Current Concepts in the Pathophysiology and Management of Hepatic Encephalopathy

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Abstract: Hepatic encephalopathy (HE) represents a broad continuum of neuropsychological dysfunction in patients with acute or chronic liver disease and/or portosystemic shunting of blood flow. The pathophysiology of this disease is quite complex, as it involves overproduction and reduced metabolism of various neurotoxins, particularly ammonia. Recent hypotheses implicate low-grade cerebral edema as a final common pathway for the pathophysiology of HE. Management of this condition is multifaceted and requires several steps: elimination of precipitating factors; removal of toxins, both by reducing them at their source and by augmenting scavenging pathways; modulation of resident fecal flora; proper nutritional support; and downregulation of systemic and gut-derived inflammation.

Keywords
Hepatic encephalopathy, urea cycle, glutaminase, ammonia, cerebral edema

Hepatic encephalopathy (HE) represents a broad continuum of neuropsychological dysfunction. As defined by the Working Party in 1998, HE can be categorized into 3 broad groups: type A, which occurs in acute liver failure (ALF); type B, which occurs in patients with bypass shunts; and the most commonly recognized form, type C, which occurs in patients with chronic liver disease.[1] Several neurologic domains are affected by HE, including consciousness, personality, emotional status, motor function, memory, and cognition. This paper will focus primarily on the pathophysiology and management of type C HE. While HE remains a diagnosis of exclusion, several interesting developments in grading and diagnostic testing have recently been summarized elsewhere.[2]

Within the category of type C HE, individual cases may follow different patterns. Many patients suffer from intermittent or "episodic HE," with episodes being either precipitated or spontaneous. Episodes of HE may be isolated events, but more commonly they are recurrent, with patients having seemingly normal cognitive functioning between episodes. Many patients remain on medications after resolution of these intermittent episodes, as both patients

and clinicians are understandably reluctant to stop treatment even in the absence of current symptomatology. While HE is generally considered to be a reversible condition, some new data suggest that patients may not return to previous levels of cognitive functioning after episodes of overt HE.[3] In addition to episodic HE, another presentation of this condition is "chronic persistent HE," which is marked by an ongoing deficit in neuropsychological functioning; these patients have good days and bad days but do not achieve complete resolution of symptoms.

The severity of presentation also differs considerably among patients. Some patients present with gross disorientation, confusion, or frank coma, while other patients may have fairly mild complaints that are often only identified and brought to medical attention by the patient's spouse or other close companion. Clinicians typically use the West Haven criteria to categorize these patients, although scales with more precise determinants are being studied.

Finally, some HE patients have no outward signs or symptoms recognizable in a typical clinical setting, but they nonetheless manifest deficiencies in several psychometric tests. Formerly called "subclinical HE," this presentation is now termed "minimal HE" (MHE). Many clinicians feel that MHE falls within the same spectrum as overt HE and can be considered to be grade 0 on the West Haven or Conn scale. A significant proportion of patients with cirrhosis are found to have MHE if properly tested; even patients with intact synthetic function or Child-Pugh class A disease are often impaired. The importance of diagnosing MHE is becoming increasingly apparent, since these patients experience decreased global functioning, increased falls, impaired driving ability, and reduced quality of life.[4-7]

Patients presenting with clinically apparent HE should be classified using grades 1–4 of the West Haven criteria; these cases are collectively referred to as "overt HE." The need to recognize and treat the diverse and often subtle presentations of HE is also becoming increasingly evident, as proper diagnosis and management are critical in order to improve quality of life, prevent recurrences and hospitalizations, and potentially prolong lives. Given the rising prevalence of advanced liver disease, clinicians should not be surprised to learn that the clinical, social, and financial impact of HE is also large and continuing to grow.[8]

Pathophysiology of Hepatic Encephalopathy

Studies investigating the pathophysiology of HE have historically focused on the accumulation of various toxins in the bloodstream and brains of animal models and patients with chronic liver disease and/or portal hypertension. Ammonia has been implicated as a key molecule in the disease for over 50 years, due to its frequent elevation in patients with cirrhosis and known cellular toxicity.[9-11] However, evidence now suggests that ammonia is only a single component in a multifactorial disease process (Figure 1).

Ammonia Production

Excess ammonia in the body has long been thought to arise from colonic bacterial species with urease enzyme activity, predominantly gram-negative anaerobes, *Enterobacteriaceae*, *Proteus*, and *Clostridium* species.[12-14] The bacterial urease can break down urea derived from the bloodstream into ammonia and carbon dioxide. Early investigations into the treatment of HE therefore focused on incapacitating the bacterial urease enzyme via immune-mediated mechanisms such as vaccination.[15]

While the intestinal flora still appear to be a significant source of ammonia, evidence from animal models of HE shows that bacteria are not required for the development of hyperammonemia, suggesting that alternative sources also play a role in ammonia production.[16,17] Research has shown that enterocytes within the small bowel (and, to a lesser extent, in the colon) also generate a large amount of ammonia via intestinal glutaminase as they metabolize their main energy source, glutamine, into glutamate and ammonia.[18] This endogenous source of ammonia may even eclipse the production of ammonia by fecal flora.[19] Neomycin, a poorly absorbed antibiotic used in the treatment of HE, appears to also have some intrinsic effect on the activity of intestinal glutaminase and may reduce ammonia by multiple mechanisms.[20]

