MEDICAL MANAGEMENT: PORTOSYSTEMIC VASCULAR ANOMALIES (PSVA)

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Key Points

- Medical management improves clinical status of PSVA dogs before surgical intervention but must be individually titrated for each patient because of differences in shunting severity.
- Protein intake must avoid a negative nitrogen achieved by titrating allowances to maximum tolerance starting at 1.2-1.5 g/kg body weight (~3.9 gm protein/100 kcal) using commercial diets.
- Adjuvant HE interventions (e.g. lactulose, metronidazole, others) should be individually tailored for each case and may only be intermittently needed once nutritional management is optimized.
- Owners should be prepared to provide interventional actions for episodic HE.
- Medical management can improve life quality and span for dogs intolerant to PSVA ligation and can achieve normal life expectancy in minimally symptomatic PSVA dogs.

It is inarguable that optimal therapy for symptomatic PSVA is shunt attenuation. However, there are several issues deserving thoughtful consideration before recommending this expensive, invasive, and sometimes non-effective intervention. Complex cases presenting to a tertiary referral hospital routinely include scenarios and queries that cannot be addressed by simple decision tree arbitration. Because outcome and morbidity associated with PSVA surgery varies among individual patients, surgeons, hospitals or institutions, clients deserve thoughtful dialog describing the spectrum of treatment options. All symptomatic PSVA dogs benefit from medical management described in these notes, yet not all dogs require all forms of therapy. As a result of improved condition, clients may question the need for surgical interventions. Because no single treatment plan fits all cases, individuation of care is the best course to follow. We have successfully managed a spectrum of PSVA patients medically. It is difficult to judge outcome of these patients against those undergoing surgical shunt attenuation because medical management is used for 1) minimally symptomatic PSVA patients, 2) dogs failing surgical intervention, and 3) dogs with a degenerative zone 3 hepatic lesion having dismal surgical outcome.

Hepatofugal Portal Circulation: the Difference between Typical PSVA & Acquired PSS

Systemic effects of hepatofugal (flow directed away from the liver) portal circulation in PSVA differ from acquired portosystemic shunting (APSS). The latter category usually reflects intrahepatic portal hypertension associated with necroinflammatory or fibrosing liver disease. Consequently, APSS usually associates with sinusoidal collagenization and capillarization that reduce ultrafiltrate formation in the space of Disse. This ultrafiltrate normally bathes the surface of the hepatocyte and functions as an exchange interface. Architectural restructuring in the liver leads to intrahepatic portal hypertension and shunting augmented by the compensatory increase in hepatic arterial perfusion (high pressure system, normal response to reduced hepatic portal circulation). Enhanced arterial perfusion increases intrahepatic sinusoidal pressure driving backward flow in the valveless portal system. Reduce hepatocyte exchange of nutrients, wastes, and metabolites and re-designation of hepatocellular phenotype (parenchymal functions), is accompanied by intrahepatic & splanchnic portal hypertension and APSS formation. Effects on protein synthesis, 3rd space fluid and protein sequestration, glucose homeostasis, and ascites formation are often obvious. In PSVA these changes do not occur as portal blood bypasses the liver in the absence of portal hypertension, altered hepatocyte function, or APSS. However, the compensatory increase in arterial circulation represents a major histologic features of the PSVA/MVD syndrome (coiled arterioles, increased arteriole twigs). Lobular atrophy reflects
hepatocyte atrophy due to deprivation of hepatotrophic substances normally delivered in the portal circulation. Hepatocellular function remains relatively unimpaired in PSVA while detoured enterohepatic portal circulation reduces first pass extraction of bile acids and ammonia from the splanchnic circulation. Pathologically, reduced detoxification of enteric nitrogenous wastes leads to hepatic encephalopathy (HE). The closest human correlate to PSVA (other than rare PSVA) occurs in patients treated with TIPS (transjugular intrahepatic portosystemic shunt) to alleviate bleeding from portal hypertension induced APSS. In these, a spectrum of HE severities directly correlate with the magnitude of TIPS shunting. Over time as the TIPS lumen diminishes, frequency and severity of HE episodes ameliorate. This scenario is similar to what we observe in PSVA cases where clinical symptomatology seemingly reflects the magnitude of shunting (e.g. dogs with intrahepatic PSVA (I-PSVA) manifest clinicopathologic features and brittle HE compared to many dogs with extrahepatic PSVA (E-PSVA). It also substantiates the clinical improvement observed in PSVA dogs only tolerating partial shunt occlusion.

