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T A B L E   O F   C O N T E N T S

Medical interventions for prevention and treatment of hepatic encephalopathy in adults with cirrhosis: a network meta-analysis

Peter N Bjerring[1], Marsha Y Morgan[2], Hendrik Vilstrup[3], Sabrina M Nielsen[4], Robin Christensen[5], Lise Lotte Gluud[1]

[1]Gastrounit, Medical Division, Copenhagen University Hospital Hvidovre, Hvidovre, Denmark. [2]UCL Institute for Liver & Digestive Health, Division of Medicine, Royal Free Campus, University College London, London, UK. [3]Department of Hepatology and Gastroenterology, Aarhus University Hospital, Aarhus, Denmark. [4]Musculoskeletal Statistics Unit, The Parker Institute, Bispebjerg and Frederiksberg Hospital, Copenhagen, Denmark. [5]Musculoskeletal Statistics Unit, The Parker Institute, Bispebjerg and Frederiksberg Hospital, Copenhagen, Denmark

Contact address: Lise Lotte Gluud, Gastrounit, Medical Division, Copenhagen University Hospital Hvidovre, Hvidovre, Denmark. liselottegluud@yahoo.dk.

ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the beneficial and harmful effects of medical interventions for prevention and treatment of hepatic encephalopathy in adults with cirrhosis.

BACKGROUND

Description of the condition

The term hepatic encephalopathy refers to the spectrum of neuropsychiatric changes that can occur in people with liver disease. The joint guideline from the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) defines hepatic encephalopathy as "brain dysfunction associated with liver insufficiency and/or portal systemic shunting" (AASLD/EASL 2014; Vilstrup 2014). Clinically apparent or overt hepatic encephalopathy manifests as a neuropsychiatric syndrome encompassing a wide spectrum of mental and motor disorders (Weissenborn 1998; Ferenci 2002). Acute hepatic encephalopathy may develop *de novo* over a period of hours or days in people with cirrhosis who were previously clinically stable. A high proportion of these individuals have a precipitating factor, such as gastrointestinal bleeding or infection (Pantham 2017). Following an acute episode of hepatic encephalopathy, people may return to their baseline neuropsychiatric state or they may retain some degree of clinical, neuropsychometric, or neurophysiological impairment; this is more likely to happen in people with severely decompensated cirrhosis or those with large spontaneous or surgically created portal-systemic shunts (Bajaj 2010). Episodes of acute hepatic encephalopathy may recur. Patients are classified as having recurrent hepatic encephalopathy if they experience two

or more episodes of overt hepatic encephalopathy within a time frame of six months (AASLD/EASL 2014; Vilstrup 2014). Less frequently, people present with persistent neuropsychiatric abnormalities, which are always present to some degree but may vary in seriousness. Often people with persistent abnormalities have extensive spontaneous portal-systemic shunting.

Changes in mental state range from subtle alterations in personality, intellectual capacity, and cognitive function to more profound alterations in consciousness leading to deep coma with decerebrate posturing. The changes in motor function may include rigidity, disorders of speech production, resting- and movement-induced tremor, asterixis, delayed diadochocinetic movements, hyperreflexia, hyporeflexia, choreoathetoid movements, Babinsky's sign, and transient focal symptoms (Weissenborn 1998; Cadranel 2001). Asterixis (flapping tremor) is the best known motor abnormality. Individuals with overt hepatic encephalopathy also show a wide spectrum of other abnormalities, including impaired psychometric performance (Schomerus 1998), disturbed neurophysiological function (Parsons-Smith 1957; Chu 1997), altered cerebral neurochemical/neurotransmitter homeostasis (Taylor-Robinson 1994), reductions in global and regional cerebral blood flow and metabolism (O'Carroll 1991), and changes in cerebral fluid homeostasis (Haussinger 2000). In general, the degree of impairment in these parameters increases as the clinical condition worsens. The term minimal hepatic encephalopathy (in the older literature referred to as subclinical or latent) refers to people with cirrhosis who are 'clinically normal', but who show abnormalities in neuropsychometric or neurophysiological performance (Ferenci 2002).

