliuresis, an effect termed aquaresis, thereby effectively treating hyponatremia.[133] Use of these drugs has not yet been investigated in veterinary medicine.

Nutrition

Patients in ALF typically exist in a hypermetabolic state with a higher than normal energy requirement, leading to a catabolic state characterized by a negative nitrogen balance.[134] Provision of adequate dietary protein is essential as catabolism of skeletal muscles leads to increased ammonia production, decreased capacity for muscle detoxification of ammonia, and increased potential for HE.[135] In patients without signs of HE, a high-quality and highly digestible protein source such as can be found in most commercially available gastrointestinal diets should be provided.[136] Protein should make up at least 15–30% dry matter kilocalories for dogs and 30–45% for cats.[80] In patients with HE, dietary protein should be limited to minimize excess ammonia production; dogs should receive 15–20% and cats 30–35% dry matter protein.[80,135] In patients with HE, nonmeat protein sources such as soy or dairy protein may produce lower blood ammonia concentrations than meat sources.[137]

Patients with ALF have decreased glycogen storage and decreased gluconeogenesis, which results in protein catabolism and fasting hypoglycemia. Accordingly, diets should provide at least 30–50% of dietary calories in the form of easily digested, complex, soluble carbohydrates such as rice, corn, wheat, or barley. In addition, providing small frequent meals may help maintain euglycemia and a positive nitrogen balance.[135]

Lipids augment the absorption of fat-soluble vitamins, enhance diet palatability, and are protein-sparing. Dogs without severe cholestasis should be provided with 15–30% dietary fat on a dry matter basis, while cats should be provided with 20–40%.[80]

The liver functions as a storage reservoir for vitamins A, D, E, K, and B12. As such, supplementation with vitamin K1 is suggested in ALF patients, especially those with evidence of cholestasis or clinical evidence of increased bleeding tendencies. Supplementation of B vitamins may be indicated in those who have been anorexic for longer than 7 days.[80] Thiamine relies on hepatic storage and functions as a coenzyme in carbohydrate metabolism and its deficiency leads to Wernicke's encephalopathy, which can manifest with signs similar to HE. In cats, signs of thiamine deficiency include cervical ventroflexion, dilated, and poorly responsive pupils, and slow conscious proprioception. In dogs, signs include depression, vestibular signs, profound muscle weakness, exaggerated spinal reflexes, cervical neck ventroflexion, and a slow menace response. Treatment is thiamine supplementation at a dose of 25–50 mg orally twice daily or 50–100 mg per cat orally once daily for 1 week.[137,138]

Enteral nutrition is generally preferred over parenteral as it serves to maintain the integrity of the gastrointestinal mucosa.[139] In patients who are neurologically competent and capable of protecting their airway from possible aspiration but are unwilling to eat on their own, placement of a feeding tube may be required. Placement of a nasoesophageal or nasogastric feeding tube is recommended, as placement requires neither anesthesia nor an invasive surgical procedure that could increase the risk for hemorrhage. Light sedation with an opioid or benzodiazepine may be utilized to allow placement of a nasal feeding tube in an uncooperative patient. Patients with severe neurologic dysfunction due to acute HE or patients that do not tolerate enteral nutrition may be candidates for parenteral nutrition.[140]

Supplementation

There are numerous "hepatoprotective" medications on the market, including SAMe, NAC, silymarin, and vitamins C and E, which decrease oxidative stress. In health, hepatocytes have potent intrinsic antioxidant systems including glutathione (GSH). In damaged livers, GSH may be less available, resulting in increased ROS concentrations leading to hepatocyte death.[141]

Silymarin, a derivative of milk thistle, is a flavonoid that scavenges ROS, prevents lipid peroxidation, and induces the antioxidant system. It may also decrease the severity of hepatic fibrosis secondary to hepatotoxic injury and mitigate the effects of ischemic liver injury due to acetaminophen, amanita mushrooms, and cyanobacteria among others.[142] The purity, potency, and oral bioavailability of silymarin vary with manufacturer and the therapeutic dose for dogs and cats is unknown. Published doses for dogs range from 50–250 mg/day[143] to 20–50 mg/kg/day.[144] In critical patients, oral bioavailability of medications may be questionable; however,

intravenous silymarin is not currently available for general use in the United States.

