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Hepatic encephalopathy in dogs and cats

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Abstract

Objective – To comparatively review the pathogenesis, clinical presentation, diagnosis, and management of hepatic encephalopathy (HE) in dogs and cats.
Data Sources – The Medline database was searched for articles related to HE in people, dogs, and cats. Articles published within the last 5 years were given special importance.
Human Data Synthesis – The pathogenesis of HE is complex and incompletely understood, but ammonia appears to play a central role. Hyperammonemia leads to accumulation of glutamine in astrocytes, with subsequent astrocyte swelling and neurological dysfunction. The development of HE in patients with hepatic cirrhosis is a poor prognostic indicator. The fermentable disaccharide lactulose and the antimicrobial rifaximin are US Food and Drug Administration approved treatments for human HE. Severe protein restriction is no longer recommended for patients with this condition.
Veterinary Data Synthesis – HE is often associated with portosystemic shunting in dogs and cats. Ammonia plays a central role in the pathogenesis of HE in dogs and cats, but other factors such as manganese and endogenous benzodiazepines may also contribute. Recently, a soy protein-based diet was found to be beneficial in treating canine HE. Severe dietary protein restriction is likely to be detrimental in affected animals. There have been no clinical trials of drugs routinely used in the management HE in veterinary medicine, but lactulose and antimicrobials such as metronidazole are well-established treatments.
Conclusions – HE is a potentially life-threatening condition that is probably underdiagnosed in companion animals. Although various treatment recommendations have been proposed, there is a lack of evidence in the veterinary literature regarding optimal strategies for the management of this condition. As our understanding of the pathogenesis of HE in dogs and cats evolves, novel diagnostic tests and therapeutic agents may become available.

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Abbreviations

AAA	aromatic amino acids
APSC	acquired portosystemic collateral vessels
BBB	blood brain barrier
BCAA	branched chain amino acids
CPSS	congenital portosystemic shunts
GABA	gamma-aminobutyric acid
HE	hepatic encephalopathy
LOLA	L-ornithine-L-aspartate
MHE	minimal hepatic encephalopathy
MRI	magnetic resonance imaging
NS	neurosteroids
PTBR	peripheral type benzodiazepine receptor
SIRS	systemic inflammatory response syndrome

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Introduction

Hepatic encephalopathy (HE) is defined as the spectrum of neuropsychiatric abnormalities seen in patients with liver dysfunction after exclusion of other known brain disease.[1] The syndrome was first described over a hundred years ago when dogs with Eck fistulas, surgically created portacaval anastomosis followed by ligation of the portal vein, were fed meat, leading to the use of the term "meat encephalopathy."[2] Although much has been learned about the etiopathogenesis and clinical features

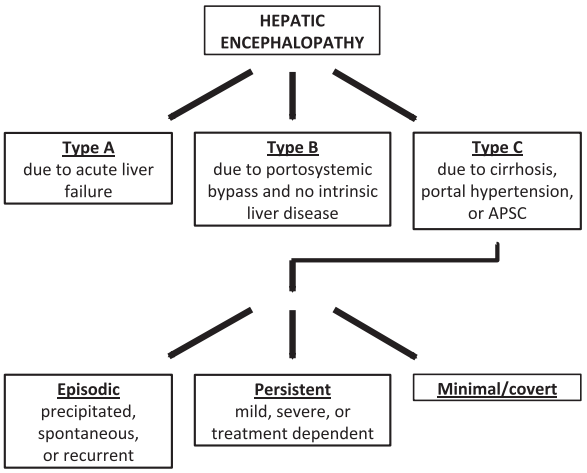
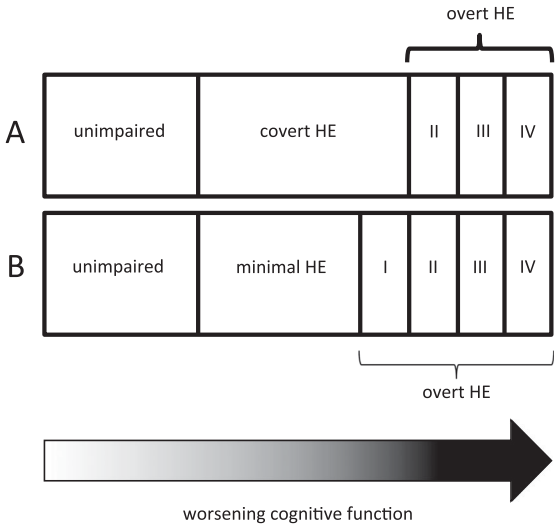


Figure 1: Hepatic encephalopathy classification scheme. Classification scheme for HE based on the 1998 World Organisation Mondiale de Gastroentérologie consensus statement.[1] This scheme is widely used in human medicine and divides cases of hepatic encephalopathy by the underlying cause and clinical features. The scheme is also applicable to dogs and cats. APSC = acquired portosystemic collateral blood vessels.



Grade	Clinical signs
I	trivial lack of awareness, euphoria/anxiety, shortened attention span, impaired performance of addition or subtraction
II	lethargy, apathy, disorientation, personality changes
III	somnolence, or semi stupor, but responsive to stimuli
IV	coma

Figure 2: Classification schemes for grading the severity of hepatic encephalopathy. Comparison between the 2010 International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) and hepatic encephalopathy grading scheme (A)[10] and the 1998 Organisation Mondiale de Gastroentérologie consensus statement scheme (B).[1] In the more recent scheme grade I overt hepatic encephalopathy and minimal encephalopathy have been collapsed into one category of covert hepatic encephalopathy. The grading scheme for overt HE is presented below. HE = hepatic encephalopathy.

of HE since those early days, there are still large gaps in our understanding of this condition.

Canine HE is often attributable to portosystemic shunting, either due to congenital portosystemic shunts (CPSS) or the formation of acquired portosystemic collateral vessels (APSC) due to portal hypertension.[3,4,a] HE in cats is usually associated with CPSS or arginine deficiency secondary to feline hepatic lipidosis.[4–6] HE is not an uncommon diagnosis in dogs and cats. In a recent retrospective study, 68% of dogs undergoing surgical attenuation of a single CPSS had preoperative neurological abnormalities.[7] Seventy percent of cats with CPSS undergoing shunt attenuation had ptyalism and 44% had episodic signs consistent with encephalopathy.[8] Clinical signs of HE in dogs and cats can range from mild manifestations, such as apathy and mental obtundation, to seizures, coma, and even death.[4] There is far smaller body of literature on HE in dogs and cats than in humans. Consequently, much of what has been published about HE in companion animals is either inferred from human studies, inferred from other animal models of HE, or is based on anecdotal observations rather than scientific evidence.

The aims of this article are to comparatively review the pathogenesis, clinical presentation, diagnosis, and management of HE in dogs and cats. Gaps in the understanding of HE in dogs and cats and areas worthy of future study are also highlighted.

The Medline database was searched for articles related to HE in people, dogs, and cats. Articles published within the last 5 years were given special importance. The reference lists of the manuscripts identified from this search were used to identify other pertinent articles.