The diagnosis of hepatic encephalopathy may present no problems. However, it may go unrecognised without sufficient background information and an obvious precipitating event. There is no gold standard for the diagnosis (Montagnese 2004), but there are a number of techniques with diagnostic utility which clinicians and researchers can use singly or in combination. The diagnosis or exclusion of overt hepatic encephalopathy should include a careful and detailed neuropsychiatric history and examination (Montagnese 2004), with particular attention paid to changes in memory, concentration, cognition, and consciousness. Two of the most widely-used scales are the West Haven Criteria, which grades mental state (Conn 1977), and the Glasgow Coma Score, which grades the level of consciousness (Teasdale 1974). The neurological examination should be comprehensive, looking particularly for evidence of subtle motor abnormalities. The assessment should consider, and exclude, other potential causes of neuropsychiatric abnormalities including concomitant neurological disorders and metabolic abnormalities, such as those associated with diabetes, renal failure, and drug or alcohol intoxication. People with hepatic encephalopathy have impaired psychometric performance (Montagnese 2004; Randolph 2009). Those with minimal hepatic encephalopathy show deficits in attention, visuo-spatial abilities, fine motor skills, and memory while their other cognitive functions are relatively well-preserved. People with overt hep-

atic encephalopathy show additional disturbances in psychomotor speed, executive function, and concentration. Psychometric test batteries to assess cognitive function form part of the evaluation. The Psychometric Hepatic Encephalopathy Score (PHES) has a high specificity for the diagnosis (Schomerus 1998; Weissenborn 2001). This test battery comprises of five paper and pencil tests which assess attention, visual perception, and visuo-constructive abilities. Test scores have to be normalised to take account of factors such as age, sex, and educational level. Normative databases are currently available in Germany, Italy, Denmark, Spain, Mexico, Korea, India, Portugal, Poland, and the UK.

Hepatic encephalopathy is associated with a number of neurophysiological abnormalities (Guérit 2009). The electroencephalogram, which primarily reflects cortical neuronal activity, may show progressive slowing of the background activity and abnormal wave morphology (Parsons-Smith 1957). Recent advances in electroencephalogram analysis should provide better quantifiable and more informative data (Jackson 2016; Olesen 2016). The brain responses, or evoked potentials, to stimuli such as light and sounds may show abnormal slowing or wave forms, or both (Chu 1997; Guérit 2009). Other potential diagnostic techniques, such as the Critical Flicker Fusion Frequency (Kircheis 2002) and the Inhibitory Control Test (Bajaj 2008), still need further validation. Blood ammonia concentrations are not routinely measured to diagnose hepatic encephalopathy (Lockwood 2004; Blanco Vela 2011b), but are often monitored in clinical trials.

Description of the intervention

Nonabsorbable disaccharides

The recommended standard of care for people with hepatic encephalopathy includes use of the nonabsorbable disaccharides lactulose and lactitol - poorly absorbed sugars - that are also used as osmotic laxatives (Johanson 2007; AASLD/EASL 2014; Miller 2014; Vilstrup 2014). The drugs are usually administered enterally (orally or via an enteral tube), but rectal administration is also possible. The main adverse events associated with their use are diarrhoea, bloating, and flatulence (Gluud 2016a; Gluud 2016b).

Antibiotics

Rifaximin is an orally administered, non-absorbable, semi-synthetic antibiotic with a broad-spectrum of effect on both Gram-positive and Gram-negative bacteria. Common adverse events include nausea, flatulence, and diarrhoea (Kimer 2014a; Kimer 2014b). Other potentially effective antibiotics include aminoglycosides (such as neomycin and paromomycin), vancomycin, and metronidazole. Aminoglycosides are normally poorly absorbed from the gastrointestinal tract after oral administration, but absorption may increase in cirrhosis as the permeability of the gut

increases; use of aminoglycosides may be associated with the development of ototoxicity or nephrotoxicity (Patidar 2014). Metronidazole is normally well-absorbed from the gastrointestinal tract and can cause neurotoxicity in people with cirrhosis, especially if drug clearance is impaired (Roy 2016; Goolsby 2018). Vancomycin is also poorly absorbed from the gastrointestinal tract after oral administration; its use is associated with both ototoxicity and nephrotoxicity, and the development of vancomycin-resistant enterococci (Chiang 2017; Flokas 2017).