Lending further support to the importance of intestinal glutaminase in the pathophysiology of HE, a group of Spanish investigators previously found that the gene encoding for glutaminase was upregulated in patients with cirrhosis, particularly those with MHE.[21] The same investigators more recently demonstrated a correlation between specific genetic variations in the promoter region of this gene that lead to enhanced glutaminase activity and an increased risk of developing overt HE in patients with cirrhosis.[22] Additionally, evidence suggests an increase in the expression of intestinal glutaminase in the enterocytes of rats following insertion of a portacaval shunt, which may explain some of the increased risk of HE seen following this procedure.[23]

Once ammonia is generated by enterocytes and bacteria in the colon, it then travels via the splanchnic venous system to the liver for detoxification, which occurs largely via the urea cycle within zone 1 hepatocytes, and, to a lesser degree, via conversion to glutamine in zone 3 hepatocytes.[24] Hyperammonemia is thought to occur because of a reduction in the metabolic capacity of the liver's urea cycle, compounded by the shunting of blood around the hepatic sinusoids, either through extrahepatic porto-

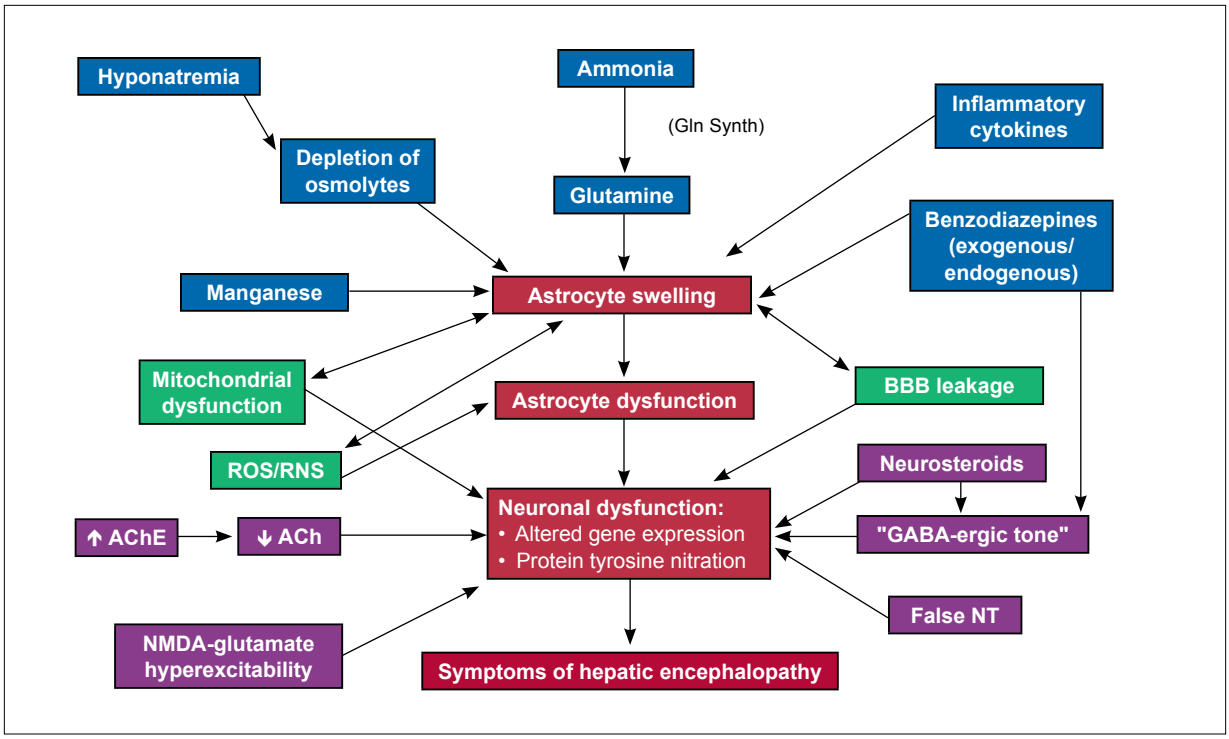

Figure 1. Hypothesis of the multifactorial nature of hepatic encephalopathy. Various neurotoxins and NTs act independently or perhaps synergistically to cause astrocyte swelling and subsequent astrocyte dysfunction. In addition, increased "GABA-ergic tone" and depletion of Ach may contribute to neurologic dysfunction in patients with hepatic encephalopathy. A vicious cycle may perpetuate the disease, as ROS trigger astrocyte swelling, and further swelling causes production of more ROS and RNS and subsequent mitochondrial energy failure.