Vitamin E, alpha tocopherol, may be useful as a free radical scavenger in liver disease. While much of the research has been focused on chronic liver conditions or cholestatic disease, there may be some basis in the treatment of ALF secondary to copper-associated hepatopathy or hepatic inflammation, as these may result in the generation of ROS in the liver. When ROS are formed, vitamin E acts as a lipid peroxidase "chain breaker," protecting membrane phospholipids from peroxidative damage.[145] Vitamin E should not be used in coagulopathic patients as it may compete with vitamin K.[146] There are several dosing schemes for vitamin E in the literature, ranging from 10 μ/kg by mouth daily with food[146] to 100–400 IU by mouth once to twice daily for dogs and 30–50 IU by mouth once daily for cats.[147]

S-adenyl-L-methionine is synthesized by ATP in all cells and is a crucial component of transmethylation, transsulfuration, and aminopropylation. Transmethylation helps to maintain cell membrane integrity and fluidity. Transsulfuration generates GSH, and thus plays a crucial role in the antioxidant pathway. Aminopropylation is important for anti-inflammatory effects. The liver is the primary site of SAMe synthesis, and thus liver failure can lead to significantly decreased levels of GSH. In nonacetaminophen-induced ALF, the recommended dose of SAMe is 20 mg/kg/day given on an empty stomach.[148,149] For cats with acetaminophen-induced ALF, a recommended therapeutic protocol is 180 mg of SAMe q 12 hours daily for 3 days, then 90 mg of SAMe q 12 hours daily for 11 days.[150] For dogs with acetaminophen-induced ALF, a 40 mg/kg dose of SAMe is given orally, followed by 20 mg/kg by mouth q 24 hours for 7 days.[23] Side effects are uncommon, but can include decreased appetite or nausea following pill administration.

N-acetylcysteine functions as a thiol donor and can be administered intravenously or enterally. It stimulates GSH synthesis, detoxifies hepatotoxins including acetaminophen, and acts as a free radical scavenger.[142] Additionally, it may improve microcirculatory blood flow thereby improving tissue oxygen delivery.[151] The use of NAC in human medicine as an antidote for acetaminophen-induced ALF is well established,[128,152,153] but its use in patients with ALF due to other causes remains controversial and various studies have found conflicting results.[154–158]

There are no established veterinary doses for NAC, but a published protocol in humans for oral NAC (diluted to a 5% solution) is a 140 mg/kg loading dose followed by 70 mg/kg every 4 hours for 17 doses.[128,153] There are several published intravenous protocols, which involve diluting the NAC in 5% dextrose and administering this solution through a nonpyrogenic filter. One such protocol is a loading dose of 150 mg/kg given over 15–60 minutes, followed by a maintenance infusion of 12.5 mg/kg/h for 4 hours, then 6.25 mg/kg/h until there is evidence of improving hepatic function such as resolution of HE, improving coagulation parameters, or declining transaminases.[128] Another intravenous protocol describes administration of a 150 mg/kg loading dose over 15 minutes, then 50 mg/kg over 4 hours, then 100 mg/kg over 16 hours.[153] In people, reported side effects following intravenous administration of NAC include intracranial vasodilation and subsequent increases in ICP. Following NAC administration, many animals are started on oral SAMe since prolonged dosing of NAC is not recommended as it can precipitate hyperammonemia.[142]

Specific therapies and antidotes

Acetaminophen toxicity

N-acetylcysteine is the best-studied antidote for acetaminophen hepatotoxicy in people. It functions by restoring glutathione concentrations, in addition to scavenging free radicals, and improving microcirculation.[159] Dosing protocols have been outlined above. Administration of activated charcoal just prior to administration of NAC in cases of recent known ingestion does not reduce the effect of NAC.[153] The use of SAMe has been compared favorably to NAC for the treatment of acetaminophen-induced ALF.[23,150,160,161]

