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Rifaximin und Polyethylene Glycol as Treatment Modalities in Hepatic Encephalopathy

Karl-Uwe Petersen

ABSTRACT

Treatment of hepatic encephalopathy (HE) is still a challenge as the efficacy of the former gold-standard lactulose has been questioned. In addition to disturbed ammonia processing due to chronic liver dysfunction, further pathophysiological mechanisms such as inflammation and infection are discussed.

Rifaximin is an antibiotic practically insoluble in water, hardly absorbable and only very little metabolized during intestinal transit. It has a broad spectrum of antibacterial efficacy and shows an excellent tolerability. Rifaximin decreased in clinical studies the plasma concentration of NH_3, improved neurological symptoms, reduced the grade of severity of HE, and diminished the risk of being hospitalized for HE. Results of a major study investigating long-term HE prophylaxis with rifaximin in patients with at least two manifest HE episodes suggest a reduction of the breakthrough risk. In patients with minimal HE, rifaximin improved the ability to execute complex tasks.

Like lactulose, polyethylene glycols (PEG) are osmotic laxatives accelerating the intestinal transit. This shortens the time available for generation of ammonia from the passing food, possibly also hastens the elimination of NH_3-forming bacteria. Most important side effects are gastrointestinal symptoms. Because of its different mechanism of action, PEG might be an attractive combination partner for rifaximin, which has been proven to be a suitable therapeutic option to maintain remission of HE. Such a combination therapy might probably result in a reduction of the PEG dose needed with the consequence of an improved PEG tolerability.

Key words: hepatic encephalopathy (HE) · lactulose · rifaximin · breakthrough risk · polyethylene glycols (PEG)

INTRODUCTION

Still today, after decades of research in laboratory and hospital, the treatment of hepatic encephalopathy (HE) must be considered an unmet challenge. There is a lack of well-tolerated treatment modalities, and doubts on efficacy have even been cast on lactulose, the reigning gold standard. Compounds with new mechanisms of action as well as novel types of combination therapy are under development or already being studied in clinical trials. So far, none of them has been fully established; in some cases, first disappointments have been communicated.

Good prospects in HE treatment seem to be offered by rifaximin, an antibiotic which has a strictly local activity in the intestine. With excellent tolerability, this drug has demonstrated efficacy in numerous clinical studies, versus placebo as well as compared to established agents. It is the scope of this expertise to discuss and evaluate the chances to further improve the efficacy of rifaximin by a combination with polyethylene glycol (PEG). PEG compounds are osmotic laxatives, which were more frequently used in HE before the advent of lactulose.

1. Pathophysiology of Hepatic Encephalopathy

As recently pointed out by Riggio et al. (2010), the pathomechanism of HE, from the first trigger through the subsequent sequence of noxious events, are by no means fully understood. Nonetheless the ammonia hypothesis has remained the explanation supported by the most convincing evidence, although roles of further factors like inflammation and infection have been evolving (Shawcross et al., 2010).

1.1. Role of Hyperammonaemia

1.1.1. Pathomechanisms

The overview by Shawcross et al. (2010) integrates the evidence for the ammonia hypothesis from the first observations in dogs with porto-caval shunts – as early as 1896 – to the most recent results on the molecular level. Ammonia (NH_3) is produced in the intestinal lumen by bacterial degradation of proteins/amino acids, purines and urea. Also bioconversion of glutamine by enterocytes gives rise to NH_3 formation (Wolf, 2010).

One of the consequences of chronic liver dysfunction is disturbed processing of the ammonia generated by metabolic activity of intestinal bacteria: The standard pathway, the synthesis of urea, is disabled for the most part and also the powerful NH_3 scavenger, glutamic acid, normally amidated to form glutamine, is no longer fully available. In this condition, the brain gains importance as an alternative detoxication site: Astrocytes are capable of utilizing ammonia for the synthesis of glutamine. In the setting of hyperammonaemia, though, this will lead to intracellular glutamine. The associated osmotic load entails water influx and cellular swelling. A low-grade cerebral edema has even been detected with minimal HE (MHE). First sequelae are neuropsychological dysfunctions, for example intermittent disorders of awareness, attention, and memory. These disorders are mild and hardly noticed in the beginning, but MHE may already be associated with an impaired ability to execute complex tasks such as driving a car. Dictated by decreasing liver function, the cognitive disorders may finally proceed to a comatous state (Blei and Córdoba, 2001; Heidelbaugh und Sherbondy, 2006; Riggio et al., 1010; Shawcross et al., 2010).

