

Compendium

Hepatic Encephalopathy: Diagnosis and Treatment

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Abstract: Hepatic encephalopathy (HE) is a neurologic syndrome resulting from the synergistic action of multiple pathologic factors, which are discussed in a **companion article**. Early recognition of the clinical signs can improve treatment outcome, as well as reduce the incidence of risk factors. Multimodal treatment of HE is usually indicated. Studies on the pathogenesis and treatment of HE in people may shed new light on further treatment modalities in small animal patients.

For more information, please see the companion article, "Hepatic Encephalopathy: Etiology, Pathogenesis, and Clinical Signs."

Liver dysfunction and portosystemic bypass result in decreased metabolism of toxins. Systemic accumulation of these toxins leads to altered neurotransmission in the brain and manifestation of the clinical syndrome known as *hepatic encephalopathy* (HE). The clinical signs of HE vary in severity depending on the

presence of certain precipitating factors. Diagnosis of the underlying cause of HE is crucial to determine the course of treatment and whether surgical intervention is indicated. Treatment is aimed at reducing the concentration of toxins, minimizing precipitating factors, and treating the direct effects of toxins on the brain.

Diagnosis of Hepatic Encephalopathy

The diagnosis of HE is based on evidence of hepatic dysfunction in a patient with neurologic deficits. Other potential causes of brain disease must be ruled out before making a diagnosis of HE^{1,2} (**BOX 1**). A complete history and physical examination are key tools in differentiating HE from other causes of neurologic deficits. HE typically results in intermittent, diffuse cerebral disease that varies in intensity from day to day, ranging from depression and lethargy to seizures and coma. Lateralizing signs (signs that localize pathology to a particular portion of the brain) are rarely observed.⁵ Signs may present in relation to feeding or medication. A history of prolonged recovery after general anesthesia or excessive sedation after treatment with tranquilizers, anticonvulsants, or organophosphates may indicate impaired hepatic metabolism.⁵ Although there is no definitive diagnostic test for HE, the following testing may help support the diagnosis.

Brain imaging can be useful in the diagnosis of HE. Computed tomography (CT) can be used to document cerebral edema and exclude diagnostic differentials such as tumors, infection, and hemorrhage. Magnetic resonance imaging (MRI) of dogs and cats with portosystemic shunts (PSSs) usually reveals widened sulci and hyperintensity on T1-weighted images of the lentiform nuclei, correlating with an excess accumulation of manganese as

Box 1. Differential Diagnosis for Hepatic Encephalopathy²⁻⁴

Metabolic encephalopathies caused by	Infections
• Uremia	• Brain abscess
• Sepsis	• Encephalitis
• Hypoxia	• Meningitis
• Hypoglycemia	— Bacterial
• Ketoacidosis	— Fungal
• Hypercapnea	— Viral (i.e., canine distemper virus, feline infectious peritonitis, feline leukemia virus, feline immunodeficiency virus)
• Thyroid dysfunction	Intracranial hemorrhage
• Cerebral edema	Hydrocephalus
• Cobalamin deficiency (dogs)	Idiopathic epilepsy
• Thiamine deficiency (cats)	Ischemic events
Brain tumors	Toxins

a result of decreased first-pass clearance of dietary manganese by the liver.⁶⁷ Hyperintensity of the cerebral cortex in T2-weighted images was associated with HE in a dog with acute and chronic forms of HE caused by a PSS.⁸

Measurement of cerebrospinal fluid (CSF) levels of glutamine, glutamate, and aromatic amino acids may be useful in cases in which diagnosis of high-grade HE (stages III or IV; **TABLE 1**) is uncertain. Increased levels of glutamine, glutamate, phenylalanine, tyrosine, or tryptophan in the CSF favor the diagnosis of HE in dogs with a congenital PSS.^{1,9,10}

The changes seen in electroencephalographic studies of patients with HE are usually nonspecific; results are similar to those seen in patients with other causes of metabolic encephalopathy.¹ Findings with some specificity for HE include reduced brainstem auditory-evoked potentials and reduced visual-evoked potentials.¹

Normal blood ammonia levels in patients with severe neurologic signs do not support the diagnosis of HE, whereas elevated ammonia levels in a severely affected neurologic patient do not exclude coexisting neurologic conditions.¹¹ In cases in which the ammonia level is normal, an ammonia tolerance test using venous blood samples can be performed; however, performing this test on a patient with encephalopathy or on an anorexic cat may worsen the clinical signs of HE. In animals without a PSS, the baseline and subsequent ammonia values are within normal limits on an ammonia tolerance test.¹² The labile nature of plasma ammonia levels is the biggest obstacle in their routine clinical use as diagnostic indicators of HE. Studies examining the accuracy of point-of-care ammonia analyzers in the veterinary setting have found moderate accuracy when compared with the standard enzymatic assay, with a tendency for false-negative results.^{13,14}

Diagnosis of Liver Disease Liver Function Tests

Liver enzyme concentrations, obtained as part of initial blood work, may be normal to increased in patients with HE, indicating