Mushroom poisoning

Recommended therapies for the treatment of Amanita toxicosis are Penicillin G 300,000–1 million units/kg/day intravenously and silymarin 30–40 mg/kg/day by mouth for 3 to 4 days.[153,162] The use of NAC adjunctive therapy or monotherapy is controversial.[163–165]

Hepatic lipidosis

Early and appropriate nutritional supplementation is the most important facet in the management of cats with HL. Forced feedings or reliance upon appetite stimulant medications are not recommended as they may result in food aversions or an overestimation of how much food the patient is consuming. Instead, early placement of a feeding tube is considered the standard of care. Often, enteral feeding using a nasoesophageal or nasogastric feeding tube (5–8 Fr) can be initiated at hospital presentation, with an esophagostomy tube (10–14 Fr) placed once the patient has been stabilized and existing coagulopathy corrected. Patients with HL often require weeks to months of assisted nutrition.[166]

Diet choice is influenced by the type of feeding tube placed in the patient, as nasoesophageal tubes require the use of liquid formulations.[167] Diets chosen should be balanced, high-protein diets.[166] Dietary protein is essential for reducing hepatic lipid accumulation in cats with a negative energy balance; protein restriction is only recommended in patients with HE.[166,167] Carbohydrate supplementation in the form of dextrose should be avoided as it can further inhibit fatty acid oxidation.[166] The diet chosen should be high protein (30–40% of the energy supplied), moderate lipid (50% of the energy), and low carbohydrate (20%).[167]

The energy goal of feeding is 40–60 kcal/kg/day. However, many anorexic cats are intolerant of large volume feedings initially, and it is often recommended to start feeding approximately one quarter of this calculated amount daily, increasing to the full calculated dose over 3 to 4 days.[166,167] Feedings can be divided and administered as slow bolus feedings every few hours, or administered as a constant rate infusion over a 24 hour period.[167] HL patients are at high risk of the development of refeeding syndrome, characterized by hypokalemia, hypophosphatemia, and hypomagnesemia.[168] Twice daily measurements of serum electrolytes is recommended and electrolytes should be supplemented as needed.[166]

Management of complications

Infection

In human patients with ALF, the most common sites of infection are the lung, urinary tract, and blood and the most commonly isolated organisms include Staphylococci, Streptococci, and enteric gram-negative bacilli.[169] Infection prevention is crucial and cleanliness should be strictly maintained by doctors and nursing staff through thorough hand washing and barrier nursing protocols.[81] The use of prophylactic antimicrobials in all ALF patients is controversial, as prophylactic parenteral and enteral antimicrobials have not been shown to improve outcome or survival in these patients.[170] Empirical antimicrobial therapy is recommended when suspicion for infection or the likelihood of sepsis is high, such as when there is progression of HE, refractory hypotension, or the presence of SIRS.[128,152] The choice for empiric antimicrobial therapy should include broad spectrum coverage for gram-positive and gram-negative bacteria, such as a third-generation cephalosporin.[128]

Coagulation disorders

While patients with ALF are, by definition, coagulopathic, spontaneous hemorrhage is uncommon. There-fore, plasma therapy is not recommended solely on the basis of a prolonged PT or aPTT.[81,152] There are no clear benefits to the use of plasma in patients without evidence of hemorrhage, and the use of blood products is associated with complications such as volume overload, transfusion-related lung injury, urticaria, or sepsis from contamination.[153] However, in patients with prolonged PT and aPTT along with clinical evidence of hemorrhage, or those undergoing invasive procedures, the recommended therapy is fresh frozen plasma as it provides all coagulation factors, including labile factors V and VIII. Frozen and fresh frozen plasma must be thawed prior to administration. The initial dose is 10 mL/kg and it should be dosed until the PT and aPTT are less than one and a half times the upper limit of normal or until hemorrhage has stopped. This recommendation is empirically derived, as there are no evidence-based data showing that the treatment of coagulopathies results in less risk of hemorrhage during invasive procedures, and there are no data showing an appropriate standard end-point of therapy.[47]

Some literature suggests treating all patients with ALF regardless of clotting times with vitamin K1 prophylactically, especially those with hyperbilirubinemia. The recommended dose is 0.5–1.5 mg/kg orally or by subcutaneous injection for 3 doses, then continued weekly if the patient remains hyperbilirubinemic. Anaphylactoid reactions have been reported when vitamin K1 is administered intravenously or subcutaneously.[56,152]