Current Published Human Research

Classification of HE

Hepatic encephalopathy is divided into 3 types according to etiology (Figure 1).[1] Type A HE is due to acute liver failure in the absence of preexisting liver disease. Type B HE is associated with portal systemic bypass without intrinsic hepatocellular disease (eg, CPSS). Type C HE is associated with cirrhosis and portal hypertension or acquired portal systemic shunting, and is subcategorized according to duration/characteristics. Minimal HE (MHE) is defined as HE occurring in patients with normal mental and neurological status but abnormal results on specific psychometric tests.[9] This term has recently

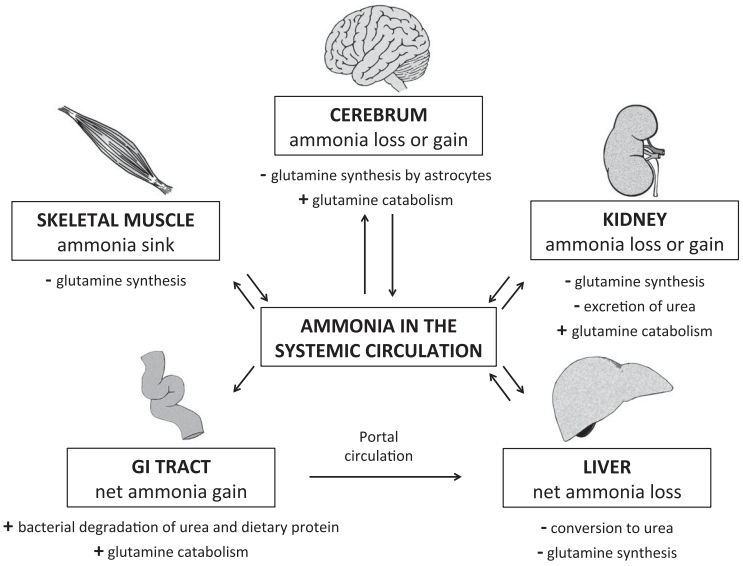


Figure 3: Ammonia metabolism and trafficking. The major organs and tissues involved in the metabolism and trafficking of ammonia. Courtesy of Dr. Randi Gold, Texas A&M University.

been replaced with the term covert HE as it underestimated the importance the importance of HE without altered mental status.[10] The most recent clinical grading scheme for HE is shown in Figure 2.[10] Patients with overt HE have impaired mental status and/or flapping tremor (except when comatose).[10]

Pathogenesis

Ammonia

In aqueous solution, ammonia is in equilibrium with ammonium ions ($NH_3 + H^+ \leftrightharpoons NH_4^+$). Ammonium ions predominate in the blood stream, where the pH is approximately 7.4.[11] Ammonia is lipophilic and highly lipid-soluble, and therefore passes freely across cell membranes. Ammonium ions are not lipid-soluble and consequently must be transported across cell membranes by carrier-mediated systems.[12] Ammonia metabolism and trafficking in the body is depicted in Figure 3.

The intestines are an organ of net ammonia gain.[13] Urease producing gastrointestinal microbial organisms produce ammonia by breaking down nitrogenous products such as urea. Historically, colonic bacteria were considered to be the main source of ammonia in the body, although gastric bacteria such as *Helicobacter pylori* can also convert urea into ammonia.[14] However, this assumption was called into question with the discovery that germ-free dogs with Eck fistulas still developed hyperammonemia and signs of HE.[15] In a reaction catalyzed by the enzyme glutaminase, glutamine is metabolized to equimolar quantities of glutamate and ammonia (glutamine $\leftrightharpoons$ glutamate + NH_3).[12] Enterocytes have a high glutaminase activity. Thus, the other enteric source of ammonia is the metabolic activity of the intestinal mucosa itself.

The liver is the main site of ammonia detoxification, which occurs via two metabolic pathways. Firstly, ammonia is converted into urea by periportal hepatocytes through a metabolic pathway known as the urea-cycle.[16] Urea is less toxic than ammonia and is water-soluble and therefore can be excreted by the kidneys. This pathway has a low affinity for ammonia but a high capacity.[16] Secondly, glutamine is synthesized by perivenous hepatocytes, which have a high glutamine synthetase activity. This system has a high-affinity for ammonia but a low capacity.[16] In liver failure, the ability of the liver to metabolize ammonia to either urea or glutamine is reduced, contributing to hyperammonemia.[17] Additionally, in patients with cirrhosis and ASPC, blood from the splanchnic circulation bypasses the liver, further exacerbating hyperammonemia.

The role of the kidneys in ammonia metabolism and trafficking is complicated. The kidneys of humans contain glutaminase and glutamine synthetase and so are capable of both the metabolism or synthesis of glutamine.[18] It has been documented that in experimental hyperammonemia, the kidneys can increase the proportion of ammonia that is produced and excreted in the urine, thus becoming organs of net ammonia excretion.[19]

Skeletal muscle can act as an ammonia "sink" in patients with acute and chronic liver disease as this tissue represents the most quantitatively important source of glutamine synthetase.[20] Loss of skeletal muscle mass in people with chronic liver disease is recognized as a

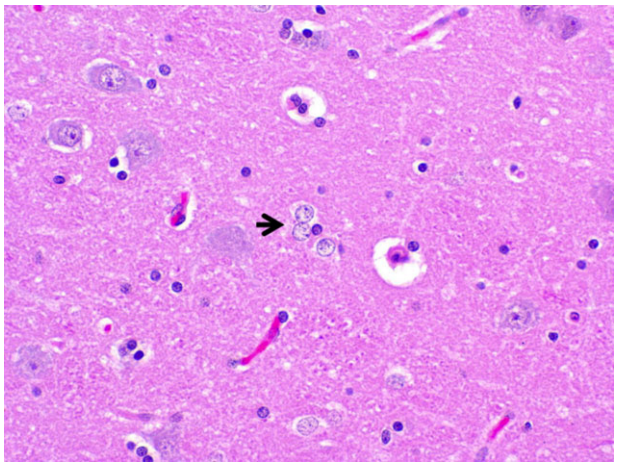


Figure 4: Alzheimer type II astrocytosis in a dog. Section of the cerebrum of a dog stained with H&E at 20X magnification. Three astrocytes showing Alzheimer type II change consistent with hepatic encephalopathy are clustered around an oligodenrocyte (arrow). These cells are pale, round, and have no cytoplasm. Courtesy of Dr. Brian Porter, Texas A&M University.

predisposing factor for HE. Net ammonia uptake by the skeletal muscle of human patients with cirrhosis has been demonstrated.[21]

The cerebrum has glutaminase and glutamine synthetase activity, located in different compartments.[12] The astrocytes have a high glutamine synthetase activity, which is important in the pathogenesis of HE, and the neurons have the highest glutaminase activity.[12] Ammonia passes freely across the blood brain barrier (BBB) in healthy individuals. In experimentally induced liver failure, the cerebrum acts as an organ of net ammonia removal.[22] It accomplishes this through the formation of glutamine by astrocytes and its subsequent release into the systemic circulation.