Table 1. Stages of Hepatic Encephalopathy

Stage I	Stage II	Stage III	Stage IV
<ul style="list-style-type: none"> Mild confusion Inappetence Dull demeanor Mild irritability 	<ul style="list-style-type: none"> Lethargy Ataxia Markedly dull behavior Personality changes Head pressing Blindness Disorientation 	<ul style="list-style-type: none"> Incoordination Confusion Stuporous Inactive but arousable Severe ptialism Seizures Occasional aggression 	<ul style="list-style-type: none"> Recumbency Complete unresponsiveness Coma Death

Table 2. Types of Hepatic Encephalopathy

Type	Clinical Signs	Examples
Type A (associated with acute liver failure)	<ul style="list-style-type: none"> Sudden onset of clinical signs Rapidly progressive 	<ul style="list-style-type: none"> Toxin Infection Ischemic insult Metabolic disease
Type B (associated with portal-systemic bypass without intrinsic liver disease)	<ul style="list-style-type: none"> Episodic clinical signs Develops gradually 	<ul style="list-style-type: none"> Intrahepatic and extrahepatic PSSs Portal vein hypoplasia without portal hypertension (formerly known as microvascular dysplasia) Congenital urea cycle enzyme deficiency
Type C (associated with severe hepatic parenchymal disease and portal hypertension, often accompanied by the presence of multiple acquired PSSs)	<ul style="list-style-type: none"> Episodic clinical signs Develops gradually 	<ul style="list-style-type: none"> Arterioportal fistulas Hepatic cirrhosis Chronic hepatitis Portal vein hypoplasia with portal hypertension

PSS = portosystemic shunt

the need to perform liver function tests. Patients with type B HE (**TABLE 2**) may present with normal or mildly elevated liver enzyme values.¹⁵ Type A HE is characterized by marked elevations in alanine aminotransferase (ALT) and total bilirubin, with variable levels of serum alkaline phosphatase (SAP). Type C HE is typified by variable levels of ALT and total bilirubin, with a marked elevation in SAP. Hypoproteinemia, hypoalbuminemia, hypoglycemia, hypocholesterolemia, and prolonged clotting times can be found in animals with impaired hepatic function regardless of etiology.¹⁵

Increased fasting ammonia and serum bile acid concentrations support the presence of a PSS in dogs and cats.^{16–19} Increased plasma ammonia concentrations are found in cases of congenital and acquired PSSs, failure of the liver to detoxify ammonia, and urea cycle defects.²⁰ Hepatic failure must lead to a 70% decrease

in urea cycle function for hyperammonemia to develop²⁰; therefore, fasting ammonia concentrations are not sensitive for detection of hepatic parenchymal disease in the absence of multiple acquired PSSs.¹⁹ Some studies have noted that ammonia levels correlate with the severity of HE²¹; however, other studies have refuted this assertion.²² Therefore, serum ammonia level alone should not be used as the definitive diagnostic test for HE or a PSS.

Serum ammonia levels are more sensitive than serum bile acid concentrations in detecting the presence of a PSS^{16,17}; however, assays of fasting and postprandial serum bile acid concentrations have largely replaced the ammonia tolerance test because of their ease of sampling and analysis. However, serum bile acid concentrations have a low specificity for PSSs, as they are also increased in the presence of cholestasis.^{16,17,19} Serum bile acid concentrations can also be affected by hemolysis, lipemia, inconsistent gastric emptying time, and the need for a postprandial sample, which often cannot be obtained in patients with acute HE.^{14,16,17}

Measurement of serum L-phenylalanine (an aromatic amino acid) may be useful for diagnosing liver disease. In one study,²³ dogs with liver disease were found to have increased L-phenylalanine serum concentrations compared with healthy dogs and with dogs with nonhepatic diseases. Although serum bile acid concentrations are elevated in animals with congenital intrahepatic and extrahepatic PSS and portal vein hypoplasia without portal vein hypertension, protein C activity may help confirm the diagnosis and differentiate between the two.²⁴ Values of protein C activity <70% differentiate PSS from portal vein hypoplasia without portal vein hypertension (most dogs with portal vein hypoplasia without portal vein hypertension have protein C activity >70%).²⁴ Clinical use of protein C activity in this capacity may help prioritize the need for costly and/or invasive tests (i.e., abdominal ultrasonography, colorectal scintigraphy, exploratory laparotomy, and radiographic or CT portovenography) aimed at definitive differentiation of these two disorders as well as referral to a specialty clinic.²⁴

Diagnostic Imaging

Ultrasonography, with or without Doppler, is a quick and noninvasive method for imaging the portal vasculature, liver, and other organs in an unsedated dog or cat, and it serves as a valuable tool in the diagnosis of the underlying cause of HE.^{8,25,26} It can be used to visualize single or multiple acquired PSSs or to determine the presence of portal vein hypoplasia without portal vein hypertension. The finding of a small, nodular liver may support a diagnosis of chronic active hepatitis.²⁶ The combination of a small liver, enlarged kidneys, and uroliths is suggestive of a congenital PSS in dogs.^{8,25} Abdominal ultrasonography can determine the presence of a large amount of free abdominal fluid, which excludes the diagnosis of a congenital PSS or a urea cycle enzyme deficiency in hyperammonemic dogs.²⁶ In dogs with a urea cycle enzyme deficiency, abdominal organs and vessels do not appear abnormal on ultrasonography.²⁶ The presence of an extremely dilated and tortuous portal branch in a liver lobe is pathognomonic for congenital arteriportal fistulas.²⁶ A dilated left testicular or ovarian vein on abdominal ultrasonography is a reliable indicator of an