Ach=acetylcholine; AChE=acetylcholinesterase; BBB=blood brain barrier; GABA=gamma aminobutyric acid; Gln Synth=glutamine synthetase; NMDA=N-metyhl-D-aspartic acid; NT=neurotransmitter; RNS=reactive nitrogen species; ROS=reactive oxygen species.

systemic collaterals, surgically created shunts (including transhepatic intrahepatic portosystemic shunts [TIPS]), or intrahepatic spontaneous shunts. In fact, excessive spontaneous shunting is often recognized in patients with severe persistent or recurrent spontaneous HE.[25]

Renal Ammonia Flux

While the liver is primarily responsible for metabolism of ammonia and the gut is primarily responsible for generation of ammonia, these organs are not the only ones involved in these processes. The renal contribution to ammonia flux, which includes both excretion and production, also needs to be carefully considered and is largely driven by acid-base status. In terms of excretion, the kidneys can remove a significant amount of ammonia in the urine, either as ammonium ion (NH_4^+) or in the form of urea. The kidneys can also generate ammonia by metabolizing glutamine via glutaminase to ammonia, bicarbonate, and glutamate. This ammoniagenesis primarily serves a role in acid-base homeostasis, since bicarbonate is also produced during the reaction; ammoniagenesis thus serves to buffer systemic acidosis as well as release hydrogen ions into the urine in the form of NH_4^+. Whether renal ammonia is released into the urine or returned to the circulation via the renal vein depends upon several factors, predominantly pH. Under physiologic conditions, approximately 30–50% of renal ammonia is released into the urine, while the remainder is returned to the circulation via the renal vein. However, during periods of acidosis, the kidneys can increase the amount of NH_4^+ released into the urine several fold.[26-28]

In contrast, alkalosis causes a significant decrease in urinary loss of ammonia and can consequently contribute to hyperammonemia.[29] Alkalosis is also believed to trigger HE events by decreasing the amount of gaseous ammonia (NH_3) that is protonated to NH_4^+; at physiologic pH, approximately 2% of ammonia exists as gaseous NH_3 and 98% is ammonium ion. Since neutral NH_3 moves across the blood-brain barrier more readily than charged NH_4^+, decreased protonation of gaseous ammonia may increase

passage of ammonia across the blood-brain barrier and exacerbate HE in the setting of alkalosis. However, studies measuring the partial pressure of ammonia (gaseous NH_3 vs NH_4^+) have shown conflicting results in terms of whether the partial pressure of ammonia accurately correlates with HE stage.[30,31]

Another factor that may contribute to pathologic hyperammonemia is the reduced excretion of ammonia and urea that occurs in patients with reduced perfusion and a decreased glomerular filtration rate. This situation is common in cirrhotic patients with dehydration and prerenal azotemia and often occurs secondary to excessive diuresis or diarrhea. A simple saline infusion can ameliorate this hyperammonemia by allowing for enhanced renal ammonia excretion.[32] Some data suggest that the kidneys can also provide net ammonia removal during periods of hyperammonemia, such as those induced by portacaval shunting in rats, in patients with cirrhosis, or in healthy controls with induced hyperammonemia.[33-35] In the setting of either simulated or clinical gastrointestinal bleeding, in contrast, ammoniagenesis by the kidneys increases up to 6-fold and seems to account for the majority of the hyperammonemia seen in this setting.[36]

Finally, the impact of hypokalemia in exacerbating HE is modulated by the kidneys. As less potassium reaches the collecting tubules, more hydrogen ions are moved into the cells, leading to a state of relative intracellular acidosis. The kidneys then generate more ammonia and bicarbonate from glutamine in an effort to balance the acid-base status of the patient. Through these complex mechanisms of acid-base homeostasis, the kidneys have the capacity to both improve and exacerbate the ammonia balance.

Ammonia Flux in Muscle

Another organ that is critical in regulating ammonia flux is the skeletal musculature. Skeletal myocytes provide ammonia metabolism by incorporating ammonia into glutamine via glutamine synthetase. Although the metabolic activity of glutamine synthetase in muscle is relatively low, the extensive muscle mass throughout the body gives skeletal muscle a significant capacity for ammonia metabolism. This glutamine production and ammonia removal may surpass that of the failing liver, but this process does not appear to lower the total burden of ammonia in the body, since the glutamine produced by myocytes is recirculated, and ammonia is regenerated at other sites via glutaminase.[19] Glutamine therefore appears to be a temporary means of detoxifying ammonia, but it does little in terms of ammonia excretion. Consequently, controversy remains as to whether muscle wasting and cachexia can lead to worsening of HE simply by reducing the body's ability to metabolize ammonia. More likely, catabolism itself presents the larger problem, as it releases excessive glutamine (and other amino acids) from muscle into the circulation, which leads to subsequent ammonia production via kidney and gut glutaminases.

Ammonia Toxicity

While ammonia is strongly associated with HE, the exact mechanisms of ammonia-induced neurologic dysfunction remain unclear. The target of ammonia toxicity in the brain appears to be the astrocyte, with development of Alzheimer type II astrocytosis being a probable histopathologic consequence of ammonia toxicity. One proposed mechanism for ammonia-induced neurologic dysfunction is cerebral edema. Glutamine, produced by the metabolism of ammonia via glutamine synthetase within astrocytes, acts as an intracellular osmole and attracts water into the astrocytes, which leads to swelling and appears to induce oxidative dysfunction of the mitochondria. While cerebral edema is widely accepted as a major contributing cause of HE in ALF, cerebral edema also appears to play a role in type C HE, as evidenced by magnetic resonance spectroscopy, although edema is typically more prominent and clinically compromising in the former group.[37,38] The low-grade edema seen in type C HE appears to induce neurologic dysfunction directly rather than via the subsequent rise in intracranial pressure seen in type A HE. Occasionally, however, patients with an acute exacerbation of chronic liver disease will also present with intracranial hypertension in the setting of HE, which can lead to fatal cerebral herniation.[39,40]

In another mechanism of astrocyte toxicity, ammonia appears to directly trigger oxidative and nitrosative stress in the astrocyte by increasing intracellular calcium, leading to mitochondrial dysfunction and cellular energy failure via opening of the mitochondrial transition pore. Additional proposed mechanisms of neuronal dysfunction include ammonia-induced RNA oxidation, activation of mitogen-activated protein kinases, and activation of nuclear factor-κB, all of which can lead to enhanced cytokine activity and an inflammatory response, as well as impaired intracellular signaling.[41]

Other Toxins

In addition to ammonia, many other molecules have been implicated in the pathogenesis of HE. Neurosteroids, such as allopregnanolone, appear to allosterically modulate the gamma-aminobutyric acid (GABA)-A receptors in the brain, enhancing the effects of GABA on these inhibitory receptors, thus leading to a suppressed sensorium via increased "GABA-ergic tone."[42,43] These neurosteroids are produced in the brain and are elevated in patients with HE.[44]

Benzodiazepines also modulate GABA-A receptors, which may explain some of the similarities between HE and benzodiazepine use. In addition, benzodiazepines

appear to trigger astrocyte swelling via a direct receptor-mediated effect. Endogenous benzodiazepines are believed to arise from bacterial production and can also activate the GABA-A receptors. Elevations in these "endozepines" have been found in some cirrhotic patients with HE but not in others, and whether endogenous benzodiazepines are a significant contributor to HE remains unclear.[45-48]

Indole and oxindole are byproducts of bacterial tryptophan metabolism with sedating properties that have been recently implicated as potential contributors to the pathogenesis of HE.[49] Other putative toxins involved in HE pathogenesis include mercaptans, short-chain fatty acids, false neurotransmitters (eg, octopamine), manganese, and GABA.[50-54]

Finally, another proposed mechanism for the development of HE suggests that activity of neuronal acetylcholinesterase (AChE) is increased in the brains of cirrhotic patients and animal models with type C HE, which results in a reduction of acetylcholine by up to 50–60%.[55,56] These changes appeared to be independent of hyperammonemia. Interestingly, no changes in AChE activity has been found in rats with type A or B HE.[55,57,58] Nonetheless, interesting and encouraging experimental data are now emerging in both animal models and patients regarding the use of AChE inhibitors for treatment of HE.[55,59]

Hyponatremia

Low serum sodium levels are quite common in patients with cirrhosis and portal hypertension due to the activation of antidiuretic hormone (vasopressin) that occurs secondary to the decrease in effective arterial volume related to splanchnic arterial vasodilation. Unfortunately, chronic hyponatremia leads to depletion of intracellular organic osmolytes, 1 of which, myoinositol, plays a primary role in intracellular water regulation. Osmolytes present in astrocytes provide a cellular defense against intracellular swelling and can be rapidly accumulated or depleted according to osmotic sensors. One theory is that chronic hyponatremia causes astrocyte osmolytes to be depleted; the cell then cannot compensate well during periods of hyperammonemia or inflammation, leading to astrocyte swelling, low-grade cerebral edema, oxidative and nitrosative stress, and astrocyte dysfunction. While hyponatremia may not be sufficient to trigger HE alone, it can be considered a "second hit" that places osmotic stress on the astrocyte. Indeed, hyponatremia has been shown to be a significant predictor for development of overt HE in patients with cirrhosis.[60,61]

Inflammation

Finally, a growing body of literature implicates an inflammatory milieu—in conjunction with hyperammonemia or other neurotoxic molecules—as being key to the precipitation of HE. This inflammation may be related to infection, gastrointestinal bleeding, obesity, or disequilibrium of resident fecal flora in the cirrhotic patient with enhanced translocation and increased rates of bacterial overgrowth. Infection has been shown to worsen the progression of HE and cerebral edema in patients with ALF, and proinflammatory cytokines seem to act synergistically with ammonia in causing cerebral edema.[62-64] Overactive neutrophils with excessive degranulation activity and enhanced production of inflammatory cytokines may also play a role in this pathogenesis. Additionally, alterations in toll-like receptor 4, a receptor responsible for recognition of gram-negative bacteria, may be at least partly responsible for the inflammatory state in the cirrhotic patient. Polymorphisms of this receptor that occur in cirrhotic patients may increase both the risk of infection and the risk of HE.[65] The blockade of this receptor is therefore being studied as a mechanism for treating both HE and ALF.

Treatment of Hepatic Encephalopathy

Treatment of HE has evolved slowly over the last 50 years, with several breakthroughs occurring during this time. However, clinicians currently operate in somewhat of a vacuum regarding formal treatment guidelines, as the most recent sanctioned clinical guidelines for overt HE were published a decade ago; updated guidelines from the American Association for the Study of Liver Diseases are expected soon.[66] Nonetheless, treatment can be structured around several key management principles that parallel the pathophysiology of the disease: management of precipitating factors, reduction of ammonia (and perhaps additional toxins), modulation of fecal flora, modulation of neurotransmission, correction of nutritional deficiencies, and reduction of inflammation. Additional management strategies for less common clinical scenarios will also be discussed.

Management of Precipitating Factors

The majority of HE episodes are precipitated by an event rather than spontaneous, with infection being the most common, although its frequency appears to be declining.[67-70] Often, precipitants are overt and obvious, but a careful history and physical examination are required in order to identify other, less dramatic contributing causes. Gastrointestinal bleeding commonly precipitates HE, even after it is successfully abated; occult chronic gastrointestinal blood loss can also lead to HE and should be evaluated and treated if possible.[71]

Dehydration, often in the setting of aggressive diuresis with volume contraction alkalosis and electrolyte distur-

bances, is a particularly common cause of HE in patients with ascites and edema. Individuals who have undergone TIPS insertion for fluid overload are particularly susceptible to dehydration or excessive diuresis if medications are not appropriately tapered after the TIPS procedure. Such dehydration-induced HE usually responds to fluid resuscitation and electrolyte repletion.[32] Clinicians should note that albumin seems to play a significant role in treatment of such patients, while other colloids may be less helpful.[72] Unfortunately, a mainstay of treatment for chronic persistent HE, lactulose, can lead to severe volume depletion and hypokalemia due to excessive stooling, paradoxically exacerbating the disease that the well-meaning clinician intended to ameliorate. Treatment of HE should include repletion of electrolytes (often lost with overzealous use of diuretics and disaccharides [DS]), particularly potassium, as potassium deficiency can exacerbate hyperammonemia by upregulating renal glutaminase and ammoniagenesis. Constipation is also believed to be a frequent cause of HE, presumably because it increases the amount of time that ammonia and other toxins can be absorbed from the gastrointestinal tract; simple osmotic stool softeners and avoidance of dehydration can help to prevent constipation. Possible noncompliance with lactulose should also be suspected.

Electrolyte derangements commonly precipitate HE events, particularly in the setting of hypokalemia and hyponatremia. Hyponatremia itself can cause neurologic dysfunction, which may be difficult to differentiate from the manifestations of HE. Cerebral edema appears to be a commonality between these 2 neurologic syndromes. Treatment of hyponatremia requires saline resuscitation for patients with hypovolemia and water restriction or vasopressin antagonists for patients with euvolemic or hypervolemic hyponatremia. Whether treatment of hyponatremia with a vasopressin antagonist will also be effective for treatment or prevention of HE remains an intriguing question.

Finally, many patients with advanced liver disease also suffer from anxiety, depression, chronic pain, or sleep disorders; as a result, these patients commonly take sedating medications intended to improve their quality of life. Because these sedatives, particularly those in the benzodiazepine and opiate classes, often trigger or exacerbate underlying HE, they should be removed from the regimen of HE patients as quickly as possible.

Reduction of Ammonia and Other Toxins

Although clinical trials have produced inconsistent evidence of overall clinical improvement associated with ammonia reduction, this intervention has nonetheless been a main goal of HE treatment for the past 4 decades, and decreased ammonia is often cited as a significant endpoint of clinical trials assessing HE treatments. While hyperammonemia alone is insufficient to explain the spectrum of symptoms seen in HE, a significant correlation is seen between the degree of ammonia elevation and the stage of HE.[31,73] The clinical significance of hyperammonemia is more pronounced in the setting of type A HE, where cerebral edema and death have been significantly correlated with the degree of hyperammonemia.[74]

The mainstay of ammonia reduction for type C HE over the past 40 years has been nonabsorbable DS such as lactulose (β-galactosidofructose) in the United States and lactitol (β-galactosidosorbitol) in Europe. However, the efficacy of these agents has been called into question by a widely cited meta-analysis that examined DS versus placebo or antibiotics for the treatment of HE.[75] The authors of this study concluded that the body of evidence for the use of DS in HE is limited and of poor quality; they also found that DS appears to be no better than placebo and worse than antibiotics for treatment of this disease. However, more recent data regarding the use of lactulose for prevention of HE recurrence appears more promising.[76,77] Despite the questionable benefit of lactulose in well-designed trials, most clinicians still believe in the efficacy of DS, and lactulose continues to be widely prescribed for HE.

The mechanism of action through which DS works is multifaceted. While intestinal "hurry" is their best-known mechanism for eliminating fecal waste products, including ammonia, DS are much more than simple cathartics. Upon entering the colon, DS are cleaved into monosaccharides by the bacterial flora, some of which (eg, *Lactobacilli* and *Bifidobacteria*) can then incorporate these monosaccharides into subsequent generations of bacteria, thereby gaining a growth advantage. The unincorporated monosaccharides are also utilized as fuel for the bacteria. This fermentation process generates lactic acid and hydrogen ions, thereby acidifying the fecal stream within the colon and causing subsequent protonation of ammonia molecules (NH_3) into ammonium ions (NH_4^+). Because the charged NH_4^+ is poorly absorbed across the colonocyte, the ion remains trapped within the colonic lumen. In addition, this protonation reaction can allow for movement of NH_3 from the bloodstream back into the colonic lumen in a classic example of stoichiometry ($NH_3 + H^+ \rightarrow NH_4^+$). Another mechanism of action that has been postulated for DS involves transformation of the fecal flora: reduction of urease-producing bacteria (which are not given a growth advantage with DS) in favor of the proteolytic species (eg, *Lactobacilli* and *Bifidobacteria*). In this regard, DS can be considered a prebiotic—ie, a "meal" for the bacterial biomass.

Another mechanism for reducing ammonia involves the use of so-called ammonia scavengers, such as intra-

venous sodium benzoate and sodium phenylacetate (Ammonul, Ucyclyd Pharma) or a prodrug of phenylacetate, oral sodium phenylbutyrate (Buphenyl, Medicis); both of these scavengers are approved for use in patients with urea cycle disorders and hyperammonemia (mostly children). Oral sodium benzoate (Ucephan, B Braun) is also sometimes used off-label for ammonia scavenging. It is available as a powder and can be obtained from specialty pharmacies. These compounds work by combining with glycine (in the case of benzoate) or glutamine (in the case of phenylacetate) to form water-soluble and renally excretable compounds (benzoylglycine or hippurate and phenylacetylglutamine, respectively) that eliminate ammonia through the urine.

The use of these drugs is a way to bypass the saturated urea cycle, but these agents still require intact renal function for elimination of ammonia. Also, while these products are available in the United States, they are not approved for HE. One downside to their use is their large therapeutic dose (measured in grams per day)—which leads to a significant sodium load (1–2 g/day at therapeutic doses) that may contribute to fluid retention in cirrhotic patients—as well as poor palatability. A new compound, glycerol phenylbutyrate (HPN-100, Hyperion Therapeutics), is a prodrug of sodium phenylbutyrate with a much lower anticipated therapeutic dose requirement and improved palatability. Glycerol phenylbutyrate is currently being evaluated for type C HE and recently met the primary endpoint in a phase III trial of urea cycle disorders.

A newer avenue being explored for reduction of ammonia is the use of orally ingested, activated charcoal. A compound called AST-120 (Ocera Therapeutics), a spherical carbon adsorbent, has been studied in patients with mild HE and cirrhotic patients with pruritus. This compound's known capability for adsorbing small molecules—not only ammonia, but also lipopolysaccharides and cytokines—makes it an attractive therapeutic option for HE. A pilot study showed that AST-120 had efficacy equivalent with lactulose and fewer adverse events.[78] Other data have noted a reduction in ammonia and cerebral edema following treatment with AST-120 in animal models of cirrhosis. A larger trial of AST-120 in patients with mild type C HE, the ASTUTE trial, has recently been completed, and results are anticipated soon.

For patients with severe HE who do not respond to traditional therapies, clinicians may consider the use of an extracorporeal device for "liver dialysis." Currently, the only such system that is clinically available in the United States is the molecular adsorbent recirculating system (MARS, Gambro), also known as albumin dialysis, which is indicated for acute poisoning. A large randomized controlled study was conducted in the United States for patients with severe HE not responding to standard care. Patients receiving MARS demonstrated more rapid and significant improvements in HE, but no benefit in mortality was found in this group of patients with terminal liver failure.[79] Other devices, including bioartificial machines with hepatocytes, have been studied for treatment of HE, but none are currently approved in the United States.[80,81]

Finally, certain patients with ongoing hyperammonemia and persistent HE despite removal of precipitating factors and optimal therapeutic management will be recognized as having large or extensive spontaneous portosystemic shunting. These shunts may be amenable to embolization via percutaneous catheterization, but experience in the United States remains limited.

Modulation of Fecal Flora

The gut microbiome's influence is becoming increasingly recognized across many diverse disease states, including inflammatory bowel disease, irritable bowel syndrome, and obesity. Bacterial flora also appear to play a significant role in the pathogenesis of HE, and modification of this flora—either through antibiotics, probiotics, or prebiotics—is important for the successful treatment of this disease. Prebiotics (of which lactulose and fermentable fibers are examples) may directly enhance the growth of bacterial strains that are potentially beneficial to the host (ie, *Bifidobacteria* and *Lactobacilli*), thereby indirectly reducing the influence of potentially more harmful resident flora (ie, urease-producing species). Prebiotics also come in the form of indigestible fibers and have shown benefit for the management of HE, particularly MHE, both when used alone and when used in combination with probiotics (in which case they are termed "synbiotics").[82-84]

Probiotics have also been studied (either alone or as synbiotics) for the treatment of HE and have shown some benefit, mostly in the setting of minimal disease.[84-88] The bacterial species that appear to be most successful include *Lactobacilli* and *Bifidobacteria*. Investigators in Belgium have also demonstrated improvements in both acute and chronic animal models of HE when these animals were treated with genetically enhanced species of *Lactobacilli* that had augmented ammonia-consumption capabilities.[89] Probiotics may also improve overall liver function, perhaps by reducing translocation and subsequent endotoxemia and by ameliorating the hyperdynamic circulation.[84]

On the other side of the treatment spectrum, antibiotics have been clearly proven to treat HE, particularly when used to prevent recurrent exacerbations. Rifaximin (Xifaxan, Salix) is a poorly absorbed relative of rifamycin that has broad antibacterial activity against both aerobes and anaerobes. Rifaximin has a preferential site of action in the small bowel (presumably due to its enhanced solubility in bile) where it typically lowers the bacterial load

100–1,000-fold; however, it stops short of obliterating all flora and is less effective in the colon.[90] A large randomized controlled study investigating rifaximin versus placebo in patients who were already using lactulose (91% of both arms) showed a highly statistically significant benefit for rifaximin in preventing recurrences of HE and decreasing hospitalizations related to HE over a 6-month period.[91] In an exploratory analysis, the trial also demonstrated an improvement in quality of life in patients receiving rifaximin, as assessed by the Chronic Liver Disease Questionnaire.[92]

Other antibiotics used to treat HE include neomycin (an aminoglycoside), metronidazole (for anaerobes only), paromomycin, and oral vancomycin. These antibiotics all have considerable limitations either related to safety (ie, ototoxicity and nephrotoxcity with neomycin; neurologic toxicity with metronidazole) or resistance (oral vancomycin); for these reasons, these agents have largely been replaced by rifaximin, which is now approved by the US Food and Drug Administration for treatment of HE. The mechanism of action for antibiotics in HE is assumed to be related to modulation of bacterial flora, but this hypothesis has not been proven. One postulated mechanism of action is the correction of small intestinal bacterial overgrowth, which is frequently identified in cirrhotic patients, although this explanation remains controversial.[93] Studies evaluating antibiotics for the treatment of HE have shown reductions in ammonia levels, but some researchers have speculated that the benefit of antibiotics also arises from an anti-inflammatory effect or downregulation of intestinal glutaminase activity. Studies are still needed to examine the effects of chronic antibiotic administration on fecal flora, as well as their effect on cytokines and other markers of inflammation in HE.

Finally, acarbose, an α-glucosidase inhibitor used in the management of diabetes, has also been studied for the treatment of HE. By reducing glucose absorption from the intestine, this drug may promote the survival of primarily saccharolytic (rather than proteolytic) bacteria, thereby reducing the generation of ammonia. A randomized, double-blind, crossover trial of acarbose in diabetic patients with mild HE demonstrated reductions in ammonia concentrations and improvements in number connection tests and HE grades.[94] Further clinical trial data are needed before this drug can become more widely used for this indication.

Modulation of Neurotransmission

The final common pathway for the pathophysiology of HE appears to be altered neurotransmission, manifested as upregulation of both GABA neuroinhibitory receptors and N-methyl-D-aspartic acid–glutamate excitatory receptors, resulting in a clash of combined inhibitory and excitatory signals. Targeting this derangement has long been an avenue for HE management, and trials have been conducted with flumazenil, naloxone, bromocriptine, levodopa, and AChE inhibitors, many of which have met with minimal clinical success. When faced with a comatose patient with HE, a therapeutic trial of flumazenil or naloxone is certainly appropriate if benzodiazepine or opiate ingestion has been identified or suspected. However, the effect of these drugs is short-lived, and minimal evidence exists to support their use.[95,96] More recently, a pilot study of the AChE inhibitor rivastigmine in patients with moderate HE showed a benefit in psychometric testing.[59]

Correction of Nutritional Deficiencies

Patients with advanced liver disease often face tremendous difficulties in maintaining proper nutritional balance. Many factors are involved in their poor nutrition, including poor dietary absorption (particularly of fat-soluble vitamins), poor intake (due to confusion, weakness, or ascites), and a baseline hypercatabolic state. This imbalance often leads to a wasting syndrome due to protein-calorie malnutrition. Since skeletal muscle appears to play some role in controlling the flux of ammonia in the body, muscle mass depletion may lead to worsening of HE, although this effect has not been consistently demonstrated.

Zinc is another potentially important factor in terms of nutritional deficiencies. Zinc serves as a cofactor for several of the enzymes involved in the urea cycle; thus, zinc deficiency, which is common in cirrhotic patients, may decrease the efficiency of the urea cycle. A recent randomized, open-label trial suggests that zinc supplementation may provide a benefit in patients with HE.[97]

A product that is frequently used for treatment of HE outside of the United States is L-ornithine L-aspartate (LOLA), which is believed to act by supplying substrates for the urea cycle and glutamine synthesis that may otherwise become depleted in cirrhotic patients with generalized protein malnutrition and amino acid deficiencies. The data regarding LOLA's use in HE were published in a meta-analysis of 3 trials and demonstrated a significant benefit in patients with grade I–II HE, but not with minimal HE.[98] However, this product is not currently available in the United States.

A new compound that is similar to LOLA, L-ornithine phenylacetate (LOPA), also known as OCR-002 (Ocera Therapeutics), has been developed and is currently being tested as a treatment for HE. This agent may work by increasing the supply of ornithine to the urea cycle, thereby enhancing the incorporation of ammonia into glutamine. Ammonia is then scavenged by subsequently conjugating phenylacetate with glutamine to form phenylacetylglutamine, which is then excreted in urine. Results

are eagerly awaited from a recently completed phase I trial of LOPA in patients with HE, and the company has announced plans for a phase II trial to begin in 2011.[99]

Another approach to addressing nutritional deficiencies in cirrhotic patients with HE focuses on correcting the Fischer ratio: the balance between branched-chain amino acids (BCAA) and aromatic amino acids (AAA). This ratio is typically 3:1 in the healthy population, but it becomes inverted in cirrhotic patients. The benefits of BCAA (valine, leucine, and isoleucine) are believed to be 2-fold: They are essential for protein production, and they are critical for the prevention of catabolism, which can worsen HE. AAA, on the other hand, appear to be precursors of "false" neurotransmitters such as octopamine or phenylethylamine. These have been implicated in the pathogenesis of HE because of their potential to inhibit neurotransmission via nonfunctional competitive blockade of receptors. A surplus of AAA can also cause problems related to the production of neurotoxic phenols and downregulation of the synthesis of excitatory neurotransmitters, such as norepinephrine and dopamine, thus further contributing to neurologic dysfunction.[52] By supplementing diets with BCAA, patients are able to continue adequate protein intake, reduce catabolism and muscle breakdown (which helps to maintain the ammonia clearance provided by muscle), and prevent the synthesis of false neurotransmitters. A meta-analysis of BCAA supplementation supported its use for improving the rate of recovery from episodic HE but did not demonstrate a survival advantage.[100] BCAA supplements are limited in clinical practice due to poor palatability and higher costs.

The most important recent development in nutritional supplementation for HE is reversal of the long-held belief that protein restriction is beneficial for patients with episodic or persistent HE. A study evaluating low-protein versus normal-protein diets for patients with episodic HE demonstrated that both groups showed similar rates of improvement; however, the protein-restricted group suffered from accelerated protein catabolism.[101]

Finally, some evidence from an Italian center supports supplementation with carnitine, either L-carnitine or its acetylated form, for treatment of HE.[102-104] Confirmation of these positive results in other centers is needed.

Reduction of Inflammation

Patients with cirrhosis have a significantly increased risk of infection related to their relative immunosuppression and dysfunctional reticuloendothelial system. This risk is almost 5 times that of noncirrhotic patients hospitalized for other indications. Indeed, infection, a prototypical inflammatory state, is a common precipitant of HE because these infections often manifest without typical signs and symptoms. Clinicians must aggressively search for and treat these infections in patients presenting with HE. Many practitioners assume an infectious process is involved in the presentation of more severe cases of HE and begin empiric antimicrobial therapy while body fluid analyses and cultures are performed. In addition, standard-of-care treatment demands the systematic performance of diagnostic paracentesis for any patient with ascites who is admitted to the hospital with decompensation. Antibiotics are clearly indicated in the treatment of infections in patients with HE, and many of these HE events will improve with conservative management alone—intravenous fluids, antibiotics, drainage of abscesses, and rest.

Even in the absence of an active infection, patients with cirrhosis are in a relatively proinflammatory state, marked by elevated levels of endotoxin, tumor necrosis factor (TNF)-α, and other proinflammatory cytokines, as well as upregulation of certain toll-like receptors.[105] This inflammatory state may be related to bowel wall edema due to portal hypertension or delayed transit time with subsequent translocation of bacteria and/or endotoxin into the bloodstream. Whether antibiotics given to HE patients without active infection have an impact on the relative inflammatory state of cirrhosis is unclear, but antibiotics do appear to improve the hyperdynamic circulation of cirrhosis and reduce both the risk of hepatorenal syndrome and death.[106]

Other potential HE therapies that have an anti-inflammatory role include pentoxifylline and the activated charcoal product AST-120. A recent large randomized controlled trial of pentoxifylline versus placebo in patients with Child-Pugh class C cirrhosis showed no benefit in overall mortality, but the study authors did demonstrate a significant reduction in complications of cirrhosis, including development of HE, in patients treated with pentoxifylline. Pentoxifylline is thought to work in these patients because of its anti–TNF-α activity, as TNF-α is typically elevated in patients with cirrhosis. A study comparing pentoxifylline with placebo or another agent for the treatment or prevention of HE is needed before pentoxifylline can become accepted as therapy for HE.

Other potential anti-inflammatory therapies for HE should also be explored. With its distinct mechanism of action, AST-120 may be able to bind very small molecules in the gut—such as TNF-α, lipopolysaccharide, or endotoxin—and thereby block their absorption. AST-120 is currently being evaluated for use in patients with mild HE.

Summary

The current management of HE requires prompt recognition of the disease state (particularly in its earliest or mildest stages), careful identification and amelioration

of precipitating factors, and judicious prescribing of a therapeutic arsenal that is often multifaceted and must be tailored to each patient. Nonabsorbable DS (lactulose in the United States) remain the mainstay of therapy for the majority of patients with episodic or mild persistent HE. Nonabsorbable antibiotics (particularly rifaximin) with or without DS have become the standard-of-care treatment for patients with recurrent or persistent HE, after removal of underlying precipitating factors where possible. Whether antibiotics will also become the standard-of-care treatment for patients with milder forms of the disease (particularly minimal HE) depends on the outcomes of anticipated trials in this patient population, but preliminary data look promising.[5,107] Ammonia scavengers have a role in the treatment of patients who are intolerant to DS and/or antibiotics, unable to afford antibiotics, or suffering from persistent or recurrent HE despite use of DS and/or antibiotics (particularly if they are confirmed to be hyperammonemic). Despite the lack of robust data, supplementation with oral zinc and/or L-carnitine seem to be reasonable treatment options for patients with HE, particularly if deficiencies of these molecules are confirmed by laboratory testing. Other interesting compounds under study for HE—including AST-120, HPN-100, LOPA, acarbose, and rivastigmine—will require additional data before being accepted into the routine management of HE. Finally, due to the severity of the underlying liver disease and the prediction of poor long-term survival, all patients with overt HE should be considered for liver transplantation.

Dr. Frederick is an advisor and member of the Speakers' Bureau for Salix, an advisor and member of the Data and Safety Monitoring Board for Hyperion, and an advisor for Ucyclyd.

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