1.1.2. Treatment options

The central importance of bacterial NH_3 generation for HE pathogenesis is reflected in the various treatment modalities. First-line therapy are lactulose, thanks to its ability to curb bacterial NH_3 formation, and antibacterial agents. Among the latter, neomycin occupies a prominent position owing to its minimal intestinal absorption. Most of the other options are still considered experimental, although it is remarkable to note that in this indication even the clinically established modalities are hardly supported by clinical trials conforming with current quality standards. An overview of the present therapeutic possibilities is given in Table 1.

Table 1. Therapeutic options in hepatic encephalopathy

Agent	Mechanism of action	Comments
Lactulose	NH_3 formation ↓	Standard treatment, although efficacy needs confirmation in state-of-the-art trials
Neomycin	Bacterial load ↓→ NH_3 formation ↓	Despite long-standing use, no dependable and unequivocal data available to support efficacy; routine use possibly needs re-evaluation; bioavailability > zero; auditory loss and renal failure possible; unsuitable for long-term administration
Laxatives	Bowel evacuation ↑→ bacterial load ↓→ NH_3 formation ↓	For acute episodes; more frequently used before introduction of lactulose
Lactitol	Similar to Lactulose	More pleasant taste than lactulose; limited regional availability
Vancomycin, Metronidazol	Like neomycin	Not as a routine medication because of tolerability issues
Zinc	NH_3 formation ↓?	Infrequent use; data equivocal
Rifaximin	Bacterial load ↓→ NH_3 formation ↓	Excellent tolerability due to virtually lacking intestinal absorption
Sodium Benzoate and Sodium Phenylacetate	Enhanced tissue metabolism of NH_3	Sodium benzoate: limited data (one clinical trial showing efficacy); trials with sodium Benzoate and a prodrug of sodium phenylacetate on-going; disadvantage: sodium load
Probiotics	Substrates ↓ for pathogenic, fermentation products ↑ for beneficial bacteria	First studies suggest efficacy, further trials needed
Flumazenil	Antagonism of endogenous benzodiazepines?	Utility not established; efficacy temporary limited, with inter-individual variability
Acarbose	Bacterial flora ↓→ production ↓ of benzo-diazepine-like agents, mercaptanes and NH_3	Effect on NH_3 demonstrated in a trial; not for routine treatment because of the possibility of a fulminant hepatitis (contraindicated in liver cirrhosis)
Branched chain amino acids	Normalization of the proportion of branched-chain compared to aromatic amino acids	No convincing proof of efficacy
Ornithine aspartate	Substrate for urea cycle → NH_3 bioconversion ↑	Potential benefit in mild to moderate HE; more studies needed
Bromocriptine	Dopaminergic transmission may be altered by NH_3?	Still experimental; one small inconclusive trial
L-Carnitine	Serves as a carrier for short-chain fatty acids across the mitochondrial membrane; animal data suggest neuroprotection in ammonia neurotoxicity	Two contradictory clinical studies

For the major part, following Phongsamran et al. (2010); further literature: Al-Sibae and McGuire (2009); Heidelbaugh and Sherbondy (2006); Schiano (2010)

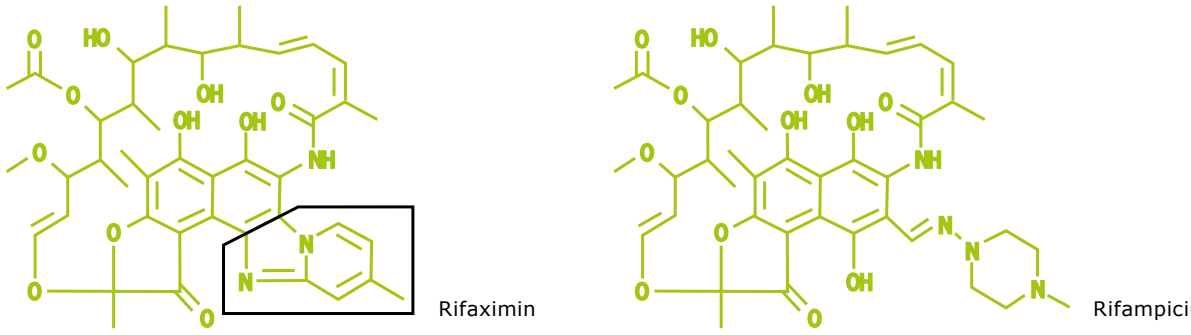

Figure 1. Chemical structure of rifaximin (left) compared with rifampicin (right). The pyrido imidazole group, which inhibits gastrointestinal resorption, is marked by a black frame.