**Portosystemic Encephalopathy & Minimal Hepatic Encephalopathy (MHE):** Hepatic encephalopathy (HE) is characterized by a spectrum of neurobehavioral / neurocognitive changes with potential for full reversibility. HE pathogenesis has been widely researched for >50 years with a number of causal theories proposed. It is widely accepted that overt HE and minimal HE (MHE) share a common multifactorial pathogenesis. MHE represents the mildest form of HE within a continuum, having with no recognizable clinical signs. In humans, MHE manifests as subtle neurocognitive deficits and psychomotor abnormalities primarily affecting immediate memory, attention, visual spatial abilities, and fine motor skills, but not overall intelligence. Identification of HE severity for humans is standardized to objective and subjective assessments (Table 1). Where this is no method for MHE characterization in dogs, it is likely that MHE exists in our asymptomatic PSVA patients. Factors contributing to HE in humans (associated with chronic liver disease) include: ammonia, cerebral edema, oxidative stress, and inflammatory mediators. While enteric nitrogenous substances (especially ammonia) are considered critical to HE, plasma NH₃ does not correlate with HE severity.

**Table 1:** West Haven Criteria for grading HE

<table>
<thead>
<tr>
<th>Grade</th>
<th>Features</th>
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<tr>
<td>0</td>
<td>No abnormalities</td>
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<tr>
<td>I</td>
<td>Trivial lack of awareness</td>
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<tr>
<td></td>
<td>Euphoria or anxiety</td>
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<td></td>
<td>Shortened attention span</td>
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<td></td>
<td>Impaired simple addition or subtraction</td>
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<tr>
<td>II</td>
<td>Lethargy or Apathy</td>
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<td></td>
<td>Time disorientation</td>
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<td></td>
<td>Overt personality change</td>
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<td></td>
<td>Inappropriate behavior</td>
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<tr>
<td>III</td>
<td>Somnolence to semi-stupor</td>
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<td></td>
<td>Responsive to stimuli</td>
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<td></td>
<td>Confused</td>
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<td>Overt disorientation</td>
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<td>Bizarre behavior</td>
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<td>IV</td>
<td>Coma</td>
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**Ammonia:** Exogenous Ammonia is largely derived from the intestines from ingested protein and systemic oxidative deamination of amino acids derived from the gut. Enteric ammonia also derives from bacterial hydrolysis of urea (ureases). Constipation as well as blood within the digestive tract each increase enteric ammonia and amino acid production and substantially contribute to HE (Table 2). In fact, hemoglobin is the most encephalogenic protein provoking hyperammonemia. Gut ammonia (colon largely) enters the portal circulation (largely by passive diffusion) and is influenced by faecal pH (pH > 6 decreases passive uptake). Portal circulation is rich in ammonia ~2–8 fold > than in the systemic circulation. Endogenous ammonia is produced in muscle, brain and renal tissue from transamination/deamination of amino acids (mainly glutamine, asparagine, alanine and histidine). It is transiently buffered in muscle (glutamate + NH₃ ⇌ glutamine) and permanently detoxified in the hepatic Krebs–Henseleit Urea Cycle. In patients with APSS, associated hepatic fibrosis and hepatocyte dysfunction augments
Portosystemic shunting in causing hyperammonemia. In PSVA, the extent of hepatofugal circulation (i.e., the magnitude of shunt flow) determines the severity of clinical signs, hyperammonemia, and delivery of enteric toxins to the systemic circulation. Earlier presentation of dogs with I-PSVA is consistent with this phenomenon (larger shunt magnitude compared to many E-PSVA) as is the variable presentation of dogs with E-PSVA (diverse differences in shunt size and hepatic portal perfusion) with some as old as 13 yrs at initial shunt discovery.