L-ornithine L-aspartate and other agents that specifically targeting ammonia

Ammonia scavengers, including L-ornithine L-aspartate, are agents that reduce blood ammonia concentration (Rose 1998; Rose 1999; Blanco Vela 2011a; Rahimi 2016; De Las Heras 2017) (Table 1). L-ornithine L-aspartate is the best known and most extensively investigated (Goh 2018); it is a stable salt of the amino acids ornithine and aspartic acid and can be administered both orally and intravenously (Rose 1998; Blanco Vela 2011a). Other agents used in people with hepatic encephalopathy that specifically target ammonia include: sodium benzoate; sodium phenylacetate; glycerol phenylbutyrate; ornithine phenylacetate, which is a combination of L-ornithine and phenylacetate; AST-120 (Spherical Carbon Adsorbent); and polyethylene glycol (Sushma 1992; Efrati 2000; Jalan 2007; Bosoi 2011; Misel 2013; Ventura-Cots 2013; Rahimi 2014; Wu 2014; Ventura-Cots 2016). The adverse events associated with the use of these drugs are mainly gastrointestinal and include diarrhoea, constipation, dry mouth, and changes in appetite (Lee 2010; Rahimi 2016).

Branched-chain amino acids

The branched-chain amino acids leucine, isoleucine, and valine are essential amino acids (Holeček 2013; Gluud 2017a); they compete with the aromatic amino acids phenylalanine, tyrosine, and tryptophan for passage across the blood-brain barrier. Plasma concentrations of these amino acids are low in patients with cirrhosis; supplements containing branched chain amino acids can be given enterally (orally or via a nasogastric tube) or intravenously. The composition of these supplements varies, but there is general agreement that leucine is the most important constituent (Morgan 1990). The use of branched chain amino acids is associated with nausea and diarrhoea (Gluud 2017a).

Probiotics

Probiotics are live micro-organisms that may confer health benefits (Schrezenmeir 2001; Dalal 2017); they are given enterally, usually orally. Probiotics generally include two groups of bacteria (*Lactobacillus* and *Bifidobacterium*) or yeasts (e.g. *Saccharomyces boulardii*) (Szajewska 2015a; Szajewska 2015b; Dalal 2017). Different species may be included within each group of bacteria (e.g.

Lactobacillus acidophilus and *Bifidobacterium bifidus*) and different strains within each species. Therapeutic effects may be strain-specific; caution must be exercised in generalising results from one species to another. While probiotics are considered safe, adverse events are reported; these include systemic infections and deleterious metabolic effects (Doron 2015; Dalal 2017).

Dopaminergic agents

Agents that increase dopaminergic neurotransmission include stimulants as well as dopamine agonists (Junker 2014; Szmulewicz 2017). The dopaminergic agonists increase dopamine activity by blocking the $\alpha2$ postsynaptic receptor or inhibiting the dopamine transporter (Minzenberg 2008). The dopaminergic agents assessed in the management of people with hepatic encephalopathy include levodopa (Vij 1979; Koshy 1982), and bromocriptine (Uribe 1979; Morgan 1980); both are administered orally.

Flumazenil

Flumazenil is a benzodiazepine antagonist that is administered intravenously (Goh 2017). The drug competitively inhibits the activity at the benzodiazepine recognition site on the gamma aminobutyric acid (GABA)-A receptor complex, but it lacks major intrinsic pharmacological or behavioural activity (Whitwam 1995). Flumazenil has a relatively high hepatic extraction ratio (Amrein 1990). In people with severe liver disease, clearance is decreased to about 25%, resulting in a prolongation of the half-life from 50 minutes to 2.4 hours in people with severe hepatic dysfunction (Amrein 1990). Randomised clinical trials evaluating flumazenil for people with hepatic encephalopathy found few adverse events (Goh 2017). Those registered included gastrointestinal complaints (nausea and vomiting), as well as non-specific symptoms (flushing, irritability, palpitations, and drowsiness).

Other interventions

Other interventions that have been assessed for the prevention and treatment of hepatic encephalopathy include zinc (Chavez-Tapia 2013; Katayama 2014; Mousa 2016), and naloxone (Jiang 2010). The use of these interventions is not widespread.

How the intervention might work

Ammonia plays a key role in the pathogenesis of hepatic encephalopathy (Butterworth 2014). The basic principle underlying most treatments currently used in the management of this condition is to reduce circulating concentrations of ammonia by interfering with its production or by accelerating its removal. The main sources of ammonia in the body are nitrogenous products in the diet, bacterial metabolism of urea, proteins in the colon, and the deamination of glutamine in the small intestine. The ammonia

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produced in the gut is absorbed into the portal vein and, together with the ammonia derived from hepatic amino acid metabolism, is taken up by periportal hepatocytes and metabolised to urea via the urea cycle. Some ammonia is taken up by perivenous hepatocytes where it is converted to glutamine via glutamine synthetase. These two systems, working in concert, tightly control blood ammonia concentrations in the hepatic veins. The kidney and muscle also play a role in ammonia homeostasis (Wright 2011). In skeletal muscle, ammonia is transformed into glutamine through the action of glutamine synthetase. In the kidneys, ammonia is generated from the deamination of glutamine.

In people with cirrhosis, this system for detoxifying ammonia can fail; first, because of a deterioration in hepatocyte function, and second, because the presence of portal systemic collateral vessels allows blood to bypass the liver. As a result, the liver does not effectively clear gut-derived ammonia from the blood; consequently, the ammonia enters the systemic circulation and impinges on the brain where it has both direct and indirect effects on cerebral function. In the brain, ammonia is detoxified in astrocytes, resulting in an increase in the synthesis of glutamine. This, in turn, results in a number of cellular events that result in astrocyte swelling, low-grade oedema, and eventually brain dysfunction (Haussinger 2000). Other proposed effects of ammonia in the brain include blood-brain barrier dysfunction, altered inhibitory and excitatory neurotransmission, and altered cerebral energy metabolism (Butterworth 2013; Butterworth 2014; Butterworth 2017).

Non-absorbable disaccharides lower ammonia levels through a number of mechanisms (Gluud 2016a): (i) a laxative effect: the colonic metabolism of lactulose and lactitol results in an increase in intraluminal gas formation, an increase in intraluminal osmolality, a reduction in intraluminal pH, and an overall decrease in transit time; (ii) bacterial uptake of ammonia: the intraluminal changes in pH result in a leaching of ammonia from the circulation into the colon. The colonic bacteria use the released volatile fatty acids as substrate and proliferate. In doing so, they use the trapped colonic ammonia as a nitrogen source for protein synthesis. The increase in bacterial numbers additionally 'bulks' the stool and contributes to the cathartic effect; (iii) reduction of intestinal ammonia production: non-absorbable disaccharides inhibit glutaminase activity and interfere with the intestinal uptake of glutamine and its subsequent metabolism to ammonia; (iv) beneficial effects on the gut microbiome: cirrhosis is associated with dysbiosis and changes in the colonic mucosal microbiome (Qin 2014)

Antibiotics lower ammonia levels by eliminating urease-producing gut bacteria and correcting for small intestinal bacterial overgrowth, which is frequently observed in people with cirrhosis (Yang 1998; Bauer 2001; Gunnarsdottir 2003; Pande 2009). Aminoglycosides are bactericidal antibiotics, which inhibit bacterial protein synthesis (Borovinskaya 2007). Metronidazole is also bactericidal and inhibits bacterial DNA synthesis (Löfmark 2010). Aminoglycosides are particularly active against Gram-negative aerobes (Magnet 2005), while metronidazole is active against both

Gram-positive and Gram-negative anaerobes (Löfmark 2010). The aminoglycoside neomycin is also a glutaminase inhibitor (Hawkins 1994). In addition to their ammonia-lowering effects, antibiotics may protect against hepatic encephalopathy by reducing the production of other bacteria-derived neurotoxins, such as phenols and mercaptans, and by reducing gut bacteria translocation into the bloodstream.

L-ornithine L-aspartate promotes hepatic removal of ammonia primarily by stimulating residual hepatic urea cycle activity and promoting glutamine synthesis, particularly in skeletal muscle (Rose 1999). It also enhances the activities of ornithine and aspartate transaminases in peripheral tissues to promote the production of glutamate, which predominantly occurs in muscle (Gebhardt 1997; Rose 1998; Blanco Vela 2011a; Blanco Vela 2011b). The other ammonia scavengers have various modes of action (Table 1). Lowering ammonia, by use of these interventions, might benefit people with hepatic encephalopathy.

Branched-chain amino acids have a beneficial effect on hepatic encephalopathy by promoting ammonia detoxification, correcting the plasma amino acid imbalance, and reducing the brain influx of aromatic amino acids. However, the effects of BCAA are complex, and several other potentially beneficial actions have been identified (Gluud 2017a; Holeček 2017).

Probiotics modulate the gut microbiome which plays an important role in the production of ammonia; their use could reduce ammonia production in the gut (Vij 1979; Victor 2014; Tilg 2016; Viramontes Hörner 2017). They may also reduce bacterial translocation to lessen endotoxaemia and systemic inflammation, both of which have been implicated in the development of hepatic encephalopathy.

Dopaminergic agents and flumazenil aim to correct known deficits in cerebral neurotransmission. Dopaminergic neurotransmission is impaired in patients with hepatic encephalopathy and the dopaminergic agent L-dopa and bromocriptine are used in an attempt to reverse this effect. Likewise, GABAergic tone is increased in patients with hepatic encephalopathy and flumazenil, which is a selective benzodiazepine-receptor antagonist, is used to offset this effect (Junker 2014).

Why it is important to do this review

Hepatic encephalopathy should be treated. A variety of options are available, but not all are suitable or appropriate for every patient. The nonabsorbables disaccharides lactulose and lactitol are the treatment of choice for the treatment and prevention of overt hepatic encephalopathy. Rifaximin is also used, preferably in conjunction with a non-absorbable disaccharide, for the prevention of recurrent hepatic encephalopathy. The use of other interventions for the treatment of overt hepatic encephalopathy is debated (AASLD/EASL 2014; Vilstrup 2014). There is still disagreement as to whether minimal hepatic encephalopathy should be routinely treated or whether only selected patients should be exposed to

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treatment (AASLD/EASL 2014; Vilstrup 2014). We, therefore, plan to undertake a network meta-analysis (NMA) in order to evaluate the effects of medical interventions for overt and minimal hepatic encephalopathy as well as for primary and secondary prevention.

OBJECTIVES

To assess the beneficial and harmful effects of medical interventions for prevention and treatment of hepatic encephalopathy in adults with cirrhosis.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised clinical trials, regardless of their publication status, language, or blinding, in our primary analyses. If we identify observational studies (i.e. quasi-randomised studies; cohort studies; or patient reports) that report adverse events caused by or associated with the interventions listed in our review, we will include these studies in the assessment of adverse events. We will not specifically search for observational studies for inclusion in this review, which is recognised as a limitation.

Types of participants

We will include trial participants with cirrhosis who have minimal or overt hepatic encephalopathy or who are at risk for developing hepatic encephalopathy. We will include all participants regardless of sex, age, aetiology, and severity of the underlying liver disease. We will exclude people with hepatic encephalopathy associated with acute liver failure or non-cirrhotic portal hypertension. We will also exclude children and adolescents below 18 years of age.

Types of interventions

We will include all medical Interventions delivered as monotherapies or in combination, and we will classify combinations of interventions as combination rather than including the individual components separately.
We will allow co-interventions if administered equally to the allocation groups. Accordingly, we will include trials in which all participants received co-interventions (e.g. diets or vitamins) in the same dose.

Types of outcome measures

We will assess all outcomes at the maximum duration of follow-up.

Primary outcomes

- All-cause mortality.
- Hepatic encephalopathy. We will assess this outcome using the primary investigators' overall assessments of: i) the number of participants without a clinically-relevant improvement in hepatic encephalopathy; or ii) the number of participants who developed hepatic encephalopathy; or both (i) and (ii).
- The number of participants who developed one or more serious adverse events. We will define serious adverse events as any untoward medical occurrence that led to death, was life-threatening, or required hospitalisation or prolongation of hospitalisation, or resulted in persistent or significant disability. We will analyse serious adverse events as the proportion of participants with one or more serious adverse events and as the number of serious adverse events per patient (Cochrane Hepato-Biliary Group Module).

Search methods for identification of studies

Electronic searches

We will search the Cochrane Hepato-Biliary Group Controlled Trials Register, Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, MEDLINE Ovid, Embase Ovid, LILACS, Science Citation Index Expanded (Web of Science), and Conference Proceedings Citation Index - Science (Web of Science) (Royle 2003). Appendix 1 gives the preliminary search strategies with the expected time spans of the searches.
We will attempt to search Chinese and Japanese databases should they become available to us via the Cochrane Hepato-Biliary Group.

Searching other resources

We will scan the reference lists of relevant articles identified in the electronic searches, and the proceedings of meetings of the British Society for Gastroenterology (BSG), the British Association for the Study of the Liver (BASL), the European Association for the Study of the Liver (EASL), the United European Gastroenterology Week (UEGW), the American Gastroenterological Association (AGA), the American Association for the Study of Liver Diseases (AASLD), and the International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN). We will contact the principal authors of trials and the pharmaceutical companies involved in the manufacture and marketing of the interventions assessed for additional information about both completed and ongoing trials.

We will also search the online trial registries ClinicalTrial.gov (clinicaltrials.gov/); the European Medicines Agency (EMA) (www.ema.europa.eu/ema/); the World Health Organization International Clinical Trial Registry Platform (www.who.int/ictrp); Google Scholar; the Food and Drug Administration (FDA) (www.fda.gov), and pharmaceutical company sources for ongoing or unpublished trials. We will develop the search strategy in collaboration with the Cochrane Hepato-Biliary Group editorial team.

Data collection and analysis

Selection of studies

Two review authors will independently screen the results of the electronic searches, perform additional manual searches, and list potentially eligible trials. One review author (Peter Bjerring) will liaise with the authors and pharmaceutical sponsors of identified unpublished trials to seek unpublished information. Two review authors will assess the full-texts of potentially eligible trials for inclusion. For trials described in more than one publication, we will select the paper with the longest duration of follow-up (as long as it still respects the original design) as our primary reference. We will list details of all the included studies in a 'Characteristics of the included trials' table. We will list all excluded trials, with their reason for exclusion, in a 'Characteristics of excluded studies' table. We will resolve any disagreement on trial suitability for inclusion or exclusion through discussion.

Data extraction and management

All review authors will participate in the data extraction process, and at least two review authors will independently evaluate each randomised clinical trial. We will request missing data and other missing information from the published trial reports through correspondence with the authors of the included trials. We will also seek information and data from unpublished trials by correspondence with trial authors and sponsors.

We will use a pre-piloted electronic data collection form, created in Microsoft Excel. The collected data will include information on the following.

• Trials: design (cross-over or parallel), settings (number of clinical sites; outpatient or inpatient; inclusion period), country of origin, inclusion period, and publication status.

• Participants: mean age, proportion of men, aetiology of cirrhosis, type of hepatic encephalopathy (diagnostic criteria and definitions/terminology), and previous history of hepatic encephalopathy.

• Interventions: type, dose, duration of therapy, and mode of administration.

• Outcomes: diagnostic criteria and definitions used in the assessment of hepatic encephalopathy.

Assessment of risk of bias in included studies

We will assess bias control using the domains described in the Cochrane Hepato-Biliary Group Module, and will classify the risk of bias for separate domains as either high, unclear, or low (Higgins 2011). We will also include an overall assessment of bias control for both mortality ands non-mortality outcomes.

Allocation sequence generation

• Low risk of bias: sequence generation achieved using computer random number generation or a random number table. Drawing lots, tossing a coin, shuffling cards, or throwing dice are adequate if performed by an independent person but not otherwise.

• Unclear risk of bias: not described.

• High risk of bias: the sequence generation method was not random.

Allocation concealment

• Low risk of bias: allocation by a central and independent randomisation unit, administration of coded, identical drug containers/vials or sequentially-numbered, opaque, sealed envelopes.

• Unclear risk of bias: not described.

• High risk of bias: the allocation sequence was likely to be known to the investigators who assigned the participants.

Blinding of participants and personnel

• Low risk of bias: blinding of participants and personnel using placebo, double dummy or similar. We will define lack of blinding as not likely to affect the assessment of mortality.

• Unclear risk of bias: not described.

• High risk of bias: no blinding or incomplete blinding, and the assessment of outcomes are likely to be influenced by lack of blinding (non-mortality outcomes).

Blinding of outcome assessors

• Low risk of bias: blinding of the outcome assessor using a placebo, double dummy or similar. We defined lack of blinding as not likely to affect the assessment of mortality.

• Unclear risk of bias: there was insufficient information.

• High risk of bias: no blinding or incomplete blinding, and the assessment of outcomes were likely to be influenced by lack of blinding (non-mortality outcomes).

Incomplete outcome data

• Low risk of bias: missing data are unlikely to make intervention effects depart from plausible values and sufficient

methods (e.g. multiple imputations) are used to handle missing data.

  • Unclear risk of bias: insufficient information.
  • High risk of bias: the results are likely to be biased due to missing data.

Selective outcome reporting

  • Low risk of bias: the trial reports clinically-relevant outcomes (mortality, hepatic encephalopathy, and serious adverse events). If we have access to the original trial protocol, the outcomes selected should be those described in the protocol. If we obtain information from a trial registry (such as www.clinicaltrials.gov), we will only use that information if the investigators registered the trial before inclusion of the first participant.
  • Unclear risk of bias: not all predefined outcomes are reported fully, or it is unclear whether data on these outcomes were recorded or not.
  • High risk of bias: one or more predefined outcomes are not reported.

For-profit bias

  • Low risk of bias: the trial appeared to be free of industry sponsorship, or other type of for-profit support that could influence the design, conduct, or results (Lundh 2017).
  • Unclear risk of bias: insufficient information about support or sponsorship.
  • High risk of bias: the trial received funding or other support from a pharmaceutical company including the provision of trial drugs (Lundh 2017).

Other bias

  • Low risk of bias: the trial appears to be free of other biases including: medicinal dosing problems or follow-up (as defined below).
  • Unclear risk of bias: the trial may or may not be free of other factors that could put it at risk of bias.
  • High risk of bias: there are other factors in the trial that could put it at risk of bias such as the administration of inappropriate treatments to the controls (e.g. an inappropriate dose) or follow-up (e.g. the trial included different follow-up schedules for participants in the allocation groups).

Overall bias assessment

  • Low risk of bias: all domains are low risk of bias using the definitions described above.
  • High risk of bias: one or more of the bias domains are of unclear or high risk of bias.

Measures of treatment effect

We will communicate our findings via risk ratios (RR) with 95% confidence intervals (CI) in the pair-wise (contrast-based, 'traditional') meta-analysis and 95% credible intervals (95% CrI) in the NMA.

Unit of analysis issues

We will include randomised clinical trials using a parallel group design and data from the first treatment period of cross-over trials. In the pair-wise meta-analysis, we will include separate pair-wise comparisons from multi-arm trials. Accordingly, if a trial compares L-ornithine L-aspartate, rifaximin, and lactulose, we will conduct separate analyses for the three comparisons.

Dealing with missing data

We will extract data on all randomised participants in order to allow intention-to-treat analyses. We plan to undertake analyses, using simple imputation (Higgins 2008), to evaluate the potential influence of missing outcome data, including 'worst-case' scenario analyses in which we will classify participants in the intervention arm with missing outcome data as failures whilst we will classify their counterparts in the control arm as successes (Cochrane Hepato-Biliary Group Module).

Assessment of heterogeneity

In the pair-wise meta-analysis, we will evaluate heterogeneity based on visual inspection of forest plots and express heterogeneity as I^2 values using the following thresholds: 0% to 40% (unimportant), 40% to 60% (moderate), 60% to 80% (substantial), and > 80% (considerable). We will include the information in 'Summary of findings' tables.
For heterogeneity in the NMA, please see the description below.

Assessment of reporting biases

We will compare outcomes reported in protocols with published trial reports. In addition, for pair-wise meta-analyses with at least 10 randomised clinical trials, we will assess reporting biases and other small study effects based on visual inspection of funnel plots and Harbord's test (Harbord 2006).

Data synthesis

As recommended by Puhan 2014, we plan to undertake pair-wise meta-analyses as well as network meta-analyses in order to provide information about the quality of evidence from the direct pairwise comparisons, indirect comparisons, and NMA.

Direct comparisons of intervention effects in pair-wise meta-analyses

Since we expect some clinical heterogeneity between trials because of likely differences in the definitions of hepatic encephalopathy and the duration of the interventions assessed, we believe that the assumption of a single fixed intervention effect across included trials is unlikely to be valid. Our primary analyses will, therefore, employ random-effects models per default. Since pooled effect estimates from random-effects models give relatively more weight to smaller studies, we will perform sensitivity analyses using fixed-effect meta-analysis models as described below.

We will perform pair-wise meta-analysis using a random-effects model for every 'intervention versus comparison contrast' with at least two trials.

Network meta-analyses

We will use the NMA as an extension of standard meta-analysis to compare multiple interventions based on randomised clinical trial evidence forming a connected network of comparisons (Lu 2004; Caldwell 2005; Ortega 2014; Salanti 2014); we plan to perform the network meta-analyses using the Bayesian method. Initially we will generate a graphical network plot to illustrate which interventions (and comparators) have been compared directly in the eligible trials, independent of selective outcome reporting. The network plot will represent the number of trials in each node and link in the diagram. Treatment effect estimates from NMA exploit both the direct comparisons within trials and the indirect comparisons across trials. We will use placebo or no intervention as the reference, combining the two, and present the comparison between different interventions in league tables.

As described above, we expect some clinical heterogeneity between trials; therefore, we plan to use random-effects per default for the network meta-analyses too. We will derive posterior estimates for Bayesian methods using Gibbs sampling via Markov Chain Monte Carlo (MCMC) simulation. We will give all means a vague prior distribution (normal distribution with mean 0 and sufficiently large variance). We will assess the statistical heterogeneity in the NMA based on the magnitude of the between-studies standard deviation (Tau). We will assume a common Tau value across all comparisons and a vague uniform (0,2) prior distribution. As a measure that reflects ranking and the uncertainty, we will use the Surface Under the Cumulative RAnking (SUCRA) curve (Salanti 2011), in order to show the relative probability of an intervention being among the best options.

