Antibiotics in the Management of Hepatic Encephalopathy: An Evidence-Based Review

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Hepatic encephalopathy (HE) is an increasingly prevalent and debilitating condition that occurs in functional hepatic insufficiency. It is marked by fluctuating neuropsychiatric and cognitive impairment, which can be severe and life threatening. Hepatic encephalopathy is a diagnosis of exclusion; thus, it is challenging to diagnose definitively and to investigate in clinical trials. High response rates in the placebo arms of well-conducted studies demonstrate that the most effective treatment for HE is the correction of known precipitating triggers. However, pharmacological therapies may also be helpful. Although the precise pathogenesis remains unknown, bacterially derived neurotoxins from enteric flora likely play an important role. Based on this hypothesis and on accumulating clinical experience documented in randomized trials, oral antibiotics have emerged as an important treatment adjunct. This article addresses the qualities of an ideal antibiotic and reviews the literature on 4 antibiotics used to treat HE: neomycin, metronidazole, vancomycin, and rifaximin, with the most promising of these drugs appearing to be rifaximin. Unfortunately, most studies of the treatment of HE are difficult to interpret due to small sample sizes, methodological flaws, vulnerability to bias, and the intrinsic challenges of studying HE. Many studies have erroneously concluded that treatments are equivalent simply because no significant difference between treatment arms was detected. Consequently, the literature generally lacks definitive data from large, randomized, placebo-controlled trials. Nevertheless, the data suggest that minimally absorbed antibiotics are emerging as a safe and effective approach for the treatment of HE.

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Key words: Hepatic encephalopathy • Metronidazole • Vancomycin • Neomycin • Rifaximin • Minimally absorbed antibiotics

Hepatic encephalopathy (HE) is a disease that occurs in patients with hepatic insufficiency that is characterized by neuropsychiatric and cognitive changes. The population at risk includes patients with acute liver injury associated with severe hepatocellular dysfunction, advanced cirrhosis with
Hepatic encephalopathy is common, affecting 10% to 50% of all patients with cirrhosis. As the severity of cirrhosis progresses, the risk of overt HE increases. Because HE is difficult to diagnose with certainty, its true prevalence remains uncertain. However, as the prevalence of cirrhosis—estimated to be 5.5 million in 1998—steadily rises in the United States, so too does the incidence of HE. Hepatic encephalopathy is generally classified by degree of severity, or grade. Grade 0 (subclinical) HE is characterized by mild neurological dysfunction that may only be apparent on sensitive neurocognitive tests. Asterixis is typically absent. Grade 1 (mild) HE is typified by sleep disturbances with reversal of day-night patterns, difficulty concentrating, and impairment with tasks such as simple arithmetic or driving. Grade 2 (moderate) HE is characterized by lethargy, slurred speech, intermittent disorientation, and often mild to moderate asterixis. Patients with grade 3 (severe) HE are usually somnolent and grossly disoriented with more prominent asterixis. Grade 4 HE describes hepatic coma; such patients may exhibit decerebrate posturing and are at risk for imminent death from brain edema and cerebral herniation. Of note, an assumption that underlies this grading system is that the different grades represent a spectrum of the same disease process and, thus, a treatment for grade 3 or 4 HE should also be effective for grade 1 or 2.

The most important aspect of treatment of HE is the correction of factors known to trigger exacerbations of HE. Such factors include gastrointestinal bleeding, uremia, constipation, ingestion of large protein loads, infections, hypokalemia, hepatic coma; such patients may exhibit decerebrate posturing and are at risk for the use of psychoactive drugs such as benzodiazepines, dehydration, hyperand hyponatremia, the use of diuretics that increase renal ammonia release, hepatic or portal vein thrombosis, and hepatocellular carcinoma. The major pharmacological treatments for HE are nonabsorbable disaccharides, such as lactulose and lactitol, and nonabsorbable antibiotics; the most promising research is in the area of nonabsorbable antibiotics.