**NH3 theory of HE:** Ammonia crosses the blood-brain-barrier (BBB) where it influences brain function, involving a cascade of events (briefly described here). Alzheimer type 2 astrocytes (type of glial cell) are the only brain cells equipped for ammonia metabolism (glutamine synthetase catalyzes conversion of NH3 → glutamine). In HE, these cells undergo functional and structural alterations increasing in size and number, predominantly in the cerebral cortex, cerebellum and brainstem nuclei. Normally, astrocytes modulate cerebral blood flow and maintain integrity of the BBB. High blood ammonia increases astrocyte glutamine. This leads to an increase in the cell osmotic gradient leading to cell swelling, activation of inhibitory GABA, and impairing excitatory neurotransmitter signaling (glutamate, catecholamine), resulting in *neuro-inhibition*. Cell swelling is mediated by oxidative/nitrosative stress, mitochondrial permeability transition, mitogen-activated protein kinases, and nuclear factor-κB (thus, both oxidative and inflammatory mediators and signals as well as ammonia are involved). High levels of ammonia also increase permeability of the BBB which also facilitates development of cerebral edema and intracranial hypertension. An increase in aromatic amines (precursors for false neurotransmitters) and an increase in benzodiazepine receptor expression enhances the inhibitory GABA neurotransmitter system, further contributing to the pathogenesis of HE. Anatomical lesions in HE are generally mild and reversible, allowing for complete and frequent reversibility of clinical signs. The most serious lesion is brain edema which imparts a poor prognosis. This lesion is infrequently encountered in PSVA patients. Hyperammonemia also biochemically impairs function of the Krebs cycle, reducing oxidative decarboxylation of pyruvate (provoking alanine and lactate accumulation) and depleting α-ketoglutarate (an important cycle intermediate). These effects limit brain ATP generation, worsened by concurrent hypoglycemia (neuroglycopenia).

The central role of ammonia in HE is corroborated by radiologic and isotope studies and positive emission tomography studies in humans with end stage liver disease as well as in animal models. Recent work supports that systemic inflammation increases risk for hyperammonemic HE. *In vivo* lipopolysaccharide enhances ammonia-induced changes in cerebral hemodynamics. One hypothesis holds that the inflammatory response changes permeability of the BBB allowing encephalogenic toxins to access the CNS. Subclinical infections initiate episodic HE in human cirrhotics in which precipitating events remained otherwise unclarified. Evidence also implicates a role for altered gut flora in HE. Altered enteric microecology secondary to altered enteric motility, reduced gastric acid production, and change in mucosal immunity, is known to accompany chronic liver disease. These features predispose to small intestinal bacterial overgrowth (*SIBO*) that is proven to increase enteric toxin absorption. Normalization of gut microecology has reversed HE and recent study of Rifaximin, a non-absorbable antimicrobial, provides corroborating evidence. Increased enteric ammonia production also may derive from enhanced promoter expression increasing enterocyte glutaminase, as shown in hepatic cirrhosis complicated by HE. Yet, despite extensive evidence supporting a predominant role of ammonia in the manifestation of HE, blood ammonia concentrations are neither correlated with brain or CSF ammonia levels nor the presence or severity of HE. That ammonia is only a part of the HE

292
spectrum is further evidenced by failure of hyperammonemia due to inborn errors of urea cycle enzyme deficiencies to produce either severe encephalopathy or coma.

Normal brain function depends on anatomical neuron integrity, sufficient energy, and efficient synaptic neurotransmission. Each of these factors are adversely affected in HE. Encephalogenic toxins additional to ammonia (some augmenting ammonia toxicity) include: GABA, endogenous benzodiazepines, methionine, mercaptans, tryptophan, tyrosine → octopamine, phenols, short chain fatty acids, and neurosteroids (agonists of GABA receptor). Enteric flora generates many of these molecules. Reduced integrity of the BBB increases CNS accessibility by encephalogenic molecules. Disrupted neurotransmission reflects formation of false neurotransmitters (largely derivatives of aromatic amino acids [AAA]) increasing secondary to preferential use of branched chain amino acids [BCAA] ) and abnormalities in GABAergic and benzodiazepine pathways.

Effective Management of HE in PSVA Must Be Tailored to the Patient:
Most manifestations of HE are reversible with medical treatment. The most important aspect of HE management is to:
1) Promptly recognize & treat precipitating factors
2) Prevent formation of encephalogenic substrates in the gastrointestinal tract.
3) Evacuate enteric substrates &toxins contributing to HE