Gastrointestinal bleeding is a complication of ALF and the use of H$_2$ blockers or proton pump inhibitors is recommended for patients with ALF.[47,127,153] Options include pantoprazole[e] 1 mg/kg once daily intravenously,[171] omeprazole[f] 1 mg/kg once daily orally,[172] or famotidine[g] 0.5 mg/kg twice daily intravenously or orally.[173] Sucralfate[h] may be acceptable as a second line therapy.[153]

Hypoglycemia

Patients with ALF are at high risk for hypoglycemia and monitoring of blood glucose should be performed every 2–4 hours.[128] Patients who develop hypoglycemia should be started on dextrose supplementation, adjusted to maintain normoglycemia. Euglycemia should be the goal of therapy as hyperglycemia has been associated with worsening of cerebral edema.[i]

Hepatic encephalopathy, cerebral edema, and increased ICP

Unlike with patients with type C HE, there are currently insufficient data to recommend therapy with lactulose or nonabsorbable antimicrobials such as rifaximin and neomycin in patients with ALF.[128,174] Instead, correction

of cerebral edema via mannitol or hypertonic saline is a mainstay of therapy. Mannitol is a rheological agent with secondary osmotic diuretic effects that is administered as a 20% solution slow infusion over 20 minutes at a dose of 1–2 g/kg.[174] Alternatively, 7.5% sodium chloride can be administered as a 4 mL/kg IV bolus given over 2–5 minutes. Following administration there is a rapid increase in plasma osmolarity that promotes transcapillary shift of interstitial and intracellular fluid into the vasculature.[140]

Insensitive indicators of increasing ICP include diminished mental alertness, vomiting, decerebrate posturing, and pupil abnormalities.[153,174] More accurate measurement of ICP using invasive, continuous monitoring remains controversial.[81,153,174] Treatment of increased ICP involves both reducing ICP as well as preventing future pressure spikes.[81] Patients should have their heads elevated 15–30° while avoiding kinking of the neck or any obstruction to jugular venous drainage such as jugular venipuncture or catheterization. In addition, normovolemia through proper IV fluid therapy should be ensured and hypotension, hypoxemia, hyponatremia, and hyperthermia should be avoided.[81,128] To minimize spikes in ICP due to agitation or painful stimuli, adequate levels of sedation and analgesia are recommended. Sedation can also serve to reduce the cerebral metabolic rate and oxygen consumption, as well as to alleviate increases in cerebral blood flow (CBF) as metabolic demand and CBF are coupled.[81] Treatment options include propofol 6 mg/kg/h IV or pure mu opioids such as fentanyl, hydromorphone, or morphine intravenously.[174] Caution must be taken when administering opioids as an IV bolus may lead to hypotension, and a significant drop in the arterial blood pressure can result in decreased cerebral perfusion.[81] Additionally, conditions known to potentiate HE, including hypovolemia, gastrointestinal bleeding, constipation, hypokalemia, and metabolic alkalosis, should be avoided.[75]

Future veterinary treatment strategies

In human medicine, several advanced therapies for ALF are currently in use or in early human trials. These include controlled hypothermia, extracorporeal liver support devices, and stem cell therapy. Nevertheless, liver transplantation remains the gold standard treatment.

Controlled hypothermia

Controlled hypothermia is rarely utilized in veterinary medicine and there are no reports of its use in managing cerebral edema in dogs or cats. There is one recent case re-

port describing its successful use in a dog with traumatic brain injury.[176] However, in people, controlled, moderate hypothermia, defined as maintenance of a core body temperature of 32–33°C (89.6–91.4°F) is an accepted adjunctive therapy to control cerebral edema and intracranial hypertension secondary to acute HE. Patients are cooled and maintained at this temperature using cooling blankets.[177] Hypothermia functions to decrease cerebral blood flow and cerebral metabolism, restore cerebral autoregulation,[178] and decrease cerebral uptake of ammonia.[179] Reported adverse effects of hypothermia include coagulopathies, impaired hepatic regeneration, insulin resistance, and increased risk of infection.[81] Further studies in veterinary patients are required before recommendations for its use in patients with ALF can be made.