Box 2. Precipitating Factors for Hepatic Encephalopathy

- Gastrointestinal hemorrhage
- Excessive protein intake
- Infection
- Medications (opioids, benzodiazepines)
- Hyponatremia
- Hypokalemia
- Metabolic alkalosis
- Renal failure
- Dehydration
- Constipation
- Overzealous use of diuretics (e.g., furosemide)

acquired PSS.²⁶ Noninvasive diagnosis of hyperammonemic states is essential because patients with portal hypertension and hyperammonemia are at increased risk of anesthetic complications. If a definitive diagnosis cannot be reached with ultrasonography, ultrasound-guided liver biopsy may be indicated.

Contrast-enhanced magnetic resonance angiography (CE-MRA) has recently been proven to be a useful, rapid (<10 minutes), noninvasive, preoperative tool for imaging the abdominal and portal vasculature and for the diagnosis of portovascular anomalies.^{27,28} It provides three-dimensional anatomic details of the portal vein and its tributaries. However, in addition to portal vessels, CE-MRA makes other abdominal vessels visible, which may make interpretation difficult.^{27,28} In addition, CE-MRA does not allow accurate identification of uroliths that are commonly associated with PSSs in dogs. Therefore, if a portal anomaly is identified with CE-MRA, then abdominal ultrasonography is warranted to identify calculi.²⁷ Knowledge of the underlying liver pathology is necessary to treat HE.

Precipitating Factors of Hepatic Encephalopathy

A number of concurrent factors may precipitate the clinical signs of HE, including excessive protein intake, infection, medications, metabolic derangements, renal failure, and dehydration^{1,3,11} (BOX 2). Proper management of HE should be aimed at reducing these exacerbating factors.

Excessive Protein Intake

Delivery of a large protein load from the gastrointestinal tract, either from an inappropriate diet or in the form of gastrointestinal hemorrhage, can precipitate the clinical signs of HE. Gastrointestinal hemorrhage may occur in patients with liver disease secondary to stress-induced ulceration, portal hypertension–induced ulceration, or decreased gastrin clearance.^{2,29} The increased gastrointestinal protein load stimulates bacterial metabolism and release of ammonia, g-aminobutyric acid (GABA), and other compounds that may act as neuroinhibitors, which are absorbed into the systemic circulation and enter the CNS. Poor hepatic function or the presence of a PSS enhances the delivery of these molecules to the brain.^{1,30} In one human study, an oral amino acid load mimicking hemoglobin was used to simulate a gastrointestinal bleed in cirrhotic patients with no evidence of HE; it produced hyperammonemia

and hypoisoleucinemia (deficiency of isoleucine, a branched-chain amino acid [BCAA]) and caused a deterioration in neurologic function.³⁰

Infection

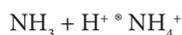
The presence of infection, particularly sepsis, may precipitate HE. Reduced leukocyte migration, decreased serum bactericidal activity, and impaired phagocytosis make patients with chronic liver disease and malnutrition particularly susceptible to infections. Infections increase protein metabolism, leading to an increase in ammonia precursors and aromatic amino acids.^{1,29} Infections can also stimulate systemic inflammatory response syndrome, which can exacerbate damage to the CNS from the cytokines tumor necrosis factor α and interleukin-6. These cytokines increase ammonia diffusion into the CNS and increase the expression of benzodiazepine binding sites.³¹

Medications

There are no safe sedatives for patients with HE. Clearance of benzodiazepines, barbiturates, chlorpromazine, morphine, opioid derivatives, and any other medications that undergo liver metabolism is reduced. With repeated dosing, these compounds tend to accumulate, increasing the degree and duration of sedation.^{1,11} Therefore, doses of drugs that undergo hepatic metabolism should be reduced in patients with HE.

Metabolic Derangements

HE is precipitated by certain metabolic abnormalities (e.g., hyponatremia, hypokalemia, alkalosis).³² Hyponatremia results in depletion of myoinositol, an organic osmolyte, from brain cells, which contributes to cerebral edema in HE.^{33,34} Nonionized ammonia (NH_3) can pass freely through cell membranes and into neurons, whereas the ionized form, ammonium (NH_4^+), cannot. The equilibrium between these two forms depends on pH.