Therapeutic Interventions
1. Dietary Modification: A relationship between diet and HE hypothesized since 1883 was proven in dogs using a surgically created PSS (Eck fistula). This pioneering study clarified that ingestion of red meat or fish evoked HE compared to a caseinate/soy protein isolate. An additional study confirmed that feeding an adequate quantity of protein and energy is essential to avert HE. Overzealous protein restriction may adversely lead to a negative nitrogen balance promoting muscle catabolism and increasing risk for HE in some PSVA dogs. Because skeletal muscle is the second largest site of ammonia metabolism (transient detoxification in the glutamine / glutamate cycle), loss of muscle mass has important implications. Muscle catabolism also releases amino acids increasing nitrogenous wastes. Nutritional support must be tailored to the individual patient as different magnitudes of shunting seeming influence dietary protein tolerance. Standard strategy used for nutritional management of PSVA dogs is illustrated in Figure 1. First, feed an appropriate species-specific protein restricted commercial diet formulated for hepatic insufficiency, initially combined with lactulose +/- metronidazole. This provides a dietary protein allowance of ~1.2-1.5 gm/kg body wt. per day (~3.9 gm protein/100 kcal food). This starting estimate is based on research in surgically created PSS in dogs. Commercially available effective canine formulations include L/d (Science Diets) and Hepatic...
Support (Royal Canin, Waltham). A modified protein quality (focused on vegetable and dairy quality protein) is used if a homemade diet is developed.

Several small meals should be fed per day to optimize digestion/assimilation; this helps reduce enteric debris that generates HE toxins. Adequate energy intake should be assured by sequentially evaluating body weight and BCS. Water soluble vitamin supplements without extra copper supplements should be provided.

Long term survival in PSVA dogs (> 10 yrs) has been accomplished using the commercial diets formulated for hepatic insufficiency, tailored to optimal protein intake for that individual. Protein content is adjusted using supplementary dairy (cottage cheese, feta cheese, hard cheese, yoghurt) or tofu sources.

The patient is sequentially assessed for body weight and condition and for clinicopathologic markers of protein insufficiency / sufficiency / excess (e.g. total protein, albumin, BUN, creatinine (reflecting muscle mass) and ammonium biurate crystalluria. Initial assessments are done at 7 to 10 day intervals. If all goes well (HE controlled, maintained weight, no ammonium biurates) additional protein supplements may be explored. This is done using 0.3 gm/protein/kg BWt additional protein support, with follow-up sequential assessments to ensure patient benefit and tolerance. Selection of the food source and amount for supplemental protein is facilitated by use of the NAT-2 website (annotated in the footnotes). Yogurt has several constituents, including lactose and milk protein, in addition to live bacterial content, that assists in control of HE in PSVA dogs when used on a regular basis. With low levels of methionine, aromatic amino acids, and ammoniagenic amino acids, vegetable protein can be used for snacks (vegetable and dairy protein better tolerated than animal protein in dogs with HE). Dietary fiber provided by some vegetables also has value in increasing enteric nitrogen incorporation / elimination, decreasing intestinal transit time and intraluminal enteric pH, and increasing fecal ammonia elimination. Human liver patients consuming a high protein vegetable-based diet demonstrated fewer HE episodes and developed increased plasma arginine and citrulline concentrations which might facilitate ammonia removal in the urea cycle.8

Additional Dietary Allowances: based on personal experience with daily maintenance of of PSVA dogs (> 10 years), even dogs with portal atresia can tolerate milk-bone like dog cookies, supervised recreation with rawhide chews (avoid swallowing large pieces, chews assist with maintaining dental health), popcorn, yogurt, cheese, ice creme, cottage cheese, fruit (not raisins), carrots, broccoli, and almonds with no ill effects. Some PSVA dogs have been maintained on "vegetarian" home cooked food for years. If acceptance of a modified liver diet needs coaxing with some form of "meat" protein, only white meat chicken is allowed (only small amounts). Owners must be warned to AVOID hot dogs, Vienna sausages, hamburger, steak, organ meats, fish, and shell fish. We have observed episodic HE in a few PSVA dogs fed eggs and in one dog fed a hydrolyzed protein diet.
2. **Enemas**: used for episodic HE are best provided by owners to thwart syndrome onset at first recognition. Enemas also may be needed to manage constipation that can provoke HE. (See Table: 2 & 3) Cleansing and retention enemas are routinely used for dogs hospitalized for HE.

3. **Colonic Catharsis**: Table 4 (↑ colonic evacuation) is typically achieved with lactulose, lactitol, or lactose +/- dietary fiber. This action reduces colonic retention of encephalogenic toxins (e.g. ammonia, SCFA), and also reduces colonic flora generating toxic products. Colonic cathartics are used if constipation is a suspected cause of episodic HE.