Liver assist devices

Liver assist devices currently available on the human market include artificial and bioartificial devices. Artificial liver assist devices are designed to remove substances from blood similar to hemodialysis, while bioartifical liver systems use human or porcine hepatocytes incorporated in an extracorporeal circuit to lend hepatic synthetic function.[180] Liver assist systems help maintain vascular tone by removing endotoxins and cytokines from circulation using continuous veno-venous hemodiafiltration, remove protein-bound toxins, and remove ammonia from circulating blood.[181–183] They have also been used successfully in the management of Amanita mushroom toxicity.[8] However, while these devices may improve the signs of HE, they have not been shown to decrease mortality.[184] Nonetheless, this therapy may remain useful in those patients who are nontransplant candidates or to provide a bridge to transplantation.[84] There are few reports on the use of liver assist devices in dogs and cats.[185,186]

Liver transplantation

The only therapy for ALF shown to substantially and reliably improve mortality rate in human medicine is liver transplantation. The use of liver transplantation has significantly improved survival rates in people from as low as 20% without transplantation to 80% with transplantation.[84] In veterinary medicine, transplantation therapy remains in its infancy. However, the research for transplantation techniques in dogs is available in the literature as canine liver transplantations serve as an experimental model for human liver transplantation therapy.[187–191]

Stem-cell therapy

Stem-cell therapy and regenerative medicine are currently being explored as an approach to restore liver mass and function as an alternative to liver transplantation.[192–195] There has been success reported in animal experimental models as well as in early clinical trials.[196–198] Recently, hepatic stem cells from dogs and cats have undergone initial characterization.[199–202] This is an exciting new area of research in the treatment of ALF in dogs and cats.

Prognosis

The prognosis for ALF varies considerably depending on the underlying etiology, degree of hepatocellular damage, capacity of the liver to regenerate, stage of the disease when treatment is initiated, the presence and rapidity of the development of disease sequelae such as HE, and response to therapy.[203]

Given the importance of liver transplantation and limited organ availability in human medicine, accurate prognosis of ALF and guidelines for timing of liver transplantation are heavily researched topics. Several negative prognostic scoring systems have been developed, some of which include factors such as persistent arterial acidosis despite fluid resuscitation, prolonged PT, and hyperbilirubinemia.[153] Other biochemical indicators that may provide negative prognostic value include reduced factor V/VIII ratio, hypophosphatemia, and hyperlactatemia.[100,103,204–206] Reported etiologies of ALF associated with a poor prognosis without a liver transplant include idiosyncratic drug injury, autoimmune hepatitis, mushroom poisoning, and ALF of unknown cause.[153]

While there are no prognostic models validated in veterinary medicine, several biochemical markers have been associated with a poor prognosis ALF in specific subsets of patients. These include granular cylindruria in dogs with aflatoxicosis, higher ALT and bilirubin at presentation in dogs with cycad seed hypatotoxicity, and lower albumin concentrations at presentation at lower nadir albumin concentration in dogs with cycad seed hepatotoxicity.[5,11] Unfortunately, the prognosis of ALF in dogs and cats is generally considered to be poor.

Footnotes

[a] 0.9% sodium chloride, Abbott Laboratories, North Chicago, IL.
[b] Plasmalyte A, Abbott Laboratories.
[c] Lactated Ringer's, Abbott Laboratories.
[d] 6% hydroxyethylstarch in 0.9% sodium chloride injection, Braun Medical Inc., Irvine, CA.
[e] Pantoprazole sodium for injection, Wyeth Pharmaceuticals, Philadelphia, PA.
[f] Omeprazole delayed release capsules, Apotex Inc., Toronto, Canada.
[g] Famotidine tablets, Teva Pharmaceuticals, Sellersville, PA.
[h] Sucralfate tablets, Nostrum Laboratories, Inc., Kansas City, MO.
[i] Kodakat SK, Gopal P, Wendon J. Hyperglycemia is associated with intracranial hypertension in patients with acute liver failure. Liver Transpl 2001; (7):C–21.

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