Antibiotics in the Management of HE

Traditionally, physicians have hypothesized that ammonia made by urease-producing colonic bacteria is one of the key neurotoxins; however, unambiguous proof of ammonia’s role remains elusive. Other bacterially derived toxins that are absorbed from the gut may also play a role, with ammonia simply functioning as a marker of the presence of other gut toxins. Regardless of the nature or identity of the toxins, if the molecules that cause hepatic encephalopathy originate from colonic flora, antibiotics with activity against these bacteria should be effective for HE. With this rationale, oral neomycin was introduced as a treatment for HE in 1957. This landmark study, which suggested that neomycin could control the symptoms of HE and even increase protein tolerance in patients vulnerable to HE, set the precedent for the use of antibiotics in the treatment of HE.

In 1977, a single study of 33 cirrhotic patients compared neomycin to lactulose and demonstrated that lactulose may also improve symptoms of HE. However, this small study was not placebo-controlled and did not truly prove equivalence. Several subsequent trials reached similar conclusions. Although the failure to find a significant difference between 2 treatments in a small study is not the same as proving equivalence, nonabsorbable disaccharides are now a mainstay of treatment for HE.

It is of note that the efficacy of lactulose in treating HE has never been proven in an adequate placebo-controlled, randomized, clinical trial. A recent Cochrane meta-analysis highlighted this shortcoming in the literature and recommended that nonabsorbable disaccharides not be used as comparators in clinical trials for HE. Instead of trials comparing various treatments to lactulose or lactitol (which is not approved for use in the...
Antibiotics in the Management of HE continued

United States), what is needed are methodologically sound, large, multicenter, placebo-controlled, randomized trials that measure clinically relevant outcomes that indicate mental state. Such studies are now being conducted, and some of the most promising results are being seen with minimally absorbed antibiotics.

Qualities of an Ideal Antibiotic for the Treatment of HE

An ideal antibiotic for HE should be safe for individual patients and for society (Table 1). Simply put, a safe antibiotic is a minimally toxic antibiotic. Safety of an antibiotic is in part determined by a combination of the following factors: systemic absorption from the gastrointestinal tract, metabolism of the drug by the host, potential interactions with other drugs, toxicities caused by the drug, susceptibility of the individual to the drug toxicities, and the importance or relevance of those toxicities to the particular patient. An ideal antibiotic for HE would have no absorption from the gut and thereby act specifically on enteric bacteria. Furthermore, it would have negligible adverse effects even if systemically absorbed.

Safety is also determined by the vulnerability of the particular patient to the specific toxicities that a drug may cause. For example, a dehydrated patient or a patient with renal insufficiency may be more susceptible to the adverse effects of a nephrotoxic medication. Similarly, an ataxic and coagulopathic patient who is already at risk for falls (and subsequent intracranial bleeding) requires continued function of the vestibular system and a drug with ototoxicity might be particularly dangerous. A drug that is toxic to the central nervous system and may cause confusion would of course be particularly undesirable in the treatment of a disorder that primarily affects the brain.

An ideal antibiotic should also be safe for society: if it selects for antibiotic-resistant pathogens, it could cause new problems even as it solves others. This is especially relevant to orally ingested antibiotics, as many intestinal bacterial species can also be pathogenic. A prominent example is Enterococcus faecalis, a common cause of infective endocarditis, urinary tract infections, meningitis, sepsis, and nosocomial infections. In fact, vancomycin-resistant enterococci are feared pathogens, difficult and costly to treat and dangerous for some patients. Similarly, Pseudomonas aeruginosa, a pathogen that is carried by approximately 10% of the population as normal colonic flora, is often found to be resistant to multiple antibiotics and is a cause of 10%-20% of hospital-acquired infections. The same holds true for Escherichia coli, the leading cause of urinary tract infections and a common cause of sepsis. All of these organisms already cause significant morbidity and mortality—especially in the population that is susceptible to HE such as immunocompromised patients with end-stage liver disease. A clinician using antibiotics for the treatment of HE should remain cognizant of this danger, especially if antibiotics are to be used on a long-term basis.

Once an antibiotic has been established as safe, it should then be proven efficacious. Unfortunately, this is often difficult in the case of HE. In order to truly establish efficacy, studies must be methodologically sound and focus on clinically relevant outcomes. For example, arterial ammonia concentration is not nearly as relevant an outcome as mental state or mortality. Similarly, asterixis and electroencephalography (EEG) findings may be important markers for physiologic changes seen in HE but they should not be primary outcomes of a study, as they are not the major clinical concerns. The focus should remain the neuropsychiatric state and survival of the patient.13,14 Furthermore, studies that report changes in the portal-systemic encephalopathy (PSE) index, a calculated number based on 5 variables (abnormal mental status, asterixis, blood ammonia levels, EEG abnormalities, and performance on a timed cognitive test such as a number connection test or an A-connection test) are subject to misinterpretation, as the PSE index may be disproportionately affected by

Table 1
Qualities of an Ideal Antibiotic for Hepatic Encephalopathy (HE)

- Safe for individual patients
  - minimal absorption from the intestinal tract
  - well tolerated with minimal toxicity
- Safe for society, including other hospitalized patients
  - does not result in antibiotic-resistant enteric pathogens, especially in the inpatient setting
- Effective for HE
  - causes measurable improvement in important clinical features of HE, including asterixis, mental state, neurocognitive function, and (ideally) mortality
  - serum ammonia and electroencephalogram patterns may be helpful markers for HE, but are nonspecific and not key clinical outcomes
variables that are not necessarily clinically significant, such as ammonia concentration. The PSE index has never been shown to be superior to HE grading and, in our opinion, should be abandoned as a primary outcome. Because HE is primarily a syndrome defined by neuropsychiatric dysfunction, the main outcomes to assess efficacy of antibiotics should investigate this outcome. Trials therefore should focus on clinically significant, objectively measured variables that are reliable indicators of mental state. Although objective, quantitative, clinically-relevant tests are still being developed and validated, some examples of objective tests of neuropsychological state include the number connection test, the A-connection test, the block design test, and the digit symbol test. Many studies have used such tests in the assessment of subjects’ mental function. Such quantitative tests are more robust and less subject to bias than subjective grading systems of mental state.

Clinical investigators have realized that proving the efficacy of antibiotics (or, for that matter, any drug) in the treatment of HE is fraught with difficulties: the waxing and waning nature of the disease, the lack of a specific diagnostic test, the status of HE as a diagnosis of exclusion, and the high response rates (as high as 40%-70% in the placebo arms of several well-conducted trials) to supportive treatment with removal of triggers. In sum, studying HE is intrinsically difficult. Nevertheless, some promising data are emerging to suggest that certain antibiotics may be important in the treatment of HE.

Unfortunately, most of the studies examining the effects of antibiotics on HE have been small, methodologically flawed, and subject to bias, thus making them difficult to interpret. Most studies fail to report all-cause mortality rates, and some report only composite or calculated data (such as an HE severity index like the PSE index) without clearly stating objective findings. Thus, assessing the clinical relevance of reported findings is often challenging. One cannot draw firm, unambiguous conclusions from such studies.

As mentioned above, another very important point when considering the literature in the HE field is this: the failure to demonstrate a difference between 2 treatments in a superiority trial (where the null hypothesis is that the 2 treatments are equivalent) is different from demonstrating equivalence. A P value greater than .05 in such a study simply means that the chance that the null hypothesis is true is greater than 5%. In other words, in comparative studies where no significant difference is seen, the correct interpretation is that we cannot disprove equivalence (and thus cannot prove superiority). This is quite different from proving equivalence, which requires a different study design and statistical analysis. This common error plagues the HE literature. In fact, such faulty reasoning was the basis for the adoption of lactulose use in HE. Interestingly, although many antibiotics have been used in the treatment of HE (neomycin, metronidazole, vancomycin, and rifaximin), they have never been shown to be superior to HE. Below, we review the data on several antibiotics in the treatment of HE:

**Antibiotics in the Management of HE**

Metronidazole: Inconclusive Data on HE and Safety Concerns for Cirrhotic Patients

Metronidazole is a drug frequently used for the treatment of anaerobic bacterial and protozoal infections. Unlike other antibiotics that have been used for HE such as neomycin, vancomycin, and rifaximin, metronidazole is not minimally absorbed. On the contrary, whether administered orally, rectally, or parenterally, metronidazole has nearly 100% bioavailability and permeates all tissues by simple diffusion. At steady state, intracellular and extracellular concentrations are equivalent. Metronidazole is mainly (82%-94%) metabolized by the cytochrome P450 system; thus, caution should be used when severe hepatic dysfunction is present.

Practitioners prescribing metronidazole should be aware of the possible adverse effects, many of which have special significance to patients vulnerable to HE. First, metronidazole can be toxic to the nervous system: practitioners have accepted without a doubt that lactulose is efficacious for HE, rigorous proof of this claim is strikingly absent from the literature. Nevertheless, in keeping with the clinical impressions of many individual physicians, an accumulating body of randomized, controlled trials—and subsequent meta-analyses—suggest that antibiotics are effective therapies for HE. Below, we review the data on peripheral neuropathy, seizures, vertigo, ataxia, headache, and mental state changes have all been reported. Most of the nervous system toxicities appear to be dose-related. Needless to say, treating cirrhotic patients already suffering from nervous system dysfunction, (ie, HE, with a hepatologically cleared drug that is known to cause dose-related nervous system toxicity) is problematic.
Table 2
Antibiotics in the Treatment of Hepatic Encephalopathy: Summary of Randomized Placebo-Controlled Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Design</th>
<th>Results</th>
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</thead>
<tbody>
<tr>
<td>Neomycin</td>
<td></td>
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<tr>
<td>Strauss et al21</td>
<td>39 hospitalized cirrhotic patients (mostly Child-Pugh Class C) with grades I-III HE, enrolled over a 5-year period</td>
<td>All patients treated with control of precipitating factors + protein restriction (≤10 g/d) + neomycin (1 g q 4 h) or placebo</td>
<td>No significant difference found in mortality or average time to regression of HE (39 ± 23 hours for neomycin and 49 ± 22 hours for placebo)</td>
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<tr>
<td>Blanc et al22</td>
<td>80 cirrhotic patients with grades II-IV HE</td>
<td>Patients treated for 5 days with either placebo (n = 40) or combination lactulose-neomycin (n = 40)</td>
<td>No significant difference seen in mortality or recovery; lactulose-neomycin was generally not well tolerated</td>
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<tr>
<td>Metronidazole</td>
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<td>Morgan et al17 *</td>
<td>18 cirrhotic patients (mostly hospitalized) with mild to severe HE</td>
<td>Patients received either neomycin 4 g/d or metronidazole 800 mg/d for 7 days and were then switched to the other treatment for 7 more days; outcomes included mental state, HE grade, asterixis, EEG, and arterial ammonia; all patients were protein-restricted</td>
<td>14 of 18 patients improved; no difference demonstrated between neomycin and metronidazole</td>
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<td>Vancomycin</td>
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<tr>
<td>Tarao et al18 *</td>
<td>12 cirrhotic patients with HE (mostly grade II), unresponsive to lactulose</td>
<td>Double-blind crossover study with all patients given oral vancomycin 2 g/d for 8 weeks and then either oral vancomycin or lactulose (titrated to 2-4 stools/day); outcomes included HE grade, EEG frequency, and arterial ammonia; all patients protein-restricted</td>
<td>Grade of HE improved in all patients after vancomycin, but the lack of a placebo group clouds the interpretation of these results</td>
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<td>Rifaximin</td>
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<td>Williams et al24 *</td>
<td>54 cirrhotic patients with mild to moderate (mostly grade I-II) HE</td>
<td>Patients treated for 7 days with rifaximin 600 mg/d, 1200 mg/d, or 2400 mg/d in 3 divided doses; change in PSE index (determined by mental state, asterixis, number connection test, EEG, and serum ammonia) assessed</td>
<td>Rifaximin 1200 and 2400 mg/d resulted in statistically significant improvement in PSE index; however, none of the individual components of the PSE index showed a statistically significant dose relationship</td>
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<tr>
<td>Bass et al25</td>
<td>93 cirrhotic patients (Child-Pugh Class B-C) with mild to moderate HE who were intolerant of nonabsorbable disaccharides; strict exclusion criteria enforced, and patients with known triggers for HE excluded</td>
<td>Patients were treated for 14 days with either rifaximin (400 mg 3 times daily) or placebo and assessed every 2-4 days</td>
<td>Rifaximin was significantly more effective than placebo (P &lt; .01) at improving asterixis; other outcomes such as mental state, blood ammonia, and performance on cognitive tests showed improvement in both groups with no significant difference</td>
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*Not a placebo-controlled trial; the reasons for including studies lacking a placebo group in this table are described in the text. HE, hepatic encephalopathy; EEG, electroencephalogram; PSE, portal-systemic encephalopathy.
The most common adverse effects of metronidazole are gastrointestinal. These include anorexia, nausea, diarrhea, abdominal cramping, and a peculiar metallic taste. These are all important, as cirrhotic patients are often malnourished, and a drug that can lead to decreased oral intake is generally not desirable. Finally, when it is taken in combination with alcohol (and many patients continue to drink despite their cirrhosis), metronidazole can cause a disulfiram-like reaction characterized by flushing, diaphoresis, palpitations, nausea, and vomiting.

No placebo-controlled trials have examined the effect of metronidazole on HE, but 1 clinical crossover trial compared metronidazole to neomycin in the treatment of several grades of HE.\textsuperscript{17} In this study, 18 biopsy-proven cirrhotic inpatients with mild, moderate, or severe HE were maintained on a protein-restricted diet and observed for 1 week to determine their baseline functional status. Patients then received either 1 g of neomycin or 0.2 g of metronidazole 4 times daily for a week. Each patient was switched to the other treatment the following week. Clinical and laboratory outcomes were recorded in a blinded fashion; these included mental state, asterixis, arterial ammonia, and EEG frequency. Interestingly, at the end of the study period, ammonia levels were not substantially reduced by either drug, in contrast to other studies that examined neomycin. Improvements in mental state and asterixis were noted regardless of whether neomycin or metronidazole was used.

Unfortunately, without a placebo group, we cannot know whether these improvements were due to the antibiotics, the protein-restricted diet, or simply the natural course of the disease. The authors maintain that in their crossover design each patient served as his own control; however, such reasoning does not necessarily hold true for a delirium with a naturally fluctuating course. Ultimately, one cannot conclude whether either drug was effective—much less whether the 2 drugs were equivalent in their presumed effect. The study was not set up as an equivalence trial: there was no equivalency aim stated, no initial establishment of an equivalence boundary, and no sample size calculation for equivalency. Furthermore, the statistical analyses were not suited to determine equivalence. To their credit, the authors do not overinterpret their results: they appropriately state that the results are suggestive and encouraging but inconclusive. This conclusion also holds true for the majority of studies in the field.

**Vancomycin: A Small, Suggestive Study on HE, but Safety Concerns for Hospitalized Patients**

Vancomycin is an antibiotic active mainly against gram-positive cocci and is administered parenterally to treat staphylococcal infections, especially methicillin-resistant Staphylococcus aureus. It is also used orally to treat metronidazole-resistant Clostridium difficile colitis. Vancomycin is poorly absorbed from the intestinal lumen, and no serious systemic toxicities seem to occur after oral administration; however, nausea and pruritic rash have been reported.\textsuperscript{18,19} Toxicities may be more likely to occur in patients with renal insufficiency and defects in the intestinal mucosa.\textsuperscript{19}

A single randomized controlled trial has examined the use of oral vancomycin to treat lactulose-resistant HE.\textsuperscript{19} In this small crossover study conducted over a period of nearly 6 months, 1 g of vancomycin was administered orally twice daily to 12 cirrhotic patients with moderately severe (mostly grade 2) lactulose-resistant HE. All patients exhibited significant improvement, and 10 of 12 patients had complete resolution of their HE. Moreover, vancomycin was associated with significantly lower arterial ammonia levels than lactulose (152 µg/mL vs 97 µg/mL, P < .001). However, in the absence of a placebo control group, we cannot be sure whether this observation reflected the natural remitting course of the disease or a true effect of vancomycin. Furthermore, the adequacy of the blinding and randomization is unclear. Although the results are encouraging, these problems, as well as the small study size, cloud interpretation of the study. Thus, vancomycin is not an antibiotic routinely used for the treatment of HE.

Perhaps a more compelling reason to avoid routine use of oral vancomycin is that it selects for vancomycin-resistant enterococci (VRE). VRE can cause life-threatening infections that are notoriously difficult to treat. VRE were responsible for over 25% of nosocomial infections in intensive care units from 1992 to 2002, and carry significant risks of morbidity and mortality.\textsuperscript{20}

**Neomycin: A Popular Antibiotic for HE—With Unproven Efficacy**

Neomycin is a broad-spectrum bactericidal aminoglycoside with activity against both gram-positive and gram-negative bacteria. Activity against anaerobes is quite limited. Traditionally, oral neomycin has been used as part of a presurgical bowel-cleansing regimen for elective procedures, as it causes marked suppression of aerobic luminal flora and reduces the risk of sepsis after colorectal surgery. Neomycin has been a popular antibiotic for the treatment of HE.

Neomycin is poorly (3%-5%) absorbed when orally ingested. Notably, its absorption is not zero, and when absorbed systemically it can be quite toxic. Case reports describing oral
neomycin's adverse effects have been published. Gastrointestinal toxicities include diarrhea and acute enterocolitis by staphylococcal or C. difficile overgrowth, a rare but serious side effect. More significantly, chronic administration can lead to ototoxicity and nephrotoxicity. Although rare, deafness has been reported; thus, patients maintained on long-term neomycin must have regular tests of renal and auditory function.14

In 1957, a pioneering study by Dawson and colleagues7 first reported the use of neomycin to treat HE. This paper describes 12 patients with acute hepatic coma and 8 others with chronic HE. The dose of oral neomycin ranged from 4 to 10 g/day. For 6 of 8 patients with chronic HE, administration of neomycin seemed to correlate with an improvement in clinical outcomes such as asterixis, coordination, feto hepaticus, and performance on mental function tests. Suggestively, for some patients, relapse occurred when neomycin was withdrawn. Of the patients with hepatic coma, 7 of 12 improved on neomycin. All were also being treated with protein withdrawal. As the authors noted, there was no placebo control group and the effect of neomycin was far from uniform. In addition, there was no statistical analysis. Thus, in spite of its stature as a pioneering paper, no solid conclusions can be drawn from this study.

Subsequently, only 2 placebo-controlled trials have been conducted with neomycin in HE, neither of which showed a significant difference between neomycin and placebo. Strauss and associates21 randomized 39 hospitalized patients with Child-Pugh Class B or C cirrhosis to receive either 6 g of neomycin daily (1 g every 4 hours) or placebo. The authors simultaneously treated precipitating factors such as gastrointestinal hemorrhage, infections, and electrolyte disturbances. After discharge from the hospital, the patients were followed for 1 year to track mortality. Interestingly, the authors found no significant difference in the time to resolution of mental state changes. In the neomycin group, HE resolved in an average of 36 hours, whereas in the placebo group, HE resolved in an average of 49 hours. This small difference did not achieve statistical significance. In addition, there was no difference in mortality at 1 year. The authors concluded that the factor precipitating HE must be treated primarily and that treatment with neomycin does not alter the regression of HE.21

In the other study, Blanc and coworkers22 randomized 80 patients with acute HE to receive a combination of lactulose and neomycin or placebo for 5 days. Although most patients in both groups recovered, no significant difference between the groups emerged. Furthermore, the lactulose-neomycin treatment was generally not well tolerated. The authors concluded that the lactulose-neomycin combination should not be used in the treatment of acute HE.

Studies comparing neomycin to lactulose have also been conducted.8,11 However, the results of such studies are difficult to interpret because neither lactulose nor neomycin has been proven effective for HE in a placebo-controlled study. In addition, these trials were established as superiority trials—not equivalence studies. As such, the lack of a significant difference between the treatments does not actually prove equivalence. In summary, although neomycin may in fact improve the course of HE for certain subsets of patients, no study has actually proven this to be true.