4. **Non-Absorbable Fermentable Carbohydrates**: (Table 4) provides several benefits including acidification of enteric pH that traps NH₃ as NH₄⁺ (ammonium ion), reduced activity of bacterial ureases and enteric peptidases, increased bacterial nitrogen fixation (increases apparent nitrogen tolerance), and colonic catharsis secondary to osmotic effects of produced organic acids. The prototype medication is lactulose, a synthetic disaccharide (galactose & fructose) not digested by mammalian enzymes but rather fermented to organic acids by enteric flora. Lactitol, a similar product, is more palatable to humans, (less sweet) but is more costly. Most animals accept lactulose without issue. Dose-limiting adverse effects include cramping, diarrhea and flatulence. Hypernatremia and hypercalcemia may result from lactulose administration; the former reflects fluid loss and the latter drug assisted calcium uptake. Large overdosage of lactulose/lactitol may result in diarrhea, electrolyte disturbances, and hypovolemia that may be severe enough to provoke HE. Lactulose and Lactitol dosing is started low and gradually titrated upward to achieve passage of several soft stools per day. There is some evidence of a synergistic effect between lactulose and a co-administered oral antimicrobial for HE suppression. While lactulose efficacy remains controversial, there are insufficient clinical trials (human) to refute its benefit. This controversy should be considered when designing long term medical management
for a PSVA patient. Some dogs do well long term with just well sculpted diet therapy, with lactulose reserved for episodic HE.

5. Enterically Non-Absorbable Antibiotics given Orally- (Table 4): this approach potentially reduces SIBO and modifies enteric flora contributing to HE (suppressing urease producers and production of encephalogenic products). Such treatment has potential for reducing bowel flora overall. There also is some evidence that neomycin may improve HE by inhibiting intestinal glutaminase. However, while systemic absorption of oral Neomycin is minimal at ~4%, both irreversible ototoxicity and renal toxicity have been witnessed in several PSVA dogs receiving chronic neomycin therapy. Thus, neomycin is not recommended as first line chronic therapy. Recent information based on work in humans, suggests that Rifaximin is highly effective in controlling episodic HE even when administered as single therapy. Rifaximin is a poorly absorbed synthetic antimicrobial with broad spectrum antibacterial activity (both aerobic and anaerobic Gram-positive and Gram-negative organisms). Yet, it also preserves beneficial host enteric microbiota. Trials in humans show a favorable tolerability profile with a lower overall risk of adverse effects compared to neomycin. However, the trade-off comes at a considerable cost, with rifaximin being >4 fold more expensive than other agents (e.g. lactulose or neomycin).

6. Enterically Absorbable Antibiotics given Orally- (Table 4): may thwart episodic HE by adjusting enteric flora and reducing formation of encephalogenic products contributing to HE. Clavamox or metronidazole, alone or in conjunction for only a few doses can interrupt an HE episode in some PSVA patients. Clavamox is especially useful in cats for this effect.

7. Oral Glucose Supplementation (Karo syrup in the home environment) may be useful in pediatric toy breed dogs with PSVA developing episodic neuroglycopenia. Synergistic effect of neuroglycopenia with other encephalogenic toxins increases risk for episodic or protracted HE.

8. Fluid Therapy (subcutaneous & oral supplementation): plays a pivotal role in averting episodic HE and is useful in the home environment. Episodic HE leads to dehydration by impairing normal water intake. Fluid therapy improves hydration status and assists in removing systemic urea. Considering that ~25% of urea fluxes into the intestines where it converts to ammonia via bacterial ureases, increased renal urea elimination assists in relieving systemic ammonia concentrations that may contribute to the HE episode.

9. Probiotics, Prebiotics, Synbiotics: Probiotics (beneficial living microorganisms), prebiotics (indigestible carbohydrates that stimulate growth and activity of beneficial enteric bacteria), and synbiotics (a combination of the two) have been used to attenuate HE. The most common application is in the use of probiotic yogurt (dairy quality protein, fermentable carbohydrate, and live bacterial culture). With this approach, consistency of treatment is important. Gut Re-Population with a Probiotic (supplementing “beneficial” bacteria) may modulate bowel flora to become less encephalogenic (colonization with non-urease-producing bacteria), and may reduce SIBO contributing to HE. Probiotics have been shown to reduce blood ammonia in humans prone to HE. Yet gut repopulation is difficult (some believe impossible) requiring frequent agent administration. Gastric acidity reduces efficacy of this treatment unless controlled release capsules are used or acid pump blockers are administered.