Metabolic alkalosis exacerbates HE because more nonionized ammonia is present. In addition, compensation for alkalosis includes the formation of alkaline urine, from which nonionized ammonia is readily reabsorbed rather than excreted, resulting in renal ammoniogenesis.^{3,11} Hypokalemia creates a concentration gradient that promotes movement of potassium from the intracellular space into the plasma in exchange for hydrogen ions and sodium. The hydrogen ion shift induces an extracellular alkalosis and an intracellular acidosis, resulting in ammonia moving freely into cells. The increased intracellular hydrogen ion concentration allows ammonia to become ionized to form ammonium, which is then trapped within cells.³ Thus, neurons (and other cells) act as one-way scavengers of ammonia (FIGURE 1).

Renal Failure

Animals in renal failure have impaired renal clearance of drugs, toxins, and metabolites such as urea and ammonia. Renal failure also predisposes patients to electrolyte imbalances, altered acid-base

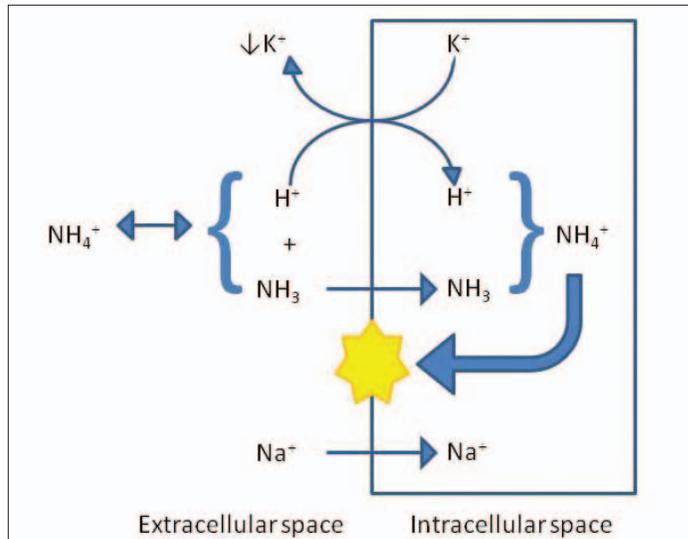


Figure 1. Hypokalemic alkalosis. Hypokalemia promotes a shift of potassium from the intracellular space to the extracellular space in exchange for hydrogen. The resulting extracellular alkalosis and intracellular acidosis cause ammonia to freely move into cells, including neurons, where it becomes ionized to form NH_4^+ . NH_4^+ becomes trapped within the cells, making them one-way scavengers of ammonia. (Adapted with permission.³)

status, and reduced intravascular volume, which contribute to altered mental status and depression.¹

Miscellaneous Risk Factors

Other factors that precipitate HE include dehydration, prolonged anorexia, administration of diuretics, and constipation. Dehydration activates the renin-angiotensin-aldosterone system, which results in the renal loss of potassium and systemic hypokalemia. Diuretics, particularly furosemide, can further deplete intravascular volume and lead to hypokalemia and metabolic alkalosis.¹ Anorexia results in a catabolic state with subsequent production of increased ammonia concentrations due to muscle breakdown.³⁵ Constipation allows greater opportunity for the formation of bacterial degradation products, including ammonia, short-chain fatty acids, and mercaptans.

Treatment

There are three aims in the approach to management of HE. The first is to reduce the incidence of predisposing factors, including providing intravenous fluid therapy to rehydrate the patient, administering gastrointestinal protectants to prevent ulceration, and avoiding the use of sedatives, to obtain a successful outcome. The second is to alleviate neurologic signs by addressing the pathophysiologic mechanisms of HE. Supportive management measures depend on whether the patient has acute or chronic HE (TABLE 3). The third is to identify the underlying hepatic condition for specific management.

Management of Acute Hepatic Encephalopathy

Cerebral edema and intracranial hypertension are characteristic of HE secondary to acute liver failure, or type A HE.^{36,37} Cerebral

Table 3. Drug Dosages Used in the Treatment of Hepatic Encephalopathy in Dogs and Cats^{35,40,45}

Medication	Dose	Adverse Effects
Acute Encephalopathy		
Mannitol	0.5–1.5 g/kg over 10–20 minutes Can repeat as needed q6–8h	Hyponatremia Hyperosmolality (>320 mOsm/L)
Chronic Encephalopathy		
Nonabsorbable disaccharides		
Lactulose	1–3 mL/10 kg PO q6–8h Adjust dose to produce 2–3 soft stools per day Rectally: 5–10 mL/kg cleansing water enema, followed by 5–15 mL lactulose diluted 1:3 with water q8h	Osmotic diarrhea, abdominal distention, cramping
Lactitol	0.5–0.75 g/kg PO q12h	
Oral antibiotics		
Neomycin	20 mg/kg PO q12h 15 mg/kg, diluted in water q6h after cleansing enema	Nephrotoxicity and ototoxicity with chronic use
Metronidazole	7.5 mg/kg PO q8–12h	Central vestibular syndrome at high doses
Rifaximin	Not used in animals In people, 400 mg PO q8h	Expensive
Dietary Supplements		
Zinc	Dogs 1–3 mg elemental zinc/kg/day ^a Cats 7–8 mg/day	Vomiting Hemolytic anemia with toxicity
Levocarnitine	Cats with hepatic lipidosis 250 mg/day PO	
Acute Management of Chronic Encephalopathy		
Benzodiazepine antagonists		
Flumazenil	0.02 mg/kg IV	Vomiting, cutaneous vasodilation, vertigo, ataxia Teratogenic
Sarmazenil	3 mg/kg IV	
Antiepileptics		
Levetiracetam	20 mg/kg IV q8h	Sedation in dogs; lethargy, inappetence in cats
Sodium bromide	600–1200 mg/kg IV, diluted in a 3% solution with 1L sterile water, over 8 h	Sedation; adverse respiratory effects in cats