One of the most appealing theories regarding the role of ammonia in the development of HE is that it causes astrocyte swelling.[23] Histological changes occur, in which swollen astrocytes change morphology and become Alzheimer type II astrocytes with nuclei that have an enlarged nucleolus, a watery interior, and a well-defined nuclear rim (Figure 4). It was previously thought that glutamine leads to astrocyte swelling by acting as an osmolyte, leading to an influx of water. It is now believed that although glutamine plays a major role in astrocyte swelling, ammonia also drives this process through other mechanisms.[24]

Ammonia has been shown to have other effects on the cerebrum, all of which may play a role in the pathogenesis of HE. Sudden exposure of astrocytes in vitro to ammonia resulted in glutamate release, which may explain the agitation, confusion, and seizures seen in people with acute liver failure.[25] When rat astrocytes were exposed to ammonia for a prolonged period of time, glutamate-binding sites and glutamate transporters were downregulated.[26] This may explain the mental depression observed in people with HE due to chronic hepatic disease. Ammonia may also contribute to neurological dysfunction by increasing BBB permeability.[27]

Inflammation and infection

There is convincing evidence from clinical studies in people that both infection and inflammation play a role in the development of HE.[28] The systemic inflammatory response syndrome (SIRS) is common in people with both acute liver failure and cirrhosis.[29,30] Sepsis is a well-established precipitating factor for the decompensation of cirrhotic patients and often reflects the translocation of bacteria from the gastrointestinal tract.[9] People with cirrhosis have been shown to have a sepsis-like immune paralysis[30] and ammonia itself has been shown to interfere with neutrophil chemotaxis[31] and phagocytosis, while stimulating spontaneous oxidative burst activity.[32] This dysregulation of the immune system predisposes these patients to both infection and SIRS.

In people evidence suggests that inflammatory mediators trigger HE by exacerbating the effect of ammonia upon the cerebrum.[33] There is much ongoing investigation into the molecular mechanisms by which this occurs. In cirrhotic patients hyperammonemia and endotoxemia cause neutrophils to be preprimed and this may lead to enhanced neutrophil migration across the BBB.[28] Once in the cerebrum, neutrophils produce a variety of factors including chemokines, proinflammatory cytokines, proteases, and reactive oxygen species.[28] This is thought to increase BBB permeability, potentially increasing the diffusion of ammonia into astrocytes.[34] Furthermore, cytokines may directly affect cerebral neurotransmission, with subsequent behavioral changes.[34]

Neurosteroids

Neurosteroids (NS) are steroid hormones found in high concentrations in the brain even after gonadectomy and adrenalectomy. They are synthesized in the central or peripheral nervous system from cholesterol or the metabolites of steroid hormones produced in the adrenal gland or gonads.[9] Neurosteroid production in the brain occurs mainly in the mitochondrial endoplasmic reticulum of myelinating glial cells (such as astrocytes) and neurons. Synthesis of NS is regulated by the peripheral type benzodiazepine receptor (PTBR).[36] There is growing evidence to suggest that NS play a significant role in HE. Firstly, components of the PTBR are upregulated in the

brain of people and experimental animals with HE. Ammonia and manganese accumulate in liver failure and are thought to increase NS synthesis by activating PTBR. Finally, NS have been shown to accumulate in the brain of people with HE.[37]

Gamma-aminobutyric acid (GABA) is the main centrally acting inhibitory neurotransmitter in mammals; receptor binding leads to an increased chloride ion influx and hyperpolarization.[38] For many years, it was hypothesized that an increased GABAergic tone associated with HE was due to the action of endogenous benzodiazepines. However, it is now known that some NS are potent allosteric modulators of GABA-A receptors.[39] Although NS do not directly cause astrocyte swelling, increased concentrations may potentiate this process in the presence of hyperammonemia.

Oxidative stress

Oxidative stress is caused by the intracellular accumulation of reactive oxygen species and reactive nitrogen species. These are usually produced as a result of anaerobic metabolism. There is considerable evidence that oxidative stress plays a role in the pathogenesis of HE. Astrocyte cell cultures exposed to ammonia develop rapid cell swelling and release reactive oxygen species.[40] Some investigators have hypothesized that cell swelling occurs too quickly to simply reflect the osmotic properties of glutamine, and that oxidative stress must play a role.[25] In addition to ammonia there are other causes of oxidative stress in astrocytes, including inflammatory cytokines, and hyponatremia.[41] Reactive nitrogen species lead to impaired intraastrocyte substance transport and are believed to cause increased BBB permeability, astrocyte swelling, and cerebral edema.[42]

Manganese

Manganese is a neurotoxin that is believed to synergize with ammonia in causing HE. Serum manganese concentrations are increased in people with cirrhosis due to decreased biliary excretion.[43] Based on magnetic resonance imaging (MRI) studies, manganese has been indirectly demonstrated to accumulate preferentially in the basal ganglia of human patients with HE.[43] These MRI changes are associated with decreased psychometric performance and fatigue[44] and have been shown to resolve after liver transplantation in patients with acute liver failure.[45] Further support of the role of manganese in HE has been provided by autopsy studies that demonstrate manganese accumulation in the brains and especially the palladia, of these patients.[46]

The mechanisms for the neurotoxic effects of manganese have not been fully characterized, but in vitro experimental work has provided some insight. In cell culture, ammonia and manganese have synergistic negative effects on astrocytes, promoting free radical production, inner mitochondrial membrane depolarization, and loss of cellular integrity.[47] It is also postulated that manganese increases astrocyte expression of PTBR, which leads to synthesis of NS and an increased GABAergic tone.[48]

Amino acid imbalance

The ratio of plasma branched chain amino acids (BCAA) to aromatic amino acids (AAA) is greatly reduced in people with cirrhosis.[49] It has been hypothesized that, in conjunction with an altered BBB permeability, this results in increased concentrations of AAA, and reduced concentrations of BCAA within the brain. This could lead to intracerebral production of false neurotransmitters, such as octopamine and β-phenylethanolamine.[50] The result of this is reduced neural excitation. There is experimental evidence to support this in several species.[50] However, a metaanalysis of clinical trials assessing the efficacy of BCAA in the treatment of people with HE did not demonstrate any positive effect, and the studies that had been performed were judged to be of low methodological quality.[51] On the basis of these findings and others, the false neurotransmitter theory has fallen out of favor.

Precipitating factors

Several factors are known to precipitate HE in human patients with liver disease, with at least one trigger identified in 88 to 90% of those affected. Individuals with one or more of these factors have a worse prognosis than those without.[52] Factors reported to precipitate HE in people, dogs, and cats and the mechanisms by which they are believed to act are listed in Table 1.[9] The most commonly reportedprecipitating factors in people include gastrointestinal bleeding (18–76% of patients), constipation (3% to 52%), diarrhea (12% to 40%), infection (3% to 52%), hypokalemia (9% to 70%), hyponatremia (25% to 38%), and excess dietary protein (9% to 52%).[53,54]

Treatment of hepatic encephalopathy

Nonabsorbable disaccharides

Nonabsorbable disaccharides such lactulose and lactitol are fermented by the gastrointestinal microbiota, resulting in the production of volatile fatty acids, a decreased colonic pH, and movement of water into the colon by osmosis. In theory these agents have several beneficial effects: (i) trapping of ammonium ions within the colon leading to decreased absorption of ammonia into the portal circulation; (ii) inhibition of ammonia production by colonic bacteria; (iii) stimulation of incorporation of

Table 1: Precipitating factors for hepatic encephalopathy

Precipitating factor	Proposed mechanism(s) of action
Sepsis	Inflammatory mediators have a synergistic effect with ammonia
	Increased blood brain barrier permeability
	Altered neurotransmission
Gastrointestinal hemorrhage	Increased protein load and ammoniagenesis
Constipation	Dehydration
	Electrolyte abnormalities
	Bacterial overgrowth and bacterial translocation
Excess dietary protein	Increased ammoniagenesis
Dehydration	Electrolyte changes
	Increased renal ammoniagenesis
Drugs	Benzodiazepines and opioids lead to sedation
	Diuretics lead to electrolyte imbalances, alkalosis, and dehydration
Hypokalemia	Movement of intracellular potassium into the extracellular space leads to intracellular acidosis and trapping of ammonium ions within cells
Hyponatremia	Enhanced astrocyte swelling
Alkalosis	Increased access of ammonia to neurons (due to a shift in in the equilibrium from ammonium ions to ammonia, which can pass through cell membranes)
Poor compliance with lactulose therapy	Increased ammoniagenesis
Bowel obstruction	Dehydration
	Electrolyte abnormalities
	Bacterial overgrowth, and bacterial translocation
Uremia	Increased renal ammoniagenesis
Superimposed hepatic injury	Decreased hepatic conversion of ammonia to urea

ammonia within bacterial proteins; (iv) reduced intestinal transit times leading to decreased bacterial ammonia release; and (v) increased fecal excretion of nitrogenous compounds.[55] The results of placebo controlled studies support the efficacy of lactulose for treating overt HE.[56,57]

Antimicrobials

Antimicrobials have also been a long-standing treatment for HE in people, with the understanding that alterations in the intestinal microbiome may reduce ammoniagenesis. Neomycin was previously commonly used for this purpose but is no longer recommended as there is inadequate evidence to support efficacy and it is associated with risk of serious renal injury and ototoxicity.[58] Interestingly, neomycin has been shown to reduce intestinal production of ammonia from the catabolism of glutamine, suggesting that it has a direct effect on enterocytes, as well as reducing bacterial ammoniagenesis.[59] Metronidazole and vancomycin have also been used to treat HE in people. These drugs maybe better tolerated in people than neomycin but their efficacy has not been rigorously established.

Rifaximin, a semisynthetic derivative of rifampicin, is US Food and Drug Administration approved for maintaining remission of HE in people. This antimicrobial is administered orally, shows minimal absorption, and has a broad spectrum of activity against both gram-positive and gram-negative organisms.[60] Additionally, this agent appears to cause a low rate of selection for resistant bacterial mutants compared to other antimicrobials.[61] Rifaximin has been shown to be well tolerated and efficacious for the prevention of recurrence of overt HE either alone or in combination with lactulose.[60,62,63] A metaanalysis concluded that rifaximin is not superior to nonabsorbable disaccharides for managing HE, but that it may be better tolerated.[64] The cost of using this drug to treat an adult person with HE was approximately $1,600 US dollars per month at the time of writing.

Flumazenil

The role of endogenous benzodiazepines in the pathogenesis of HE is controversial.[65] Flumazenil is an intravenous benzodiazepine receptor antagonist that has been used for the short-term treatment of overt HE and a subset of comatose patients have been reported to awaken when given this drug.[66] Metaanalysis of controlled clinical trials with flumazenil did find a transient beneficial effect in a subpopulation of patients with HE due to cirrhosis, but there was insufficient data to indicate a survival benefit.[67] The only consensus among investigators is that flumazenil is useful when treating patients with HE who have taken benzodiazepines.

L-ornithine-L-aspartate

The efficacy of *L-ornithine-L-aspartate* (LOLA) for the treatment of HE has been assessed in several clinical trials. L-ornithine is a substrate of the urea cycle and L-aspartate is a substrate of the reaction that converts

ammonia to glutamine. Therefore, LOLA is believed to increase the rate of ammonia detoxification through both pathways. The authors of a recent metaanalysis study of clinical trials assessing the efficacy of LOLA concluded that this agent is well tolerated and efficacious in treating patients with mild to moderate overt HE, but not covert HE.[68] Based on these positive initial findings further investigations into the efficacy of LOLA for treatment of HE are warranted.

L-carnitine

Several potential mechanisms by which L-carnitine may be beneficial in ammonia toxicity have been proposed.[69] These include prevention of glutamate-mediated neurotoxicity in N-methyl-D-aspartate type glutamine receptors. A systematic review identified three high quality clinical trials assessing the efficacy of L-carnitine in treating HE.[70] These studies reported positive effects such as decreased serum ammonia concentrations and improved neuropsychological test scores in comparison to accepted therapies. These results are promising and further clinical trials are warranted.

Prebiotics, probiotics, and synbiotics

Modification of the gastrointestinal microbiota using prebiotics, probiotics, or synbiotics is a promising avenue for the treatment of HE. It has been suggested that these agents favor intestinal colonization with acid-resistant nonurease producing bacteria, thereby reducing ammoniagenesis.[71] However, there is not a strong evidence base to support the use of probiotics or prebiotics, other than lactulose. The authors of a metaanalysis study evaluating the efficacy of prebiotics, probiotics, and synbiotics for the treatment of MHE concluded that their use is associated with a significant improvement in MHE. Among the individual agents, lactulose appeared to have the most beneficial effect, followed closely by probiotics and synbiotics.[72] The authors of another metaanalysis study concluded that there is no convincing evidence that probiotics have a significant effect on patients with HE and that the methodological quality of the clinical trials to date is far from optimal.[73] Because of this controversy, further well-designed large-scale clinical trials of these agents are needed.

Current Veterinary Information

Classification of HE

The scheme used to classify HE in people[1] by underlying cause can be applied to dogs and cats if the definition of type C HE is broadened to include cases associated with all intrinsic hepatocellular disease and portal hypertension or acquired portal systemic shunting. However, HE is only recognized in dogs and cats with appropriate clinical signs, ie, patients with overt HE. Covert HE is commonly recognized in people[9] with chronic liver disease, and it would appear likely that a similar cases exist in companion animals. However, currently there is no way to diagnose covert HE in dogs and cats as the paper and pencil or computer-based neuropsychometric tests used in people are not applicable to veterinary patients. Additionally, there are no universally accepted guidelines to grade the severity of overt HE in dogs or cats, although some authors have adapted human grading schemes for use in dogs (Table 2).[74]

Underlying causes of HE

Portosystemic shunting permits ammonia-rich blood from the portal circulation to bypass the liver and flow directly into the systemic circulation, and is an important cause of HE in dogs and cats.[75] Portosystemic shunting can be due to congenital portosystemic vascular anomalies (including intrahepatic shunts and extrahepatic shunts; Type B HE) or can be due to the development of APSC (Type C HE). Acquired portosystemic collateral blood vessels are a consequence of prehepatic or hepatic portal hypertension.[76] This drives the growth of small shunting vessels and ultimately results in redirection of portal flow into the systemic circulation.

It is also possible that acute liver failure without portosystemic shunting could lead to severe ammonia dysmetabolism and subsequent HE (Type A HE). However, this seems to be less common than Type B or Type C HE in dogs[3,a] or cats.

Congenital urea-cycle enzyme deficiencies are uncommon disorders in which the liver's ability to convert ammonia into urea is diminished. Affected individuals are hyperammonemic and manifest clinical signs identical to HE. Although these disorders are not included in schemes used to classify HE in human patients[1] they are considered as a cause of HE in dogs and cats for the purposes of this article. Hyperammonemia due to arginosuccinate synthetase deficiency has been reported in dogs, including a kindred of Irish Wolfhounds.[77] Hyperammonemia was also reported in a cobalamin deficient 8-month old Border Collie.[78] Signs consistent with HE, such as ptyalism, are sometimes reported in cats with feline hepatic lipidosis.[5] Arginine is a substrate of the urea cycle and cats have a relatively high requirement for this amino acid. Arginine deficiency can lead to hyperammonemia in cats with feline hepatic lipidosis.[79]

In a retrospective study of 80 dogs diagnosed with HE; CPSS (reported in 64% of the dogs) and intrinsic hepatic disease with APSC (reported in 25%) were the most

Table 2: Grading scheme for canine hepatic encephalopathy[74]

Grade	Clinical signs
0	None
I	Mildly decreased mobility, apathy, or both
II	Severe apathy, mild ataxia, or both
III	Hypersalivation, severe ataxia, head pressing, blindness, circling, or some combination of these signs
IV	Seizures, stupor, or coma

commonly reported causes. Six percent of these dogs had intrinsic hepatic disease, without ultrasonographic evidence of APSC, and 5% had hepatic parenchymal disease but were not evaluated for the presence of APSC.[a] Similar results were obtained from a study using abdominal ultrasound to identify the causes of hyperammonemia in 90 dogs. In this study, CPSS was reported in 68%, APSC (including arterio-venous fistulae) in 19%, and no macroscopic shunting was noted in 12%.[3] The results of these studies highlight the importance of CPSS and APSC in causing canine HE. No such studies have been reported in cats but in the authors' experience CPSS are the most common cause of HE in this species as well.

Pathogenesis

Ammonia

There is good evidence that ammonia dysmetabolism plays a central role in canine and feline HE. Dogs with surgically created portacaval shunts with portal vein anastomosis (ie, Eck fistulas) have been shown to develop HE and high blood ammonia concentrations.[2] The signs of HE worsen with ingestion of a meat-based meal, supporting the theory that breakdown of dietary proteins and other nitrogenous substances by colonic bacteria contributes substantially to ammonia production.[2] The intestines are believed to be the main source of ammonia. However, it is now recognized that ammonia is produced by enterocytes when they metabolize glutamine as well as by the bacteria that populate the large bowel.[15] Dogs with CPSS were shown to have higher CSF concentrations of glutamine than control dogs, suggesting that the canine cerebrum converts excess ammonia to glutamine.[80] To the authors' knowledge, the impact of ammonia on astrocyte metabolism and swelling in dogs and cats has not been studied in depth. Dogs and cats with HE are often hyperammonemic, and successful treatment of HE is usually associated with a reduction in serum ammonia concentrations. However, patients may have HE despite a blood ammonia concentration within the reference interval[81] suggesting that other mechanisms also play a role in the pathogenesis of HE.

Infection and inflammation

In people, inflammatory mediators potentiate the effects of ammonia upon the central nervous system, and there is evidence that this also occurs in dogs. Firstly, in a retrospective study of dogs with CPSS and hyperammonemia, concurrent SIRS was associated with an increased odds for the development of overt HE.[82] A recent study of dogs with CPSS showed that those with overt HE had a higher mean serum C-reactive protein concentration than those without.[83] As dogs with induced APSC have been shown to develop endotoxemia,[84] those with spontaneous portosystemic shunts may also be at increased risk of SIRS because of increased concentrations of circulating endotoxin. However, the relationship between inflammation and canine HE needs to be better defined. To the authors' knowledge, this relationship has not been studied at all in cats.

Neurosteroids

Neurosteroidogenesis has been shown to occur in the oligodendrocytes and Purkinje neurons of the cerebral cortex of dogs.[85] Autoradiographic studies have confirmed the presence of PTBR receptors in the canine brain, but at much lower densities than in cats, guinea pigs, mice, and rats.[86] However, PTBR receptor densities have not been studied in dogs with HE.

Deranged GABAergic neurotransmission, suggesting an increased GABAergic tone, has been documented in dogs with HE.[87] Further support for the role of an increased GABAergic tone in the pathogenesis of canine HE is provided by the apparent improvement in clinical signs noted following administration of benzodiazepine-receptor partial inverse agonists. In a study using dogs with HE due to Eck fistulae, there was a positive response to treatment with the benzodiazepine-receptor partial inverse agonist sarmazenil. Drugs in this class can negatively modulate GABAergic tone irrespective of the properties of the ligand occupying the benzodiazepine receptor. These dogs did not respond to the benzodiazepine receptor antagonist flumazenil, which implies that endogenous benzodiazepines are unlikely to play a role in the pathogenesis of canine HE.[88] To the authors' knowledge, the role of NS and endogenous benzodiazepines in the pathogenesis of feline HE have not been reported.

Oxidative stress

Although oxidative stress plays an important role in various canine and feline hepatic diseases, the role of oxidative stress in the pathogenesis of HE has not been reported in these species.

Manganese

Dogs with CPSS have increased whole blood manganese concentrations compared to healthy dogs.[89] Blood manganese levels have not been reported in cats with HE. When the brains of dogs and cats with CPSS were evaluated using MRI, 10 of 13 dogs and 1 of 3 cats had hyperintensity in the area of their lenticular nuclei on T1-weighted images.[90] This finding is suggestive of manganese deposition. However, studies where brain manganese concentrations are being measured are needed to better define the role of manganese in the pathogenesis of HE in dogs and cats.

Amino acid imbalance

There is some evidence to support the role of amino acid imbalance in the pathogenesis of canine HE. Firstly, dogs with chronic liver disease and HE have been shown to have increased serum concentrations of the AAA L-phenylalanine.[91] Furthermore, in dogs with surgically created portacaval shunts, the development of HE coincided with an increase in plasma and CSF concentrations of AAA and a decrease in plasma BCAA concentrations. Plasma and CSF concentrations of the false neurotransmitters octopamine and phenylethonolamine are also increased. Administration of a solution of amino acids calculated to restore the BCAA to AAA ratio resulted in improvement of HE.[50] The results of studies looking at dogs with HE due to CPSS also support the role of amino acid imbalance.[80]

Precipitating factors

A number of factors that can potentially precipitate HE in dogs and cats have been described in the veterinary literature (Table 1). These include: a high protein meal, gastrointestinal hemorrhage, hypokalemia, azotemia and/or dehydration, alkalosis, diuretic administration, blood transfusion, sedative use, systemic inflammation and/or infection, and arginine deficiency in cats.[4] However, the evidence base to support the role of many of these factors in veterinary species is weak or nonexistent. In a retrospective study of 80 dogs with HE, 46% had at least one of the potential predisposing factors. Hypokalemia was recorded in 9% of dogs with HE, SIRS in 8%, disseminated intravascular coagulopathy or other coagulopathies in 6%, and hyponatremia also in 6%.[a] However, this study was descriptive and therefore does not prove an association or causation. Another study found that SIRS was associated with overt HE in dogs with CPSS.[82] Further investigation of the factors that may predispose dogs and cats to HE is needed.