10. Adjust Drug Dosages, when appropriate, anticipating reduced first pass hepatic extraction. Minimize or avoid use of drugs capable of precipitating or aggravating HE (Table 2) or resulting in protracted anesthetic recovery.

11. Avoid Vitamin Deficiencies: provide a daily water soluble vitamin supplement. Thiamine deficiency can provoke metabolic encephalopathy confused with HE.
12. Zinc supplementation: a trace metal essential for function of >300 metalloenzymes, including two urea cycle enzymes and glutamine synthetase that controls temporary detoxification of ammonia in muscle and astrocyte ammonia shuttling. While an inverse relationship between serum zinc and ammonia concentrations has been described in human patients, plasma zinc concentrations cannot predict tissue zinc status. However, we have documented subnormal hepatic zinc concentrations in ~45% of dogs with PSVA. Among mechanisms contributing to zinc deficiency are: reduced dietary intake (low protein diets deliver lower zinc concentrations), reduced intestinal absorption, reduced hepatointestinal extraction, portosystemic shunting (leads to increased urinary loss), and altered protein and amino acid metabolism. Although prescription diets formulated for management of hepatic insufficiency contain supplemental zinc, dose sufficiency and zinc availability remain unexplored in PSVA patients. Little information is available regarding the clinical efficacy of zinc supplementation in HE; some evidence suggests it improves amino acid metabolism and some results are conflicting. Nevertheless, patients with subnormal tissue zinc concentrations and perhaps patients with recalcitrant HE for which an underlying precipitating event or factor remains undiscovered, should receive oral zinc supplementation. A safe dosing strategy is to give 1-3 mg elemental zinc/kg body weight per day, measuring plasma zinc before and several weeks after treatment initiation to document 1) a lack of toxicity and 2) a slight increase in plasma zinc concentration.

13. Seizure control: dogs with PSVA in our large data set seemingly have increased risk for epilepsy. Avoid diazepam intervention in these patients. Zonisamide (a sulfa drug) and Keppra are preferred in our hospital to phenobarbital or KBr. We do not prophylactically treat PSVA patients lacking a seizure history with anticonvulsants before ligation surgery. Postoperative seizures are exceeding rare, developing in <1/150 cases.

14. Flumazenil: the once popular benzodiazepine theory of HE is now refuted. Flumazenil, a benzodiazepine antagonists, was used to reverse benzodiazepine associated neurotransmission issues associated with HE. With increased clinical assessment and research into its efficacy it is clear that flumazenil does not reliably alter HE unless benzodiazepines have been administered. Initial positive responses following drug administration relapse within a few hours of treatment. Routine use of flumazenil in humans with HE is not recommended.

15: Alternative therapies for HE: BCAA vs AAA Adjustment: In patients with PSS and hepatic insufficiency, an increased ratio of aromatic amino acids (AAA, phenylalanine, tryptophan, tyrosine) : branched chain amino acids (BCAA, leucine, isoleucine, valine) reflects preferential metabolic (hepatic and peripheral) utilization of BCAA. Since BCAA and AAA share a common BBB transporter, this altered ratio favors transport of AAA into the CNS where they function as false neurotransmitters contributing to HE. While adjustment of the AAA:BCAA ratio has been proposed to beneficially modulate HE, controlled studies fail to justify consensus on their use. Studies in Eck fistula dogs (model of PSVA) demonstrate that oral supplementation with BCAA provides no benefit. However, there is some evidence that parenteral BCAA (humans patients with cirrhosis) provides benefit in acute HE for crisis intervention.