2. Lactulose

2.1. Pharmacodynamics

Lactulose is a disaccharide composed of galactose and fructose. As this molecule resists human intestinal enzymes, it reaches the colon to be cleaved by bacterial enzymes. Instrumental are (not exclusively) lactobacilli and bifidobacteria (Olano and Corzo, 2009), which also benefit from this substrate. Further lactulose degradation generates short-chain fatty acids, lactic and acetic acid, so that lactulose can also perceived as the prodrug of an osmotic laxative. The concurrent acidification converts the colon into an environment hostile to urease-forming bacteria; at the same time, the balance of the large bowel flora is shifted in favour of increasing bifidobacteria and lactobacillus numbers (McFarlane et al., 2006). Another consequence of luminal acidification is protonation of NH_3 to form the ammonia ion (NH_4^+), which is poorly absorbed, and hence more readily excreted with the faeces than NH_3. Also the laxative effect enhances faecal nitrogen excretion (de Preter et al., 2006; Al Sibae und McGuire, 2009; Phongsamran et al., 2010).

Interestingly, the mechanisms of action accepted for lactulose have not been confirmed in all pertinent studies. For example, Beaven et al. (1987) were unable to detect a change in the plasma concentration of NH_3, neither in healthy volunteers nor in patients with liver cirrhosis. Similarly, the acidification of the stool by lactulose may vary considerably or can be entirely lacking and an enhanced faecal elimination of NH_3 or NH_4^+ has not been observed in all studies (Elkington, 1970; Agostini et al., 1972; Bown et al., 1974). Of course, this does not exclude a local acidification, for example in the proximal colon (Naaeder et al., 1998; Bouhnik et al., 2004). After all, the contribution of NH_4^+ formation to an increased excretion of ammonia (the "ammonia trapping") is probably overrated. Actually, the bulk of faecal nitrogen excreted in response to lactulose is found in the bacterial, but hardly in the ammonia fraction (Weber et al., 1997).

On the other hand, favourable effects of lactulose on the systemic NH_3 load are well-documented (Phongsamran et al., 2010; Riggio et al., 2010), so that mechanisms like a modulation of the bacterial flora (Patil et al., 1987) and an inhibition of bacterial ammonia production (Vince und Burridge, 1980) seem to carry the highest importance. Also to appreciate is the cathartic effect of lactulose, by which large amounts of bacteria – including NH_3-generating species – are removed from the colon, as well as limited amounts of ammonia, with the consequence of a reduced absorption (Bongaerts et al., 2005).

2.2. Tolerability

Invariably associated with the bacterial breakdown of lactulose are disorders like nausea, abdominal cramping, bloating, flatulence and diarrhea (Bass, 2007; Schiano, 2010), which are of particular importance for patient compliance (Bass, 2010). This has been quantified in a retrospective chart review. Eligible were outpatients diagnosed with hepatic encephalopathy, who had received lactulose for ≥ six months and were switched to rifaximin upon its availability in the United States. For this treatment, a duration of ≥ six months was also required. Lactulose was associated with the typical side effects and the proportion of patients, who reported taking at least 75 % of prescribed doses, was 92 % during the rifaximin period but only 31 % with lactulose (Leevy and Phillips, 2007).

2.3. Efficacy in Clinical Studies

About 50 years ago, lactulose was introduced into therapy of HE. Meanwhile, its effects have been reported in a large number of clinical studies with, however, rather a limited number of patients in most cases (Phongsamran et al., 2010). This established modality was challenged in 2005 in a metaanalysis, which yielded a modest advantage of lactulose over placebo when all of the 22 evaluated studies were taken into account, but was unable to detect a significant effect on the grade of HE and on

mortality when the analysis was restricted to the two randomised high-quality trials. The authors (Als-Nielsen et al., 2005) summarized that there was insufficient evidence to accept or reject efficacy of lactulose in HE. Antibacterials showed a superior efficacy in this analysis. As a consequence of this situation, it was concluded that lactulose was no suitable comparator in clinical studies: Putative comparable efficacies of a new drug could actually mean that the two study drugs share inefficiency. The high importance of placebo-controlled studies has also been emphasized in a recent consensus document (Bajaj et al., 2011).

Since 2005 special aspects of lactulose efficacy have been investigated in further studies. Favourable effects were reported in secondary prophylaxis after a first episode of HE and on cognition and health-related quality of life (Riggio et al., 2010). Still lacking, however, is evidence appropriate to restitute the previous predominance of lactulose.

2.4. Evaluation

When gauged by the tough criteria of an improvement of the grade of HE and a reduction of mortality, there is insufficient evidence to support the efficacy of long-term treatment of HE with lactulose. Attempts of therapy are justified by the expectation to ameliorate special aspects such as cognition and, in secondary prophylaxis, to prevent further episodes of HE. A serious problem seems to be the less-than-optimal compliance. This has been recognizable in clinical studies and is likely to be more of a problem in general practice.

3. Rifaximin

Rifaximin is a rifamycin congener, which is distinguished from rifampicin the best known member of this class of drugs, by a pyrido imidazole group. By virtue of this group, rifaximin is practically insoluble in water and hence hardly absorbable from the intestine.

3.1. Pharmacodynamics

Rifaximin binds irreversibly to the β-subunit of the prokaryotic DNA-dependent RNA polymerase to block the binding of the enzyme to the DNA and hence the initiation of chain formation in RNA synthesis. The suppression of RNA transcription translates into inhibition of protein synthesis. As rifaximin does not interact with the eukaryotic form of RNA polymerase, mammalian cells remain unaffected. Rifaximin shows bactericidal efficacy. Its broad spectrum of antibacterial activity covers a large number of gram-positive and gram-negative aerobic and anaerobic bacteria, including practically all relevant species of the intestinal microbiota, and hence also the significant urease producers (Scarpignato and Pelosini, 2005; Petersen, 2009).

Aside from its broad antibacterial spectrum, the most intriguing advantage of rifaximin lies in its virtual lack of systemic availability. A maximal plasma concentration of 3.8 ng/ml became measurable after a single oral dose of 400 mg in fasting subjects; after a meal, C_{max} amounted to 9.6 ng/ml (Salix, 2009). As these minute quantities were eliminated with a half life of less than 6 hours, no relevant accumulation on repeated dosing is expected. 80 – 90 % of a dose were recovered in the intestine in animal studies, whereas less than 0.2 % were distributed into liver and kidneys and < 0.01 % into other tissues (Brunton et al., 2006). 97 % of a single oral dose of 400 mg were excreted with the faeces in unchanged form. This strongly suggests that rifaximin does not undergo metabolism during intestinal transit. Only 0.32 % of a dose were found in the urine (Salix, 2009).

3.2. Tolerability

Thanks to its negligible absorption rifaximin shows an excellent tolerability. The most frequent adverse events in the pivotal studies were intestinal disorders like flatulence, abdominal cramps and nausea, complaints, which were best explained by the treated disease and showed a higher incidence in the placebo than in the active drug group (Petersen, 2009).

Table 2. Adverse events possibly related with the study medication during the 6-months maintenance therapy study in patients with hepatic encephalopathy (Bass et al., 2010)

Adverse event	Rifaximin (n = 140)	Placebo (n = 159)
Pneumonia	2.9 %	0.6 %
Bacterial peritonitis	1.4 %	2.5 %
Hematochezia	1.4 %	0.6 %
Gastritis	1.4 %	0
Infection with Clostridium *difficile* Clostridium	1.4 %	0
Gastrointestinal bleeding	0.7 %	1.9 %
Bacteremia	0.7 %	1.3 %
Sepsis	0	1.3 %

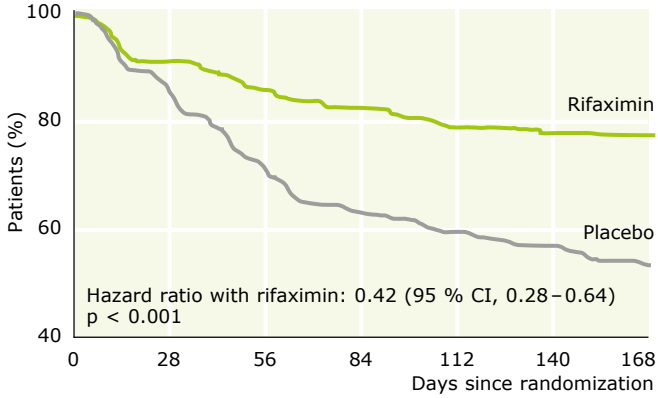

Figure 2. Time to the first breakthrough episode (primary endpoint) of a hepatic encephalopathy during treatment with rifaximin respective placebo (Bass et al., 2010)

3.3. Efficacy in Clinical Studies

The importance of non-absorbable antibacterials for treatment of HE has long been recognized. The available compounds, however, come with their own problems, so that antibiotic treatment is not a first-line choice in maintenance therapy (table 1). Also remarkable, the widely cited option to use neomycin is hardly supported by appropriate clinical studies (Phongsamran et al., 2010).

As opposed to neomycin, the efficacy of rifaximin in HE can be considered proven. Positive study results include a decrease of the plasma concentration of NH_3, an improvement of neurological symptoms, a reduction of the grade of severity of HE, and a lesser risk of being hospitalized for HE. In comparisons with lactulose und neomycin, rifaximin showed equal or better efficacy as well as advantages in tolerability (Lawrence und Klee, 2008; Phongsamran et al., 2010).

Of special importance is a prevention study (Bass et al., 2010), in which patients with a history of at least two episodes of a manifest HE were randomized to receive either placebo or rifaximin over 6 months. More than 90 % of the patients received concomitant therapy with lactulose. A total of 13.6 % of patients in the rifaximin group had to be hospitalized with a diagnosis of HE, which was significantly less than with placebo (22.6 %). 152 of the initial number of 299 patients were included in an extension of this study. Together with a new cohort of 114 patients they received maintenance treatment with rifaximin. Additional lactulose was permitted. First results seem to confirm protective efficacy: A group of 60 patients, who had stayed in remission during the first study period, showed a significant reduction of the breakthrough risk over a period of 680 days (Pordaad et al., 2009, as cited by Phongsamran et al., 2010). Rifaximin has been recently approved for secondary prophylaxis of a manifest HE in the U.S. (Phongsamran et al., 2010).

The impaired ability to execute complex tasks in MHE has recently attracted increased attention. Of particular relevance is a decreased fitness to drive a car. Bajaj et al. (2011) investigated the effect of rifaximin versus placebo on the performance in a driving simulator (driving and orientation), before and after an eight week treatment period. 21 current drivers were included in each group. Significant decreases in the incidence of all driving errors, speeding tickets, and illegal turns were observed in the active drug group, while a complete lack of improvement was found in the placebo group.

3.4. Evaluation

Maintenance therapy of HE with rifaximin is an evident and, on account of its excellent tolerability, reasonable option. It is encouraging to see that rifaximin´s efficacy is sustained over prolonged periods and also covers MHE. Thus, it seems that the possible development of bacterial resistance, which is of no practical relevance to short-time treatment (Petersen 2009), does not limit the success of long-term treatment either. Combinations with other relevant drugs are possible and justifiable, as long as tolerability and – as a direct consequence – compliance are not negatively affected by the combination partner.

4. Polyethylene Glycol

Polyethylene glycols (PEG) (macrogols) are osmotic laxatives. Various PEG-based solutions like PEG 4000 and PEG 3350 are available, the numeral indicating the mean molecular weight. These compounds are used in electrolyte solutions which are composed in a way that they pass the intestine without causing relevant absorption or secretion of fluid and electrolytes. Examples of their utility include bowel cleansing before diagnostic procedures and alleviation of constipation in palliative medicine (Klemens und Klaschik, 2008). In the latter setting, they are preferred over lactulose due to their better tolerability (Klaschik et al., 2003).

4.1. Pharmacodynamics

Polyethylene glycols are osmotic laxatives, which pass the intestine unchanged. They do neither influence local acidity nor the bacterial metabolism (Klaschik et al., 2003). A reduction of the faecal bacterial mass (Bouhnik et al., 2004) could be secondary to the enhanced frequency of bowel evacuation. An important role can be assigned to accelerated intestinal transit (Fritz et al., 2005). As pointed out in a patent on combined treatment with PEG and lactulose, this acceleration shortens the time available for generation of ammonia from the passing food, especially its protein fraction (Halo, 2007). Further information on the efficacy of PEG in HE is awaited from a running clinical trial comparing PEG with Lactulose (NIH, 2011).

4.2. Tolerability

Clinical preparations of PEG 3350 used for bowel cleansing contain the laxative at 100 g. Neither dehydration nor electrolyte shifts are to be expected with this formulation. As PEG does not undergo bacterial degradation, the lack of fermentation explains the absence of gas production (Clemens und Klaschick, 2008). However, reported adverse effects include nausea and vomitus, bloating, and abdominal cramps (Belsey et al., 2007; MHRA, 2006).

When used as a laxative, PEG is considered better tolerable than lactulose. This may be the major reason for its preferential use to mitigate constipation in palliative medicine, for example during opioid maintenance (Clemens und Klaschik, 2008). Even though, in principle, the same side effects are listed as for bowel preparation (MacLeod et al., 2008), there seem to be differences in frequency. In a prospective study, patients with chronic constipation received on average 17.5 g PEG per day over 24 weeks. Reports on epigastric complaints were not more frequent with PEG than with placebo (13/33, 39 % versus 17/37, 46 %). 22/33 (67 %) of the PEG patients complained about nausea, compared to 17/37 (46 %) with placebo. One case of vomitus was reported in each group (Corazziari et al., 2000).

4.3. Efficacy in Clinical Studies

Before the advent of lactulose, laxatives like PEG were customary therapeutic options in HE, especially in acute manifestations (Anonymus, 2010). There is also mention of PEG utility in the differential diagnosis of states of confusion: Disorders related to HE show a positive response to lactulose or PEG (Wolf, 2010). Still today PEG is occasionally used for a fast elimination of nitrogen toxins in acute cases of HE (Roblin et al., 1994; Kiba et al., 2003; Park et al., 2005). However, there are practically no modern clinical studies to confirm the efficacy of PEG in HE.

Over the past few years, possibly also incited by the doubts about the efficacy of lactulose, the previous use of PEG as a modality in HE has met with renewed interest. A point in case is a recent communication on a congress presentation (Anonymus, 2010): Reported is a study presented by A. Gaddis, in which maintenance treatment of HE with a combination of rifaximin with lactulose was replaced by Rifaximin/PEG 3350. All patients had complained of side effects typical for lactulose and requested a change of treatment. The lactulose-related symptoms disappeared under a combined treatment with 400 mg rifaximin, t.i.d., and 17 g PEG, o.d., over 16 – 50 weeks. A sustained efficacy is supported by the absence of HE-based hospitalization.

4.4. Evaluation

The efficacy of polyethylene glycol could be evaluated analogous to lactulose based on osmotic laxation. It is conceivable that a similar dose regime will also allow PEG to act as a well-tolerated modality able to keep HE patients in remission.

It needs to be considered, however, that the expected reduction of the NH_3 load will, beside a possible bacterial washout, to a large part be achieved by a shorter contact time available for fermentation of suitable food ingredients by the intestinal flora. In individual cases the required dose levels might cause tolerability problems. This risk could be lessened by a combination therapy, which might allow lower dosages of PEG (see next section).

5. Combination of PEG and Rifaximin as a Therapeutic Option in HE

Rifaximin acts by eliminating bacterial sources of NH_3 production. In such treatment, sterility of the intestine is neither to be expected nor to be aimed for, and certainly not in maintenance treatment of unlimited duration. As a consequence, there will be a basal production of ammonia by the residual bacterial population, just as lactulose reduces NH_3 generation without abolishing it. A reasonable complement may be offered by PEG, which is capable of reducing intestinal NH_3 production by a different mechanism, predominantly by an acceleration of intestinal transit. Mostly for the sake of enhanced tolerability, it seems possible to reduce the PEG dosage in such a combination compared to PEG monotherapy. On the other hand, a decreased dose level of rifaximin would be hardly an option, as the antibacterial potency requires certain minimal concentrations in the intestinal lumen.

As there are practically no actual clinical studies on the performance of PEG in HE, it would be mandatory getting evidence of PEG efficacy alone and in combination with Rifamimin in further studies.

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