Severe Hepatic Encephalopathy

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10-15-19

The most useful definition of hepatic encephalopathy (HE) in veterinary medicine is probably 'neurologic dysfunction caused by liver disease and/or portosystemic shunting.' Patients may be lethargic, obtunded, have behavioral changes, head pressing, blindness, seizures, tremors, generalized weakness, and progress to coma and death. Signs can be insidious or profoundly acute in onset, and slowly or rapidly progressive. In small animal patients portosystemic shunting is a more common cause of HE versus functional liver failure or cirrhosis. There are no specific physical examination findings that will diagnose HE, thus clinicians must maintain a high index of suspicion and the patient's history will be very important in establishing the diagnosis in the emergency setting. High arterial or venous ammonia is supportive of a diagnosis of HE, but normal ammonia levels do not rule out HE. Elevated circulating ammonia and systemic inflammation are believed to be the primary drivers of HE and treatment is largely aimed at their reduction. The following discussion focuses on patients with severe, immediately life-threatening HE.

Initial stabilization is the same for all severe HE patients regardless of the underlying pathophysiology, begins as it does with all critical patients. Ensure the airway is open and protected, and the patient is ventilating adequately. As HE progresses patients lose their gag reflex, have a depressed respiratory drive, and develop muscle weakness. The most severely affected patients may be stuporous or comatose requiring intubation and sometimes assisted/mechanical ventilation. If assisted ventilation is necessary, end tidal CO2 should be maintained between 30-40mmHg.

Establish IV access, collect blood for analysis, and initiate IV fluid therapy. Initial therapy with a balanced isotonic crystalloid such as Plasmalyte A or Normosol R is preferred. Normal saline is also acceptable. Some clinicians avoid use of lactate containing fluids (Lactated Ringer's solution) based on the physiologic rationale that the lactate must be metabolized by the liver. There is no evidence to support or refute this rationale. If LRS is the available isotonic fluid, it should be used. Most patient are dehydrated and/or hypovolemic due to decreased intake from abnormal mentation, and fluid losses from vomiting/diarrhea/polyuria. Volume resuscitation should begin with boluses of 20ml/kg (dogs) or 10ml/kg (cats) IV over 10-15 minutes and repeated up to 4 times in the first hour of treatment to resolve hypotension. Patients who remain hypotensive despite fluid resuscitation should be supported with vasopressors. The author prefers norepinephrine as the first-line pressor however there is no evidence to support any particular vasopressor over another as the first choice in veterinary patients with HE. Patients who are not responsive to fluid therapy plus vasopressors may benefit from supraphysiologic doses of glucocorticoids.

IV fluids should be continued at maintenance plus estimated ongoing losses until the patient's mentation normalizes and the animal is taking in adequate volume spontaneously. Recognizing patients receiving IV fluids may not be compelled to drink, the IV fluids should be decreased as the patient improves. During the acute phase, IV fluids help to dilute circulating ammonia, reduce ammonia formation, and speed ammonia elimination from the body.

Serum chemistry, electrolytes, ammonia (if available at the point-of-care), and a complete blood count should be performed as early as possible, but collecting samples should not delay treatment. Urine should be collected for urinalysis and urine culture (UTI is a common cause of decompensation in animals with portosystemic shunting disease), but sample collection should not delay treatments.

Seizures should be controlled as soon as possible using levetiracetam 30-60mg/kg IV q8h, or propofol 2-6mg/kg (titrated to effect). Propofol can be given as a continuous infusion if needed. Benzodiazepines are likely to control the seizures however may result in profound and prolonged sedation if the patient's liver lacks the ability to metabolize them. They can be used if they are the only available agent, and are often administered to patients with active seizures before the diagnosis of HE is made. Fluamzenil is the reversal agent for benzodiazepines. Monitor reversed patients carefully as the flumazenil may be metabolized faster than the benzodiazepine and the patient may require additional reversal agent.

Cerebral edema caused by excess circulating ammonia is common and should be treated with mannitol. Mannitol should NOT be given to hypovolemic patients, however. Patients should be quickly volume resuscitated, then given mannitol 0.5-1g/kg IV over 15-20 minutes. This dose can be repeated 3-4 hours

later up to 2g/kg/d. Patients receiving more than one dose of mannitol should have serum electrolytes monitored and fluid therapy adjusted as needed. It is important to remember that patients receiving mannitol will subsequently have an osmotic diuresis. Urine losses should be estimated and replaced with balanced isotonic crystalloid or free water, depending on the electrolyte status of the patient.

Ammonia reducing therapy should commence as early as possible. Enemas remove colonic contents and reducing substrate for ammonia-producing bacteria. Physical removal of blood from the GI tract (from GI bleeding) prevents hemoglobin from becoming a substrate for ammoniagenesis. Begin by administering cleansing enemas using warm tap water or warm crystalloid fluids until the effluent is clear. Then retention enemas are administered. Options include lactulose, neomycin, povidone iodine, or warm water. The author prefers lactulose enemas however there are no studies evaluating efficacy of lactulose over other options in veterinary medicine. There is one study in humans that found lactulose or lactitol containing enemas to be superior to warm water enemas. The author uses 3ml/kg lactulose mixed with 7ml/kg warm water given via rectal Foley catheter, retained for 30-60 minutes, and repeated hourly up to 3 times. Once the patient is able to take oral medications transition to oral lactulose at 0.25ml/kg PO q6h. Patients receiving more than one enema should have electrolytes monitored as electrolyte and free water derangements can occur.

There are many factors implicated in precipitation of HE. Patients should be evaluated for inflammatory foci and sepsis. Electrolytes, hydration status, and acid/base status should be evaluated early and monitored. The most common conditions contributing to acute fulminant HE in animals presenting to the emergency department in the author's experience are infections (most commonly UTI) and/or GI bleeding in animals with pre-existing liver or portosystemic shunting disease, consitpation (more common in cats), and hepatotoxin exposure. Ampicillin sulbactam 30mg/kg IV q8h is the author's antibiotic of choice. This covers aerobic and anaerobic Gram positive and negative bacterial infections in most tissues reasonably well. Other drugs/combinations that provide similar coverage are equally reasonable. Empiric treatment of GI ulcers is reasonable early in the course of treatment in all HE patients and clearly indicated in patients with evidence of GI bleeding. Histamine blockers such as famotidine, proton pump inhibitors such as pantoprazole, and physical gastroprotectants such as sucralfate are reasonable choices. Combination treatment with histamine blockers and proton pump inhibitors is not necessary - PPI alone (no histamine receptor blocker) is adequate. N-acetylcysteine can be administered in the case of known or suspected hepatotoxins, in addition to treatments specific to the toxicity if any treatments are available.

Most acute HE patients will begin to show improvement within 1-2 hours of aggressive treatment, and those with chronic conditions typically continue to make slow but steady improvement over 12-24 hours. Patients with acute hepatic injury secondary to toxicity may take longer to improve (or continue to deteriorate) depending on the toxin and degree of injury.

Plasma transfusions are reserved for patients with documented coagulopathy and active bleeding. Most patients with liver disease will have deranged PT and aPTT however despite these findings patients may be hyper- or hypocoagulable.

References

Gow, AG. Hepatic Encephalopathy. *Vet Clin North Am Small Anim Pract. 2017 May;47(3):585-599*
Webster, RL. Hemostatic Disorders Associated with Hepatobiliary Disease. *Vet Clin North Am Small Anim Pract. 2017 May;47(3):601-615*
Thawley, V. Acute Liver Injury. *Vet Clin North Am Small Anim Pract. 2017 May;47(3):617-630*