L-Ornithine-L-Aspartate (OA): a substrate for ureagenesis that converts ammonia to urea and glutamine, thereby reducing blood ammonia. Investigated experimentally in models of ammonia toxicity and cirrhosis as well as in humans with liver disease, OA shows promise as an alternative pathway of NH₃ detoxification. Under normal physiological conditions, NH₃ is removed by formation of urea in periportal hepatocytes and by glutamine synthesis in perivenous hepatocytes, skeletal muscle, and brain. In solution, OA separates into its component amino
acids, L-ornithine and L-aspartate. Ornithine acts as a substrate for both the urea cycle and for ornithine transaminases. Treatment increases circulating glutamine concentrations and activity of muscle glutamine synthetase (GS) without increasing CSF glutamine. It is hypothesized that both substrates for the GS reaction (glutamine, glutamate) decrease in CSF when OA is administered. There are several controlled trials demonstrating that OA can reduce ammonia and mild to moderate HE in humans. Both IV and oral administration has been effective (dose range: 2-8 g/day PO, IV 20 g/day) when combined with dietary protein restriction. Adverse gastrointestinal side effects have been reported in 50% of treated patients. This intervention has potential as a salvage therapy for HE in animals but has not been investigated in either the dog or cat to my knowledge.

Sodium Benzoate: In many species, benzoic acid (or benzoates) are conjugated with glycine yielding hippurate which is rapidly excreted in urine. This reaction indirectly removes NH₃ as each mole of benzoate excretes 1 mole of nitrogen (glycine transfers the nitrogen to benzoate). In humans, this reaction provides NH₃ detoxication comparable to lactulose. However, the capacity for glycine conjugation varies among species and when this capacity is exceeded, conjugation of benzoate with glucuronic acid proceeds. The dog and cat differ substantially in their metabolism of benzoate compared to humans and rodents. In dogs, glucuronic acid conjugation predominates thereby diminishing the benefit of benzoate as a detoxication mechanism for NH₃. The cat is highly susceptible to lethal benzoate toxicity although they do primarily excrete benzoates as hippuric acid. However, cats have limited capacity for glucuronic acid conjugation. Ingestion of benzoic acid (in food or medications e.g. benzoate, benzyl alcohol, benzocaine) has imposed severe and fatal toxicity in cats with intake as low as 0.2% being lethal. (Toxic signs include ataxia, hyperesthesia, muscle fasciculation, blindness, aggression, seizures, respiratory failure, coma, and death). In the absence of glycine or glucuronic acid conjugation, benzoic acid is known to strongly inhibit hepatic fatty acid oxidation by reducing free CoA; it remains unclarified if this contributes to the feline toxicity syndrome. While chronic dosing in healthy dogs does not provoke side effects at < 1 gm/kg body weight, the metabolism of benzoate in dogs does not permit its use as an alternative means of ammonia detoxification.

Sodium Phenylacetate / Sodium Phenylbutyrate: In man this therapy is used for management of inborn errors of ammonia detoxification. Sodium phenylacetate has been superseded by the congener phenylbutyrate because of its unpleasant lingering odor. Phenylbutyrate is activated to its CoA ester and subsequently metabolized by hepatic β-oxidation to phenylacetyl-CoA. Thereafter it is conjugated with glutamine yielding phenylacetylglutamine excreted in urine. Stoichiometrically, 2 moles of nitrogen are excreted for each mole of phenylbutyrate administered. In man sodium phenylbutyrate is usually dosed at 250 mg/kg per day but dosages as high as 630 mg/kg/day have been used, given IV or PO. Limited side effects in humans include acid-base dysregulation, altered serum phosphate concentrations (high and low), and oral mucositis (if residual drug remains in the mouth). There is no information on comparable application in the dog or cat.

L-Carnitine for HE: (L-CN)- is a conditionally essential nutrient involved in transport of activated fatty acids (Acyl-CoA) across the mitochondrial membrane. In the mitochondria L-CN beneficially regulates the ratio of acetyl-CoA:CoA to facilitate continued fatty acid β-oxidation. L-CN has a beneficial effect on brain energy metabolism suppressed by severe
hyperammonemia. Studies in a portocaval-shunted rat model of HE show that L-CN curtails the ammonia driven increase in alanine and lactate production that contribute to astrocyte and cerebral edema. It also increased CSF taurine and brain glutamate concentrations without changing NH$_3$ or glutamine. A taurine lowering influence (in astrocytes) may impart a neuroprotective influence thwarting cytotoxic brain edema. Beneficial responses shown in a few clinical studies of liver patients may reflect a propensity for subnormal total and free plasma CN concentrations, corroborated experimentally in animals with surgically created portocaval-shunts. Hypocarnitinemia is easily corrected by oral administration; effective dosages in cirrhotic humans ranged between 2 to 5 gm divided PO BID where it significantly improved cognitive function after 30 and 60 days of administration.

Footnotes: