Published in final edited form as:
Metab Brain Dis. 2013 June ; 28(2): 307–312. doi:10.1007/s11011-013-9383-5.

Antibiotics for the Treatment of Hepatic Encephalopathy

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Abstract

The treatment of hepatic encephalopathy (HE) is complex and therapeutic regimens vary according to the acuity of presentation and the goals of therapy. Most treatments for HE rely on manipulating the intestinal milieu and therefore antibiotics that act on the gut form a key treatment strategy. Prominent antibiotics studied in HE are neomycin, metronidazole, vancomycin and rifaximin. For the management of the acute episode, all antibiotics have been tested. However the limited numbers studied, adverse effects (neomycin oto- and nephrotoxicity, metronidazole neurotoxicity) and potential for resistance emergence (vancomycin-resistant enterococcus) has limited the use of most antibiotics, apart from rifaximin which has the greatest evidence base. Rifaximin has also demonstrated, in conjunction with lactulose, to prevent overt HE recurrence in a multi-center, randomized trial. Despite its cost in the US, rifaximin may prove cost-saving by preventing hospitalizations for overt HE. In minimal/covert HE, rifaximin is the only systematically studied antibiotic. Rifaximin showed improvement in cognition, inflammation, quality-of-life and driving simulator performance but cost-analysis does not favor its use at the current time. Antibiotics, especially rifaximin, have a definite role in the management across the spectrum of HE.

Keywords

rifaximin; neomycin; covert hepatic encephalopathy; metronidazole; vancomycin; economics

Introduction

Management of HE has traditionally been with non-absorbable disaccharides for lowering the production and absorption of ammonia[1]. Antibiotics have been mainly used as alternatives to the non-absorbable disaccharides in improving HE symptoms[2]. This review will highlight the role of antibiotics in the acute treatment and prevention of HE obtained through a detailed literature, abstract and guidelines search for studies that responded to the MESH terms “antibiotics and hepatic encephalopathy”. There will also be a brief description of the role of antibiotics in treating infections as a precipitant of overt HE, on minimal or covert HE, and evaluation of economic considerations in antibiotic therapy.

Rationale

The prevention of production and absorption of gut-derived neurotoxins along with reduction in endotoxemia and inflammation underlie the rationale for antibiotic use in HE. A major component of these toxins is ammonia, while, other gut-derived products, oxindole,

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phenols, mercaptans, and short-chain fatty acids, have also been implicated[3]. It has also been shown that cirrhotic patients have significantly altered stool microbiome, which can also impact cognition[4]. Lowering systemic ammonia and reduction of inflammation and endotoxemia can be achieved through antimicrobials[567]. Based on this gut-specific action, most antibiotics used have been gut nonabsorbable in nature. Neomycin, vancomycin, paromomycin, metronidazole, and recently rifaximin, have been shown to be effective in acute and chronic therapy of HE[8].

Systemic antibiotic use for infections that can precipitate overt HE

Bacterial infections are significant precipitants of overt HE, especially spontaneous bacterial peritonitis, and in situations where bacterial translocation is increased such as an upper GI bleeding episode[9]. The recommended antibiotics in this situation depend on the infection and local microbial susceptibilities but are broad-spectrum, systemic agents that are aimed at the infection rather than HE itself[2]. In contrast, antibiotics specifically for HE are gut-specific and are not effective for treating potential infections during the acute episode.

Antibiotic use in covert and overt HE

These are antibiotics specifically directed towards HE; most studies pertaining to antibiotic use have concentrated on the acute overt HE episode or prevention of overt HE recurrence (table). Only rifaximin has been studied for covert/minimal HE and therefore it will be discussed in the section pertaining to rifaximin.

Aminoglycosides (Neomycin and Ribostamycin)

Neomycin and ribostamycin are the aminoglycosides that have been studied. Only one study comparing ribostamycin to lactulose in 15 patients has been performed, that showed equivalence; rest have used neomycin. Neomycin has activity against most gram-negative aerobes, except pseudomonas, and staphylococcal species. It inhibits bacterial protein synthesis via binding to the bacterial 30S ribosomal subunit and in some reports, has also been shown to inhibit intestinal glutaminase. There is limited data on the effectiveness of neomycin, since its use predated our current concept of evidence-based or randomized trials and it was the standard to which lactulose was initially compared to when it was first studied. A randomized, double blind, controlled trial comparing neomycin versus placebo in acute HE demonstrated no significant difference in symptomatic improvement[10]. In addition, other randomized controlled studies comparing neomycin to lactulose found no significant difference between the two agents [111213]. Dosing of neomycin is usually 1000mg every six hours for up to six days in an acute episode of overt HE and 1–2g daily for chronic use.