**Rifaximin: A Promising and Safe Alternative Antibiotic**

Perhaps the most promising antibiotic for use as a therapy for HE is rifaximin, a cousin of rifampicin that has a broad spectrum of antimicrobial activity against gram-positive and -negative bacteria, including aerobes and anaerobes. The list of bacteria susceptible to rifaximin includes numerous enteric pathogens, some of which may contribute to the pathogenesis of HE.23 A significant benefit of rifaximin is that it is minimally absorbed when taken orally—less than 0.4% of the drug is absorbed in patients with HE, and nearly all of it is excreted unchanged in the feces. Absorption is minimal in all patients examined to date, including those with HE. Because of this lack of systemic absorption, dosage adjustments are not required in patients with hepatic dysfunction.23

Furthermore, rifaximin appears to be extremely safe: over 3000 patients have received the drug in clinical trials, and when compared to placebo, no significant adverse effects have been seen. Rifaximin, now approved in numerous countries, was first approved for use in Europe over 18 years ago, and it was approved for use in the United States by the Food and Drug Administration in 2004 for the treatment of diarrhea. Currently, the main disadvantage of this agent is its cost.

Several trials have examined the effect of rifaximin on HE. In 2000, Williams and associates24 conducted a randomized, double-blind,
dose-finding study of 54 cirrhotic patients with mild to moderate HE. Each patient was given 1 of 3 different doses of rifaximin for 7 days; other pharmacological treatments for HE were avoided throughout the study period. The primary outcome measure was the PSE index. After 1 week, the PSE index demonstrated a statistically significant improvement in the 2 groups given the higher doses of rifaximin. A nonsignificant trend suggested that the highest dose had the greatest effect. Although the study lacked a placebo group, the fact that increasing effects were seen with increasing doses of the drug is encouraging. However, on closer scrutiny, the results are not so clear cut. The PSE index is a calculated score in which 5 individual components are arbitrarily scored and weighted; interestingly, not 1 of the 5 components of the PSE index individually showed any evidence of a dose relationship. This raises the possibility that the drop in PSE index was merely an artifact of the calculation rather than a clinically significant change attributable to rifaximin. In spite of its flaws, the results of this small study are encouraging and at least demonstrate that rifaximin is safe and potentially effective for grade 1-2 HE in cirrhotic patients.

A particularly encouraging study on rifaximin was presented at the annual meeting of the American Association for the Study of Liver Diseases in 2004. In a multinational, prospective, randomized, double-blind, placebo-controlled trial, Bass and colleagues examined 93 cirrhotic patients with mild to moderate HE who were unable to tolerate lactulose or lactitol. (Interestingly, contrary to popular opinion, a recent Cochrane review concluded that nonabsorbable disaccharides such as lactulose and lactitol have never been proven effective for HE. In fact, the few early placebo-controlled trials involving lactulose actually found no benefit over placebo.) Exclusion criteria were strict: patients were required to have none of the many...
known triggers for HE. The authors closely followed the subjects for 2 weeks and measured mental status, asterixis, blood ammonia levels, and performance on several cognitive tests. Both the placebo and the rifaximin groups exhibited a marked improvement in mental status and cognitive tests, but rifaximin was significantly better at improving asterixis. Importantly, this is the first placebo-controlled trial of any antibiotic that demonstrated efficacy for HE.

Six other studies have compared rifaximin to lactulose or neomycin.27-32 However, these studies are plagued by the same problems as the studies that have compared neomycin to lactulose: neither lactulose nor neomycin has been proven efficacious for HE in a placebo-controlled trial. All of these comparison studies were set up as superiority trials, not equivalence trials. Nevertheless, rifaximin still appears to be a promising treatment for HE.

Conclusion: An Exciting Time for HE Research and Treatment

Now is an exciting time for research in HE. New studies are challenging traditional assumptions, and the stringent principles of evidence-based medicine are being applied to the field.13,33 Although past studies have not proven the efficacy of minimally absorbed oral antibiotics, newer studies are beginning to reveal their potential. In fact, a recent Cochrane meta-analysis suggests that antibiotics may be superior to other treatments such as nonabsorbable disaccharides including lactulose.

An ideal antibiotic must be safe and effective for treating HE. With these goals in mind, oral neomycin, vancomycin, metronidazole, and rifaximin have all been studied in the management of HE. The risks and benefits of the different antibiotics for HE are summarized in Table 3. So far, the most promising antibiotic appears to be rifaximin.

Although it is clear from the high response rates in placebo arms that the cornerstone of HE treatment remains the correction of precipitating factors, minimally absorbed oral antibiotics may be an important adjunct, and new agents such as rifaximin may provide a safe and effective approach to the treatment of HE.

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