Clinical presentation

As the most common causes of HE in dogs are CPSS and APSC the signalment of affected dogs reflects this. In a study of 80 dogs with HE the median age at the onset of clinical signs was 33 months with a range between 1 and 186 months.[a] The authors are not aware of any studies showing which breeds of dog are predisposed to HE but in a review of 2,400 dogs, the breeds most likely to be have CPSS (in descending order) were: Havanese, Yorkshire Terrier, Maltese, Dandy Dinmont Terrier, Pug, Miniature Schnauzer, Standard Schnauzer, and Shi Tzu.[92] There are no studies evaluating which breeds most that are most likely to developing APSC. However, the breeds that are predisposed to chronic hepatitis are the most likely to develop them. Dogs can develop APSC at a wide range of ages but in general these dogs are older than those with CPSS. The mean age of dogs with chronic hepatitis in a retrospective study was around 7 years (84 months).[93]

It is not clear which if any cat breeds are predisposed to HE and large-scale epidemiological studies will be needed to ascertain this. However, several breeds of cat have been reported to be affected by CPSS: domestic shorthair, Persian, British Shorthair, Ragdoll, domestic longhair, Birman, British Blue, and Tonkinese. There was no apparent sex predilection and the median age at presentation for CPSS was 8 months with a range from 3 to 59 months.[6] Cats with feline hepatic lipidosis tend to be older and in a study of 77 cases the median age at diagnosis was 96 months with a range between 12 and 192 months. No breed predilections were found.[5]

The clinical syndrome of HE is well recognized in dogs and cats. The findings are often initially subtle and episodic in nature but can progress in intensity and frequency.[4] Eating may exacerbate clinical signs. The most common historical findings in 80 dogs with HE were: obtundation (33%), altered behavior (29%), head pressing (28%), ataxia (26%), apparent seizures (24%), vomiting (24%), lethargy (23%), ptyalism (23%), apparent blindness (19%), and shaking (14%).[a] On neurological evaluation, the most common findings were obtundation (31%), ataxia (20%), weakness (10%), conscious proprioceptive deficits (9%), seizures (8%), circling (6%), cranial nerve deficits (5%), stupor (5%), and tremor (4%). Some of the dogs in this study may have had concurrent diseases and these findings are not necessarily specific for HE, but are representative of the spectrum of clinical signs seen in dogs. These findings were similar to those of study that reported the clinical signs seen in 168 dogs with CPSS.[94]

The signs of HE in cats are similar to those in dogs.[4] Ptyalism, anorexia, weakness, vomiting, and lethargy occur in cats with feline hepatic lipidosis and these signs may be attributed to HE.[5]

Diagnosis

In veterinary medicine, the diagnosis of HE is made based on the presence of consistent clinical signs, the exclusion of other causes of encephalopathy, laboratory findings, imaging studies, and response to treatment. As previously discussed, currently there is no way to evaluate dogs and cats for covert HE.

Episodic signs of encephalopathy, which worsen after a meal, are particularly suggestive of HE.[4] Other metabolic causes of neurological signs, such as uremia and hypoglycemia, can usually be ruled out by performing a serum chemistry profile and a urinalysis. Intracranial imaging, infectious disease testing, and CSF collection and analysis are rarely necessary.

Routine laboratory tests such a complete blood count, serum biochemistry profile, and urinalysis may provide useful evidence of a disease/disorder associated with HE. For example, dogs with CPSS often have a microcytosis, hypoalbuminemia, hypercholesterolemia, and low or low normal serum urea and glucose concentrations.[95,96] Dogs with APSC often have increased serum liver enzyme activities and may have signs of hepatic insufficiency, such as hyperbilirubinemia, and hypoalbuminemia.[93] Increased serum alkaline phosphatase activities and hyperbilirubinemia would be expected in a cat with feline hepatic lipidosis.[5] Comorbid conditions and precipitating factors for HE, such as electrolyte abnormalities or azotemia, may also be identified upon evaluation of a serum biochemistry panel.

Venous plasma venous ammonia concentrations are commonly increased in dogs with HE but may be within the reference interval.[81] This is also likely to be true in cats. In individual dogs, fasting ammonia concentrations poorly predict the severity of HE.[81] Regardless, measurement of venous plasma ammonia concentrations, where available, is a routine part of the diagnostic evaluation in dogs and cats with potential HE. This is in contrast to the situation in people where ammonia measurement is not relied upon when diagnosing HE.[9]

Appropriate sample handling is critical when measuring plasma ammonia concentration as ammonium ions are extremely labile in plasma and ammonia may be released by red blood cells ex vivo. Samples should be collected in a lithium heparin or EDTA tube, placed immediately on ice, and the plasma should be separated from the red blood cells as soon as possible. The plasma must be kept cooled and should be analyzed within 30 minutes of collection. Plasma ammonia may be measured with an in-house dry chemistry analyzer[b] although this method was only considered to reliably agree with a reference method for plasma ammonia concentrations greater than 150 μM.[97] A point of care blood ammonia analyzer[c] was recently found to be suitable for use in dogs and cats.[98]

Portosystemic shunting is the most common cause of HE in dogs, and all affected patients should be evaluated for this possibility. In the authors' experience, the same is true for cats. Plasma ammonia measurement is sensitive for the detection of portosystemic shunting in dogs and cats.[99] Generally, hyperammonemia indicates portosystemic shunting or hepatic insufficiency, although animals with urea cycle enzyme deficiencies may also have increased blood ammonia concentrations. Measurement of pre- and postprandial serum bile acid concentrations is a useful test for diagnosing hepatobiliary disease, including portosystemic shunting, in dogs and cats. A definitive diagnosis of portosystemic-shunting requires diagnostic imaging or surgical exploration. Several imaging modalities are useful for this purpose, including angiography, abdominal ultrasonography, portal scintigraphy, computed tomography angiography, and MRI angiography.[100] These imaging modalities, apart from portal scintigraphy, frequently allow the anatomic characterization of the shunt vessel(s).

For patients with acquired liver disease, a histological diagnosis is often necessary to define the underlying cause. In animals with urea cycle deficiencies, efforts must be made to exclude both macroscopic and microscopic shunting.

Treatment

Treating the underlying cause of HE

Shunt attenuation is often recommended for patients with CPSS. There are various techniques, depending on the location of the shunt vessel, including surgical placement of an ameroid constrictor or cellophane banding for an extrahepatic CPSS and transjugular embolization for intrahepatic CPSS. Generally, signs related to HE improve after shunt attenuation,[6] although incomplete closure can lead to persistent compromise. Dogs with a poorly developed portal vasculature may develop portal hypertension after shunt closure. This triggers the development of APSC with possible recurrence of HE. Postoperative seizures can also occur, the pathogenesis of which is unknown.[101] Post-CPSS attenuation seizures can occur in dogs and cats that do not have HE or other metabolic causes of seizures.[102] Typical histological changes of the cerebrum in animals undergoing necropsy include selective "ischemic" neuronal necrosis and other changes that are consistent with ischemia or hypoxia.[101,102] Withdrawal of endogenous benzodiazepines post-CPSS attenuation has also been proposed as a potential mechanism.[104] Attenuation of APSC is contraindicated as these shunts are a compensatory response to portal hypertension and closure results in an acute exacerbation of portal hypertension.

Cats with signs of HE due to feline hepatic lipidosis should be provided with a balanced, high protein diet. These are often administered via an enteral feeding tube. This helps resolve the arginine deficiency that leads to the hyperammonemia.