Though neomycin is FDA approved for HE, its continued clinical use is not recommended given its extensive side-effect profile. Common adverse events include intestinal malabsorption, nephrotoxicity, and ototoxicity. These side effects are common in chronic use because systemic absorption is much higher in hepatic and renal failure, as compared to roughly 4% for subjects without this organ dysfunction, increasing the systemic exposure (Figure). It is due to these side effects and lack of demonstrated clinical benefit that neomycin use has fallen out of favor for HE treatment.

Metronidazole, Vancomycin and Paromomycin

There have been limited studies on the efficacy of metronidazole and vancomycin in the management of HE. In a small study by Morgan et al., 11 mild to moderate HE patients and 7 chronically affected HE patients were treated for one week with 250mg oral dose of metronidazole twice daily with similar efficacy as neomycin[14]. However given its prolonged

rate of elimination in HE patients and increased risk for irreversible peripheral neurotoxicity metronidazole is not recommend for the management of an acute episode or for chronic management of HE[15].

Oral vancomycin, on the other hand, may be safer for the management for an acute HE episode, and has been studied in a limited group of HE patients who were resistant to lactulose[16]. Nevertheless, the limited studies, high expense, and with increased prevalence of vancomycin-resistant enterococci and other bacterial resistance, preclude its routine use[1718].

Paromomycin has been compared with rifaximin for the treatment of acute episodes of HE in three studies. Only one trial showed improvement in cognitive testing that was greater in rifaximin; rest showed equivalence[192021]. Metronidazole, paromomycin and vancomycin are not FDA approved for treatment of overt HE.

Rifaximin

Rifaximin is gut-specific antimicrobial agent for the management of HE that is FDA-approved for prevention of overt HE recurrence. It has a broad spectrum of activity against both gram positive and gram negative organisms, and specifically against anaerobic enteric bacteria[22]. It binds to the b-subunit of the bacterial DNAdependent RNA polymerase and disrupts RNA synthesis. However, unlike its derivative, rifamycin, less than 1% is absorbed systemically after oral administration, resulting in greater concentration in the gastrointestinal tract. This systemic exposure increases with worsening liver disease severity (Figure)[23]. It also has minimal effects on normal gut flora, though increased doses were shown to initially decrease GI flora such as *enterococcus, Escherichia coli, Lactobacillus spp., Bacteroides spp., Bifidobacterium spp.* and *Clostridium perfringens* all of which returned to initial values after a wash-out period[24].

Rifaximin has minimal side effects – headache, flatulence, abdominal pain, constipation, nausea, and vomiting – and no reported drug interactions make it relatively safe. It has been demonstrated to be superior to lactulose and other antimicrobials in numerous trials in patients with mild to moderate severe HE[2526272829303132 33](table).

In a randomized, double-blind, placebo controlled prospective trial, Bass et al. compared rifaximin, dosed at 550mg twice daily, to placebo over 6 months in patients with two prior overt HE episodes and showed a reduction in risk of developing HE[34]. In addition the risk of hospitalization was significantly reduced in the rifaximin group. This study showed reduction in venous ammonia and improvement in health-related quality of life in patients randomized to rifaximin [7, 35]. Additionally a recent study by Neff et al, showed that rifaximin used for greater than 6 months to be an effective agent for HE, particularly in patients with a model for end-stage liver disease (MELD) score less than 20[36].

Rifaximin is one of the few antimicrobial agents that has been tested in patients with covert/ minimal HE. The RIME trial randomized minimal HE patients into rifaximin and placebo and found that rifaximin therapy was associated with a significant improvement in cognitive performance and health-related quality of life compared to placebo[37]. Another study in minimal HE extended these findings on to the real-world outcomes of driving, in which patients randomized to rifaximin not only improved their cognition, but also significantly bettered their driving simulator performance and reduced systemic inflammation, but only psycho-social aspects of quality of life improved[38].

Economic Analysis for HE Treatment with Antibiotics

The economic analysis of HE is important given the daunting and ever-increasing costs of health care. Therefore a pragmatic approach includes the cost analysis of the drug as well as the savings if subsequent negative outcomes, i.e. hospitalizations are prevented[39404142]. As with any management for a medical condition, the risks and benefits have to be considered. Both non-absorbable disaccharides and neomycin have dose limiting side-effects and ambiguous effectiveness. While, on the other hand, rifaximin, has a more tolerable side-effect profile as well as being more efficacious, but is more expensive.

A comprehensive decision analysis published by Huang et al. (2007) addressed this dilemma through a cost effectiveness of 6 different strategies in the management of HE. The six arms were: (1) no HE treatment; (2) lactulose monotherapy (3) lactitol monotherapy; (4) neomycin monotherapy; (5) rifaximin monotherapy; and (6) up front lactulose with crossover to rifaximin if there was a poor response or intolerance to lactulose[43]. Through using decision-analysis software, the study concluded that the “do nothing” arm was the least efficacious and rifaximin salvage was most efficacious. However it was also noted that rifaximin monotherapy was not cost effective and that lactulose monotherapy and rifaximin salvage therapy was less expensive and more effective than alternate therapies. Conversely, studies have shown that since rifaximin may be associated with a lower rate of hospitalizations, this could result in overall cost-saving since the costs of hospitalizations far outweigh the costs of the therapy[4445]. In minimal or covert HE however, where hospitalizations are few and the therapy has to continue for a longer period potentially, rifaximin was not cost-saving for the prevention of motor vehicle accidents compared to lactulose from a societal perspective[46].

Conclusions

Antimicrobial agents form a substantial component of the armamentarium against HE. Although several agents have been used, the antimicrobial agent with the most published experience is rifaximin. The use of rifaximin has evolved over several decades and is one of the most widely used antibiotics for overt HE. However further studies into appropriate place of antimicrobials as first or second line therapeutic strategies for HE are needed.

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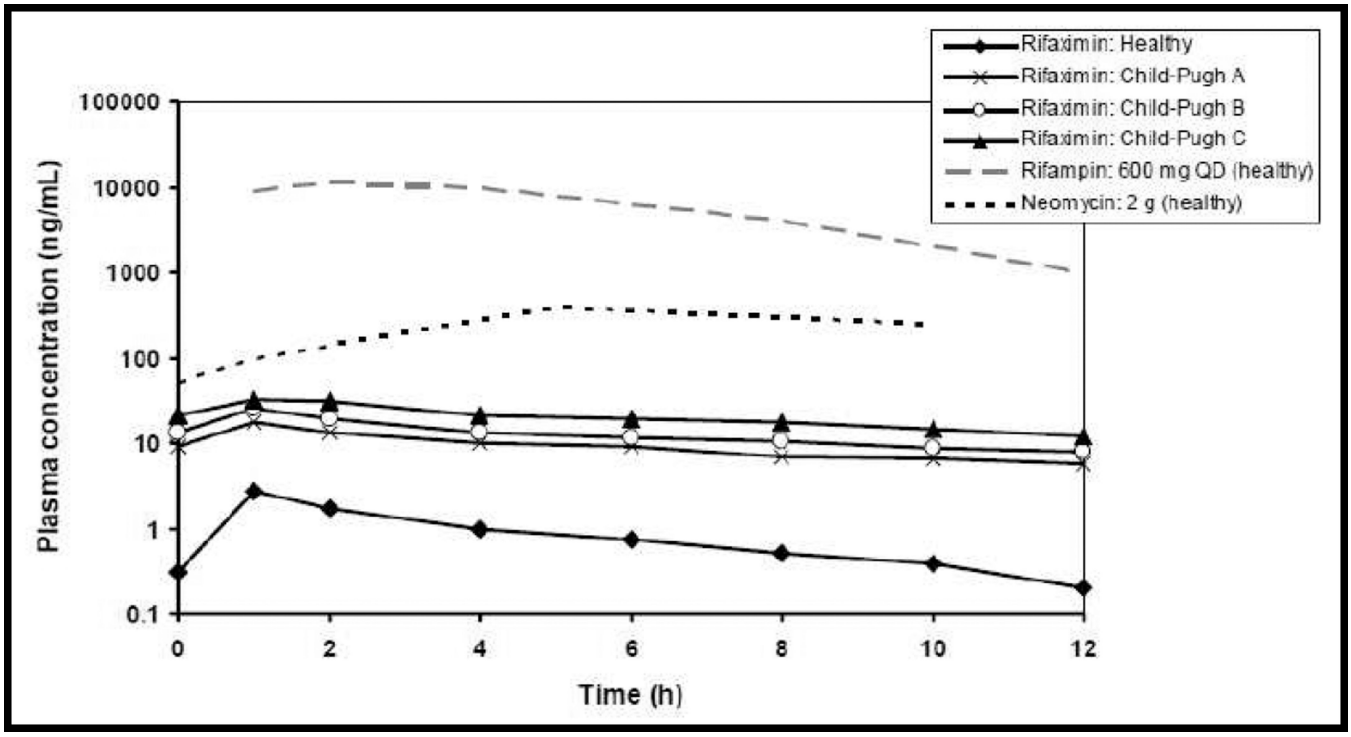

Figure. Pharmacokinetics of rifaximin compared to neomycin and rifampin[19]

The figure shows that the systemic exposure to rifaximin compared to neomycin and rifampin in healthy individuals. The comparative exposure to rifaximin increases with worsening liver disease severity

Table 1

Summary of overt HE acute, long-term and recurrence trials with antibiotics

Type of study	Number of trials and sample size	Results
Aminoglycosides (Neomycin or Ribostamycin)		
Acute therapy (5–30 days)		
Vs placebo	1 (39)	Time to HE grade change in which both were equivalent in seven days (Strauss et al)
Neomycin vs non-absorbable disaccharides	2 (105)	Equivalent efficacy compared to lactulose using mental status, ammonia, EEG and PSE index (Orlandi et al, Atterbury et al and Blanc et al from Cochrane 2004)
Chronic therapy (>30 days)		
Vs non-absorbable disaccharides	2 (48)	Equivalent efficacy compared to lactulose using mental status, ammonia, EEG and PSE index (Russo and Conn 1977 from Cochrane)
Both acute and chronic		
Vs non-absorbable disaccharides	1 (173)	Equivalent efficacy (Orlandi et al 1981 Cochrane)
Vancomycin [all acute therapy (5–30 days)]		
Vs lactulose	2 (72)	Improvement in mental status in one trial of 12 patients but equivalence in the others
Metronidazole (both acute and chronic)		
Vs. neomycin	1 (18)	Equivalence in EEG, ammonia and clinical status
Paromomycin (all acute therapy studies, 5–30 days)		
Vs. rifaximin	3 (82)	Ammonia reduced in both groups; two trials showed equivalence while one showed that rifaximin was superior to paromomycin with respect to psychometric tools
Rifaximin		
Acute therapy studies (5–30 days)		
Rifaximin vs. placebo	1 (93)	Asterixis improved only with rifaximin. PSE index, mental status, and intellectual function improved similarly in both groups
Rifaximin 200 mg vs 400 mg vs 800 mg	1 (54)	PSE index improved only in 400-mg and 800-mg groups.
Rifaximin vs other antibiotics	7 (227)	Ammonia improved more with rifaximin than neomycin (1 RCT) or similarly in both (6 RCTs). PSE index improved similarly in both groups (1 RCT). Intellectual function or mental status improved similarly in both groups (5 RCTs). Asterixis improved faster with rifaximin than with neomycin (1 RCT).
Rifaximin vs non-absorbable disaccharides	5 (276)	Higher ammonia improvement with rifaximin (3 RCTs) or similarly in both groups (2 RCTs). PSE or symptoms improved more with disaccharides
Long-term studies (3–6 months cyclical)		
Rifaximin vs non-absorbable disaccharides	2 (80)	Ammonia and mental status improved with both trials with all strategies compared to baseline. Higher improvement in PSE index, EEG and mental status with rifaximin. In the second study, rifaximin+/-lactitol did better than lactitol alone with mental status.
Rifaximin vs. neomycin	1(60)	Improvement in psychometric/neuro-physiologic tests, mental status and ammonia were similar across both groups.
Prevention of recurrence		
Rifaximin vs. placebo	1 (299)	Reduction in recurrent HE episodes and hospitalization in the rifaximin group with significantly higher improvement in neuro-physiological,

Type of study	Number of trials and sample size	Results
		quality-of-life and ammonia in the rifaximin group. 91% of patients were on lactulose in both groups.

Adapted from Bajaj JS Hepatol 2010 with permission[29]. PSE index: a composite score for HE consisting of 100 × [Mental status (Conn score) × 3 + asterixis grade × 1 + NCT grade × 1