^aElemental zinc content in zinc acetate, 30%; zinc gluconate, 14.3%; zinc sulfate, 23%.

edema is rarely observed in human patients with stage I or II HE. However, the risk of cerebral edema increases in stage III and IV HE.²⁹ Clinical signs of elevated intracranial pressure, including hypertension, bradycardia, irregular respirations, decerebrate posture, and pupillary abnormalities (i.e., miosis, mydriasis) should guide when to institute measures to decrease intracranial pressure and thus improve survival.²⁹ Transcranial Doppler ultrasonography, which detects increases in the pulsatile index of the right middle cerebral artery, left middle cerebral artery, and basilar artery, is also a valuable, noninvasive tool in the evaluation of intracranial hypertension in dogs.^{38,39}

Mannitol, an osmotic diuretic, can control cerebral edema in the short term. Mannitol decreases intracranial pressure through reflex vasoconstriction of brain vasculature. This effect is accomplished by reducing blood viscosity, reducing CSF production, and osmotically drawing extravascular edema fluid into the intravascular space. Mannitol also functions as a free radical scavenger, which may help improve HE. Mannitol has been shown to correct episodes of intracranial hypertension in human acute liver failure patients and has been associated with improved survival.²⁹ Administration of intravenous mannitol (0.5 to 1.5 g/kg over 10 to 20 minutes) is therefore recommended to treat intracranial hypertension. This dose may be repeated provided that hypernatremia does not develop and serum osmolality does not exceed 320 mOsm/L.^{29,40}

Management of an Acute Exacerbation of Chronic Hepatic Encephalopathy

Animals with chronic HE (types B and C) may present with an acute crisis demonstrating significant neurologic signs such as obtundation and seizures. Acute episodes may require hospitalization and treatment for short-term management of clinical signs. Long-term medical management with dietary manipulation, nonabsorbable disaccharides, and antibiotics is typically successful in controlling clinical signs of chronic HE once an acute crisis has resolved.

Benzodiazepine Antagonists

Benzodiazepine antagonists such as flumazenil (0.02 mg/kg IV) and sarmazenil (3 mg/kg IV), may be effective for short-term alleviation of clinical signs of HE in human and animal patients.^{40–44} However, it is uncertain how long their effects last. There is no evidence that flumazenil has any significant effect on recovery or survival of HE patients.^{41,44} Therefore, flumazenil cannot be recommended for management of chronic HE, but it may be helpful in the management and diagnosis of HE in a comatose patient.

Antiepileptics

Seizures can occur in patients with HE in the acute setting.⁴⁵ Diazepam should be avoided in these patients because it is mainly metabolized by the liver and can result in excessive sedation and respiratory depression.⁵ Intravenous levetiracetam (20 mg/kg IV q8h) is preferable for acute management of seizures. Adverse effects may include sedation in dogs and lethargy and decreased appetite in cats.^{4,40} Sodium bromide (600 to 1200 mg/kg IV, diluted in a 3%

Key Points

- Treatment of hepatic encephalopathy (HE) should include reducing risk factors that may precipitate clinical signs, such as gastrointestinal hemorrhage and metabolic derangements.
- There is no definitive diagnostic test for HE.
- Acute HE is commonly associated with intracranial hypertension and cerebral edema. Transfer to a tertiary care facility with an intensive care unit is recommended in these cases.
- Ultrasonography is a noninvasive method for imaging the portal vasculature, liver, and other organs in an unsedated dog or cat, and it is a valuable tool in the diagnosis of the underlying cause of HE.
- The mainstay of treatment for HE due to a portosystemic shunt includes lactulose and oral antibiotics.

solution with 1 L sterile water, given over 8 hours) may also be considered in dogs due to its lack of hepatic metabolism; however, this medication may exacerbate sedation in an already obtunded patient.^{4,40}

Long-Term Management of Chronic Hepatic Encephalopathy Nutrition

It has been shown that patients with chronic liver disease develop severe muscle wasting from being in a continuous catabolic state. A low-protein diet can lead to increased muscle protein catabolism, promoting further hyperammonemia.³⁵ In the absence of a functional liver, skeletal muscle tissue serves a primary role in detoxifying ammonia.⁴⁵ The current practice is to feed patients with HE as much protein as they can tolerate, or, in

other words, restrict protein to a level that is just enough to prevent HE.^{35,45} Protein is restricted only if all measures to increase protein tolerance fail.³⁵ Protein tolerance can be increased by adjunct treatments, including orally administered antibiotics (neomycin and metronidazole) and lactulose, provision of nonmeat protein sources, and diet supplementation with soluble fiber.^{35,45} If protein restriction is necessary, a minimal intake of 2.1 g protein/kg body weight/day is recommended for dogs; 4.0 g/kg body weight/day is recommended for cats.⁴⁵ Commercially prepared prescription diets, such as Hill's Science Prescription Diet l/d (Hill's Pet Nutrition) and Royal Canin Hepatic Support (Royal Canin USA), are appropriate for protein restriction in HE patients.^{45,46} If the patient becomes neurologically asymptomatic, the level of protein in the diet can be slowly increased by 0.3 to 0.5 g/kg at 7- to 10-day intervals using dairy or vegetable protein.³⁵

Red meat, fish, and eggs can result in heme metabolism, with ammoniagenic potential.^{35,45,47} Dietary proteins from soybeans and milk proteins (i.e., casein, cottage cheese, whey) are well tolerated by animals with liver failure and may allow an increase in protein intake in encephalopathic patients.⁴⁵ Studies have evaluated the effectiveness of soy-based diets for the management of HE. In a study comparing soy protein to poultry-based low-protein diets for dogs with a congenital PSS, plasma ammonia levels were significantly lower after use of the soy diet compared with the meat-based diet. However, the HE grade improved similarly with both

diets.⁴⁷ Vegetable protein diets are thought to have increased soluble fiber, resulting in catharsis (similar to lactulose).⁴⁵⁻⁴⁷ If a vegetable protein diet is elected for a feline patient, adequate taurine and arginine must be present in the diet. Taurine can be supplemented at 1 g/kg soy-based diet.³⁵ Manganese content should be limited in the diet due to its implication in the pathogenesis of HE in animals with a PSS.⁴⁸ Owners interested in feeding home-cooked diets should consult with a veterinary nutritionist, who can help guide appropriate dietary supplementation. help guide appropriate dietary supplementation.³⁵ Frequent, small meals should be fed, which can decrease catabolism and optimize digestion in cirrhotic patients.⁴⁵

Nonabsorbable Disaccharides

The use of nonabsorbable disaccharides, including lactulose and lactitol, remains the mainstay treatment of chronic HE. Nonabsorbable disaccharides are fermented by bacteria in the intestine to yield acetic, butyric, propionic, and lactic acids. Fermentation provides an acidic environment capable of converting ammonia to ammonium.

Ammonia freely diffuses across the mucosal barrier of the colon, whereas ammonium becomes "trapped" and is eliminated in feces. The acidic environment also changes the composition of the bacterial flora, which helps to eliminate toxins that would otherwise accumulate. The breakdown of lactulose produces four osmotically active particles that draw water into the colonic lumen, increasing fecal water content and resulting in osmotic diarrhea. This reduces colonic bacterial load by increasing colon motility.

Lactulose is associated with a significant improvement in the severity of chronic HE in people⁴⁹ but with only a small increase in survival time and no difference in severity of HE or overall outcome in patients with acute liver failure.⁵⁰ There are no studies evaluating the use of lactulose in veterinary patients with HE. Based on human studies, lactulose (1 to 3 mL/10 kg PO q6-8h) and lactitol (0.5 to 0.75 g/kg PO q12h) are recommended for the treatment of HE in dogs and cats.^{40,51} The dose of lactulose should be adjusted so that the patient produces two or three soft stools per day. In patients too mentally dull for oral administration, lactulose can be given rectally (5 to 10 mL/kg cleansing water enema, followed by 5 to 15 mL lactulose diluted 1:3 with water q8h).⁵¹ Adverse effects of lactulose administration include abdominal distention, cramping, and diarrhea.⁴⁰ Nonabsorbable disaccharides should be used with caution because osmotic diarrhea causes isotonic fluid loss, and hypernatremia can result if decreased mentation does not allow for adequate water intake.

Antibiotics

The goal of oral antibiotic treatments is to reduce the mass of ammonia-producing bacteria in the colon. Neomycin, an aminoglycoside antibiotic, alters the composition of the bacterial flora in the colon, thus decreasing the number of ammonia-producing bacteria. Two studies comparing the use of lactulose and neomycin in human patients with portosystemic encephalopathy found neomycin to be as effective as lactulose in improving signs of

HE.^{52,53} There are no veterinary studies on the use of neomycin in small animals with HE. One major advantage of neomycin compared with lactulose is that it does not cause diarrhea. Therefore, neomycin (20 mg/kg PO q12h)⁴⁰ should be considered in patients intolerant of lactulose. Neomycin can also be administered via a retention enema (15 mg/kg diluted in water q6h after cleansing enema).⁴⁰ Neomycin, although poorly absorbed from the intestines when given orally, is highly nephrotoxic and should never be given parenterally. Despite its poor absorption from the gastrointestinal tract, some neomycin does enter into the systemic circulation and can result in irreversible nephrotoxicity and ototoxicity with chronic use.⁵⁴

Studies on the use of oral metronidazole in treatment of HE are limited in human medicine and lacking in veterinary medicine. One study found metronidazole to be as effective as neomycin and lactulose in controlling the clinical signs of HE.⁵⁵ Another study demonstrated that metronidazole was not as effective as neomycin in lowering blood ammonia levels.⁵⁶ The use of metronidazole for the treatment of congenital PSSs is recommended when diet and lactulose are ineffective.³⁵ Metronidazole undergoes extensive hepatic metabolism; therefore, the dose must be reduced in patients with HE (7.5 mg/kg PO q8-12h) to avoid toxic effects.³⁵ Advantages of using metronidazole over lactulose or neomycin include decreased risk of diarrhea and nephrotoxicity. Maintenance therapy at high doses has been associated with a central vestibular syndrome characterized by ataxia and nystagmus.^{57,58}

Rifaximin is a semisynthetic derivative of rifamycin that is virtually nonabsorbed from the gastrointestinal tract. Rifaximin has been shown to be effective in the treatment and prevention of HE in people.^{32,59} In comparison to neomycin and lactulose, rifaximin has proven to be more effective in lowering blood ammonia levels and improving clinical signs associated with HE.^{1,32,60} There are no studies in small animals pertaining to the use of rifaximin in HE. The major advantage of rifaximin is that no dosage adjustments are necessary in human patients with hepatic or renal disease (400 mg PO q8h).⁵⁴ However, rifaximin is very expensive. It is currently recommended for human patients who are refractory to or intolerant of lactulose treatment.⁵⁴ A current dose for small animals does not exist at this time.

Probiotics

Probiotics are live microbiologic dietary supplements that have beneficial effects on the host beyond their nutritive value. Probiotics reduce the substrates for potentially pathogenic bacteria and provide fermentation end products that support potentially beneficial bacteria. Stool samples from human patients with HE have shown that probiotic supplementation decreases the numbers of *Escherichia coli*, *Fusobacterium* spp, *Clostridium* spp, and staphylococci and increases numbers of non-urease-producing *Lactobacillus* spp.^{32,61,62} Probiotic use has also been found to decrease plasma ammonia levels⁶³ and improve neurologic scores compared with placebo in human patients with HE.⁶⁴ Delivering a probiotic in the form of live-culture yogurt with dairy-quality protein offers an inexpensive and acceptable form of treatment.^{32,61,64} Most

commercially available probiotic products sold for use in companion animals include *Lactobacillus* or *Bifidobacterium* spp.⁶² Fortiflora (Purina Veterinary Diets) contains the lactic acid bacterium *Enterococcus faecium* SF98. ProStoraMax (Iams Veterinary Formula) is a chewable probiotic containing canine-derived *Bifidobacterium animalis*. ProViable-DC (Nutramax Laboratories, Inc) is a multistrain probiotic. Probiotic formulas administered to patients should ideally originate from the species being treated and be nonpathogenic.⁶²

Zinc

Zinc, an essential trace element, is important in the regulation of protein and nitrogen metabolism. Zinc deficiency has been implicated in the pathogenesis of HE due to a PSS.^{35,65,66} Zinc deficiency impairs the activity of the urea cycle enzymes and glutamine synthetase, impairing nitrogen detoxification. Zinc supplementation maintains urea cycle function and provides cytoprotective effects against hepatotoxic agents through its antioxidant activity.³⁵ Unfortunately, human studies of zinc supplementation for HE have had inconsistent results with regard to efficacy, dosage, duration, and types of zinc,³² and veterinary studies are lacking. Dietary supplementation with zinc is recommended in small animal patients with refractory HE due to a PSS or in patients with subnormal tissue zinc concentrations (1 to 3 mg elemental zinc/kg/day using zinc acetate).^{35,45} Measuring plasma zinc concentration before and several weeks after initiation of treatment allows assessment of systemic toxicity and response to treatment.^{35,45} The target serum zinc level is 200 to 500 µg/dL.⁴⁰ Zinc supplementation can be associated with vomiting and hemolytic anemia.^{40,67}

Branched-Chain Amino Acids

Patients with HE have an increased ratio of aromatic amino acids (AAAs) to BCAAs.⁶³ Restoration of the appropriate balance of amino acid levels might be of benefit; however, there is no consensus concerning BCAA diets in the treatment of HE in people.^{63,68} One study in dogs with chronic HE did not see any improvement in patients fed a diet with a high BCAA:AAA ratio compared with a low BCAA:AAA ratio.⁶⁹ This study concluded that it was not the content of the dietary amino acids but rather the total protein intake that may have a beneficial effect.⁶⁹ The use of diets enriched with BCAAs for the treatment of HE cannot be recommended in veterinary patients at this time.

Future Therapies

L-Ornithine-L-Aspartate

L-Ornithine-L-aspartate (LOLA), an endogenous form of ornithine and aspartate, reduces blood ammonia levels by providing substrates for the intracellular conversion of ammonia to urea and glutamine. Although one study using LOLA in human acute liver patients did not find any significant changes in survival,⁷⁰ LOLA has been demonstrated to improve blood ammonia concentration and HE grade in human patients with chronic mild to moderate HE.⁷¹ Although this intervention has potential as an adjunctive therapy for HE, there are no known studies of the use of LOLA in veterinary patients.

Molecular Adsorbent Regenerating System

The Molecular Adsorbent Regenerating System (MARS; Gambro, Sweden) is an extracorporeal assist device that uses albumin dialysis for the specific removal of albumin-bound toxins.⁷² MARS lowers plasma levels of bilirubin, bile acids, AAAs, copper, digoxin-like substances, indoles, mercaptans, short- and medium-chain amino acids, nitric oxide, prostaglandins, phenols, and benzodiazepine-like substances. It is postulated that the use of MARS may improve clinical HE via reduction of blood ammonia levels, clearance of AAAs, and clearance of endogenous benzodiazepines. However, studies thus far have been of short duration, and no conclusions can be made regarding long-term efficacy and effect on survival.⁷³ MARS may have potential use in the veterinary field to stabilize patients with types A and C HE that are unresponsive to more conservative treatment until the underlying factors can be corrected.

Stem Cell Therapy

Current research investigating hepatic stem cell therapy may provide a new treatment modality for patients with acute and chronic liver failure. Methods for obtaining colony-forming liver progenitor cells from healthy dog livers have already been established.^{74,75} Liver regeneration could be stimulated by injecting diseased livers with progenitor cells or by stimulating the endogenous progenitor cells to proliferate and differentiate, which makes liver progenitor cells of great preclinical importance for currently untreatable liver diseases.^{74,75} Stem cell therapy may hold future promise for the treatment of patients with types A and C HE by regenerating healthy liver tissue in the presence of acute liver failure.

Conclusion

HE is a common syndrome resulting from acute or chronic liver disease. The prognosis of HE in acute liver failure is guarded. The presence of intracranial hypertension from acute liver failure is extremely challenging to treat. Only a fraction of these patients survive.²⁹ Chronic HE is almost always reversible. If signs do not resolve within 72 hours of treatment, an ongoing precipitating factor should be suspected.⁵⁴ The multifactorial nature of this syndrome allows for a variety of treatment options. New modalities of treatment that may add to therapeutic options for cats and dogs are currently being researched in human patients and laboratory animals.

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1. Which factor can precipitate development of hepatic encephalopathy (HE) in an animal with a portosystemic shunt?

- a. gastrointestinal hemorrhage
- b. infection
- c. sedation with diazepam
- d. hypokalemic alkalosis
- e. all of the above

2. Which laboratory value, if significantly elevated in serum, does not correlate with HE?

- a. ammonia
- b. bile acid
- c. L-phenylalanine
- d. C-reactive protein
- e. alanine aminotransferase

3. Which of the following does not support a diagnosis of HE?

- a. high serum ammonia level
- b. resolution of clinical signs in response to treatment with cathartics
- c. decrease in cerebrospinal fluid glutamine
- d. a small liver and uroliths on abdominal ultrasonography
- e. hyperintensity of lentiform nuclei on MRI T1-weighted images

4. Lactulose can be an effective treatment for HE because it

- a. directly reduces cerebral edema
- b. decreases ammonia absorption in the colon.
- c. increases the urinary excretion of ammonia.
- d. provides substrates for the intracellular conversion of ammonia to urea and glutamine.
- e. binds to false neurotransmitters in blood.

5. Which statement is true with regard to antibiotic therapy in the treatment of HE?

- a. Metronidazole can result in central vestibular signs at high doses.
- b. Neomycin is effective when given parenterally.
- c. Neomycin administration results in diarrhea.
- d. The dose of metronidazole does not require adjustment in patients with HE.
- e. Rifaximin is associated with development of irreversible nephrotoxicity with chronic use.

6. Which statement regarding nutrition in patients with HE is false?

- a. A diet low in branched chain amino acids is ideal in patients with HE.
- b. Patients with chronic liver disease are in a catabolic state.
- c. Dietary protein restriction should be just low enough to prevent HE.
- d. A diet based on vegetable protein is preferred to a diet based on animal protein in dogs with HE.
- e. Adequate taurine and arginine must be present in feline diets.

7. Mannitol decreases intracranial hypertension in HE patients by

- a. reducing cerebrospinal fluid production.
- b. osmotically drawing extravascular edema into the intravascular space.
- c. decreasing blood viscosity.
- d. acting as a free radical scavenger.
- e. all of the above

8. L-Ornithine-L-aspartate therapy may be effective in treating HE because the drug

- a. alters the gastrointestinal bacterial flora.
- b. directly decreases cerebral edema.
- c. enhances conversion of ammonia to urea and glutamine.
- d. antagonizes benzodiazepine-like substances.
- e. directly increases dopamine concentrations in the brain.

9. The Molecular Adsorbent Regenerating System does not lower plasma levels of

- a. bilirubin.
- b. benzodiazepines.
- c. aromatic amino acids.
- d. copper.
- e. albumin.

10. The clinical signs of intracranial hypertension associated with type A HE do not include

- a. hypertension.
- b. tachycardia.
- c. miosis.
- d. decerebrate posture.
- e. irregular respiration.