General supportive care and treatment of precipitating factors

It is very important to identify and address any potential precipitating factors and to provide general supportive care to dogs and cats with HE. Dogs and cats with HE may vomit or may not have a normal intake of food and water. This can be lead to dehydration and electrolyte abnormalities. As previously discussed electrolyte abnormalities can precipitate further episodes of HE. Fluid therapy plans should be made based upon the patient's individual needs and should take into account changes in fluid volume and changes in fluid distribution.[105] Balanced crystalloid solutions are often used in the treatment of dehydrated patients and are often initially used in hypovolemic patients.[105] Hypokalemia can be treated by the provision of potassium supplemented intravenous fluids. As some patients with HE have hypoalbuminemia they may also have decreased colloidal osmotic pressure. Consequently, clinicians should be aware of the possibility of changes in body fluid distribution, especially when giving crystalloid solutions. Therapy with artificial colloid solutions, such as hydroxyethyl starch, can be used in addition to crystalloid solutions to provide vascular support in patients with shock and those with increased vascular permeability.[105] Transiently increased colloid osmotic pressure and a decrease in peripheral edema or body cavity transudates were observed after administration of hydroxyethyl starch to hypoalbuminemic dogs.[106] However, artificial colloids are not indicated in chronic hypoproteinemia unless there is hypovolemia or excess movement of crystalloid fluids to the interstitium. The reason for this is that in patients with chronic hypoproteinemia the interstitial as well as the intravascular colloid oncotic pressure is usually low. Therefore, administration of artificial colloids with a much higher colloid osmotic pressure could cause hypervolemia.[107] Additionally, dogs and cats with hepatic disease often have disorders of hemostasis and the use of artificial colloids could worsen these by leading to decreased platelet aggregation,[108] decreased von Willebrand factor, decreased factor VIII,[109] cause hemodilution, and lead to increased fibrinolysis.[110] Furthermore, the use of hydroxyethyl starch (hetastarch) has also been associated with acute kidney injury in a subset of critically ill human patients, such as those with sepsis[111] and this may also be a concern in companion animals. Concentrated human albumin solutions are effective at increasing serum albumin concentrations in severely hypoalbuminemia dogs but they have been associated with a relative high incidence of serious side effects, such as type III hypersensitivity reactions in healthy dogs.[112] Fresh frozen plasma and other blood products may be needed in patients with coagulopathies. Care should be exercised when giving stored red blood cells to patients with HE as ammonia concentrations can increase substantially during storage.[113] Cats with feline hepatic lipidosis and dogs with cholestasis may be vitamin K deficient. Consequently, supplementation with subcutaneous or intramuscular injections of vitamin K at a dose of 0.5–1.5 mg/kg repeated three times at intervals of 12 hours may be required.[114]

Warm water enemas are advised in severely affected dogs and cats with HE. The warm water enemas can be given at a dose of 10 mL/kg every 4–6 hours until signs improve.[115] They help remove blood and fecal matter from the colon and therefore decrease bacterial ammonia production. They are also indicated for constipated patients with HE of all severity grades.

Comatose or stuporous patients are at increased risk of aspiration; so endotracheal intubation may be indicated to protect the patient's airways. The adequacy of the patient's ventilation should be assessed using end-tidal carbon dioxide measurement if they are intubated or measurement of the arterial partial pressure of carbon dioxide. Mechanical ventilation should be started in patients who cannot ventilate adequately.

If signs suggesting cerebral edema such as, worsening forebrain deficits, and increased systemic blood pressure possibly with reflex bradycardia, are noted, mannitol (0.5–1 g/kg IV) should be administered.[115] Slight elevation of the patient's head may facilitate venous drainage and help reduce intracranial pressure. Assisted ventilation to reduce the arterial partial pressure of carbon dioxide and inducing cerebral vasoconstriction has also been recommended as a short-term strategy to reduce intracranial pressure. However, care must be taken not to decrease the arterial partial pressure of carbon dioxide below 30 mm Hg as this can worsen cerebral ischemia.[116]

Patients with HE should be evaluated for the presence of infection, SIRS, or sepsis. Patients suspected to have bacterial infections should be treated empirically with antimicrobials until the results of culture and susceptibility testing are available. Those suspected to be septic should be treated with broad-spectrum intravenous antimicrobials. The diagnosis and management of SIRS and sepsis in dogs and cats are discussed elsewhere.[117]

Dogs with hepatic disease are predisposed to gastroduodenal ulceration.[118] Dogs with intrahepatic CPSS seem to be especially at risk and in a retrospective study of dogs undergoing endovascular treatment gastrointestinal ulceration was documented in 19% of the dogs

postprocedure. When gastroduodenal ulceration or erosion is present or is suspected it should be treated with gastric acid suppressing drugs such as omeprazole, pantoprazole, or famotidine. Omeprazole has been shown to be more effective than famotidine or ranitidine at suppressing gastric acid production in dogs.[119,120] This drug appears to be most effective when it is dosed twice daily.[120] Sucralfate is a gastric protectant that may also be used when gastrointestinal hemorrhage is suspected.

Nutrition

Although several commercially available diets are marketed for dogs and cats with HE, the optimal diet formulation has not been established. Patients who are anorexic, especially cats, often require the placement of a feeding tube so that enteral nutrition can be provided.

Traditionally, dogs with HE were fed protein-restricted diets (ie, diets that contain 12–15% protein on a dry matter basis) such as those designed for patients with renal insufficiency. These have been superseded by diets formulated for dogs with liver disease, which are the preferred choice of the authors. These diets are moderately protein-restricted (typically 14–18% protein on a dry matter basis), and often have other characteristics such as reduced copper and sodium contents, and are supplemented with zinc and antioxidants. As in people[121], severe protein restriction is no longer recommended for dogs with HE as this can lead to protein malnutrition. It is important to note also that dogs with liver disease that do not have signs of HE likely do not benefit from dietary protein restriction.[122]

In addition to careful selection of an appropriate dietary protein load, the protein source should also be considered. Nonmeat protein-based diets are often recommended for dogs with HE. A diet based on dairy protein was less encephalogenic than one based on meat protein in dogs with Eck fistulae.[123] Some commercially available hepatic support diets use vegetable-based protein sources such as soy.[74] In a study of dogs with CPSS fed two low-protein diets, one with meat and the other with soy, both diets decreased the severity of HE. However, improvements in ammonia concentrations and coagulation parameters were significantly greater in dogs fed the soy-based diet.[74] Once the signs of HE are controlled with a commercial hepatic support diet, it has been recommended to add nonmeat protein to the patient's diet to help prevent protein malnutrition.[124]

Cats have higher dietary protein requirements than dogs as they cannot downregulate protein catabolism even during being withheld from food.[125] Therefore, severe protein restriction is inappropriate for this species, and the Association of American Feed Control Officials minimum recommended protein content for feline maintenance diets is 26% protein on a dry matter basis.[126] Commercial hepatic support diets with moderate levels of high quality protein (24–31% protein on a dry matter basis) have been recommended for cats with HE due to CPSS. As for dogs, commercial feline liver support diets often have a reduced copper content and are supplemented with antioxidants. To the authors' knowledge there are no studies confirming the efficacy of these diets in treating or preventing feline HE. Due to the unique metabolic requirements of cats, the use of vegetable protein sources is not advised. Cats with feline hepatic lipidosis should be fed a high quality protein diet that contains adequate arginine and taurine.[114] It has been recommended to provide 30–40% of the dietary metabolizable energy from protein.[127] Often these cats need to be fed via a feeding tube initially so a calorie dense diet is preferable.

Lactulose

Lactulose is commonly used to treat HE in dogs and cats. However, there are no studies that have critically evaluated the efficacy of this drug. Lactulose can be given orally to patients with chronic HE. It is usually started at a dose of 1–3 mL per 10 kg of body weight every 6–8 hours for dogs and cats.[115] The dose is then adjusted until the patient passes three to four soft stools per day. In acutely compromised patients, lactulose can be given per rectum after a cleansing warm water enema. The same dose is used but is diluted to 30% with warm water and retained for at least 30 minutes.[115] However, it has not been proven that this has any benefits over a plain warm water enema. Lactulose is generally well tolerated but excessive administration can lead to diarrhea, with electrolyte abnormalities such as hypokalemia and hyponatremia.[128]

Neomycin

Neomycin is a poorly absorbed aminoglycoside antibiotic that is sometimes used to treat HE in dogs and cats. Neomycin is usually given orally at a dose of 20 mg/kg every 8 hours in dogs and cats.[4] Often neomycin is given in conjunction with lactulose in dogs and cats. Theoretically, neomycin may reduce the effectiveness of lactulose under these circumstances, as bacterial digestion of lactulose into volatile fatty acids may be limited.[129] The gastrointestinal absorption of neomycin is approximately three percent following oral or rectal administration, but can be increased in patients with decreased gastrointestinal motility or bowel wall damage. Substantial systemic absorption can cause ototoxicity and nephrotoxicity.[130] In people, neomycin is no longer used in the treatment of HE for these reasons.[58]

Metronidazole

Metronidazole is another antimicrobial that is sometimes used for the treatment of HE in dogs and cats. Again, clinical trials describing efficacy for this purpose have not been reported in veterinary species. Metronidazole is usually given at a dose of 7.5 mg/kg every 8–12 hours in dogs and cats with HE.[4] Metronidazole is metabolized by the liver and can have neurological side effects that may mimic those of HE.[131] However, these are more likely to occur at the higher dosages used for other purposes.

Ampicillin

Ampicillin given intravenously at a dose of 20 mg/kg every 6–8 hours can be used in place of oral neomycin or metronidazole in dogs or cats that cannot receive oral medications.[4] The use of oral ampicillin for the treatment of HE has also been reported.[132]

Rifaximin

The pharmacokinetics of rifaximin has been reported for dogs and this drug has been reported to be well tolerated in this species.[133] The lack of apparent adverse effects is a potential benefit compared to neomycin and metronidazole. However, the safety and efficacy of this drug in dogs and cats with HE have not been established. Current costs are also likely to be prohibitive.

Anticonvulsants

Anticonvulsant drugs should be administered to patients with HE if seizures occur and in patients that seizure after attenuation of a CPSS. Additionally, they are sometimes given to patients with CPSS prior to shunt attenuation in an attempt to reduce the occurrence of postoperative seizures.

The use of diazepam and midazolam to treat seizures due to HE is controversial and there are no clinical trials that have evaluated the efficacy of these drugs in this setting. As diazepam is hepatically metabolized its half-life may be prolonged in dogs and cats with HE. Therefore, the dose and frequency that is used should be reduced in order to avoid causing profound sedation.[134] In people benzodiazepine administration is considered to be a precipitating factor for HE.[9] Additionally, diazepam when used orally has been linked with the development of fulminant hepatic failure in cats.[135]

Levetiracetam is a rapidly acting anticonvulsant with few side effects that can be given intravenously or orally to dogs and cats.[136,137] As its principal route of excretion is renal, it is a suitable option for patients with hepatic compromise. There is evidence from a recent retrospective study that administration of levetiracetam to dogs with CPSS prior to shunt attenuation is well tolerated and may reduce the occurrence of postoperative seizures.[7]

Despite its long half-life phenobarbital can be used in an emergency by giving it intravenously at a higher loading dose. Phenobarbital has been shown to be effective at controlling seizures in dogs after surgical attenuation of CPSS.[101] However, it can lead to sedation and at higher doses it can cause respiratory depression.[138] Additionally, phenobarbital is metabolized by the liver and has been shown to cause hepatic injury when used chronically in dogs[139] although this is less of a concern with short-term use.

Propofol given at subanesthetic doses as intravenous constant rate infusion has successfully been used to treat seizures occurring after attenuation of CPSS in cats and dogs.[140,141] This drug has a fast onset of action and is therefore suitable for use in an emergency situation. However, it leads to dose-dependent sedation/anesthesia, dose-dependent respiratory depression,[142] and when used in cats for longer periods of time it can cause Heinz body anemia.[143] Careful monitoring of the cardiovascular and respiratory systems is needed when propofol is used to treat seizures.

Potassium bromide can be used as an adjunct to other anticonvulsant drugs in dogs. Potassium bromide has a very long half-life, delayed onset of action, and can only be given orally or per rectum. Therefore, its use is limited in an emergent situation. To the authors' knowledge its efficacy in treating seizures due to HE or those that occur after attenuation of CPSS in dogs has not been reported. This drug also causes ataxia, sedation[146], and possibly pancreatitis when used in conjunction with phenobarbital.[145] The use of potassium bromide is contraindicated in cats as it can lead to severe lower respiratory tract disease.[146]

Zonisamide has been reported to be efficacious when used as an adjunctive treatment for refractory seizures in dogs[149] as well as for the treatment of seizures without other anticonvulsant drugs.[148] However, its efficacy in dogs with seizures due to HE or seizures that occur after attenuation of a CPSS has not been reported. Transient sedation, ataxia, vomiting, and renal tubular acidosis have been reported to be potential side effects in dogs.[147,149] When dosed at a relatively high dose of 20 mg/kg every 12 hours zonisamide was associated with a high incidence of adverse effects including anorexia, diarrhea, vomiting, somnolence, and ataxia in cats.[150] There are no studies that critically evaluate the efficacy of this drug in controlling seizures in this species.

Application to veterinary emergency and critical care

HE is a relatively common but potentially life-threatening complication of hepatobiliary disease in

dogs and cats. Veterinarians working in emergency or critical care settings must be able to promptly recognize, diagnose, and manage this condition. Although increased blood ammonia concentrations strongly suggest HE, it is important for clinicians to be aware of the limitations of this diagnostic tool. It is also essential that predisposing factors are quickly identified and addressed and that appropriate supportive care is provided.

Recommendations for future studies

Further investigation into the pathogenesis of HE in dogs and cats may, in time, lead to the development of novel treatments. Areas that merit particular attention are the roles of inflammation, manganese, oxidative damage, and NS. Techniques such as magnetic resonance spectroscopy and positron emission tomography, that allow the pathogenesis of HE to be studied in vivo, may help answer these and other questions.

The prevalence of covert HE in dogs and cats has not been investigated. As the neuropsychometric tests used to diagnose this in people cannot be applied to our species, other methods, such as electrophysiological testing should be evaluated. If covert HE is identified, its impact on patient outcome needs to be considered.

Although there are several well-established treatments for HE in dogs, none of them are supported by robust scientific evidence. Clinical trials of the drugs currently used to treat HE are needed to help optimize treatment protocols. Future avenues of investigation may include rifaximin (assuming a less costly generic formulation becomes available); modification of the gastrointestinal microbiota using prebiotics, probiotics, or synbiotics; and the role of nutrition, including the efficacy of supplementation with carnitine and LOLA.

Footnotes

[a] Lidbury JA, Ivanek R, Suchodolski JS, Steiner JM. Clinical feature of hepatic encephalopathy in dogs: 80 cases (1991–2011). J Vet Int Med 2012;26(3):781 (Abstract).
[b] VetTest, Idexx Laboratories, Westbrook, ME.
[c] PocketChem BA, Menarini Diagnostics, Florence, Italy.

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