Model convergence

We will assess convergence of Markov chains and define convergence as achieved when plots of the Gelman-Rubin statistics indicate that widths of pooled runs and individual runs stabilise around the same value and their ratio is around one (Brooks 1988).

Transitivity for network meta-analysis

We assess patient and study characteristics across the studies that compare pairs of treatments. Potential effect modifiers could include such traits as average patient age, sex distribution, disease severity, and a wide range of other biologically plausible features. In order to provide estimates that we are confident with, we will assess whether the distribution of effect modifiers is similar, for example, across studies of A versus B and A versus C. Balance between these will increase the plausibility of reliable findings from the indirect comparison of B versus C through the common comparator A; i.e. if this balance is present, we will judge the assumption of transitivity to hold. We will present systematic (tabulated) information regarding patient and study characteristics whenever available.

Assessment of inconsistency

We will assess statistical consistency based on both a loop-specific and a global approach. We will mainly assess consistency by the comparison of the conventional NMA model, for which consistency is assumed (e.g. fixed-effect), with a model that does not assume consistency (e.g. random-effects; a series of pair wise meta-analyses analysed jointly). Moreover, as also recommended by the GRADE Working Group, we will calculate the difference between direct and indirect evidence in all closed loops in the network; inconsistent loops were identified with a significant (95% CrI that excludes 0) disagreement between direct and indirect evidence. We define a loop of evidence as a collection of studies that links treatments to allow for indirect comparisons; the simplest loop is a triangle formed by three direct comparison studies with shared comparators.

Comparison adjusted funnel plots

We will compare adjusted funnel plots to account for the fact that trials may estimate effects for different comparisons. Initially, we plan to order interventions based on the year they were introduced, assuming that newer interventions are more likely to be assessed (and 'favoured', i.e. the overall results suggest a benefit to participants). In the 'comparison-adjusted' funnel plot, the horizontal axis presents the difference between the trial-specific intervention effect sizes from the corresponding comparison-specific summary effect.

Rating the certainty in the effect estimates

We will base rating the quality of treatment effect estimates from NMA on estimates from direct, indirect, and NMA (combined direct and indirect) evidence, as well as quality ratings for the direct and indirect comparisons. We will apply the following four steps to assess the quality of treatment effect estimates from NMA.

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- Present direct and indirect treatment estimates for each comparison of the evidence network. The direct estimate of effect is provided by a head-to-head comparison (e.g. trials of A versus B), and the indirect estimate is provided by two or more head-to-head comparisons that share a common comparator (for example, we infer the effects of A versus B from trials of A versus C and trials of B versus C) (Bucher 1997).
  - Rate the quality of each direct and indirect effect estimate.
  - Present the NMA estimate for each comparison of the evidence network.
  - Rate the quality of each NMA effect estimate.

Subgroup analysis and investigation of heterogeneity

We plan to evaluate intervention effects in the following types of trials.
- Trials classified as at high risk compared to trials at low risk of bias.
- Trials evaluating participants with different types of hepatic encephalopathy (overt, minimal, or prevention).

Sensitivity analysis

We plan to undertake sensitivity analyses, including the following.
- Fixed-effect model meta-analyses: we will only report these analyses if the overall result of the fixed-effect and the random-effects meta-analyses differ.
- 'Worst-case' and 'best-case' scenario analyses as described in the Dealing with missing data section.

Presentation of results

We will follow the PRISMA for Network Meta-Analyses while reporting (Hutton 2015), and will present effect estimates with 95% CrI for each pairwise comparison calculated from the direct comparisons and NMA as well as the cumulative probability of the treatment ranks in graphs (SUCRA, as described above). We will plot the probability that each intervention was best, second best,

third best, etc. for each outcome in rankograms with the CrI of the probabilities in the ranking probability tables. We plan to include an appendix with the raw data and the codes used for analysis.

Quality of the evidence

We will include 'Summary of findings' tables for all outcomes. The 'Summary of findings' table will include the effect estimates with 95% CrI and an assessment of the quality of direct and indirect effect estimates taking into account the risk of bias, inconsistency, directness of evidence, imprecision, and publication bias. The table will include proportion of participants with each outcome (in each intervention group) based on the direct estimates, indirect estimates, and NMA estimates as well as the number of trials and participants.

Recommendations for future research

We will include recommendations for future research based on the findings of our Cochrane Review.

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* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1. Modes of action of the pharmacotherapeutic agents that specifically target ammonia

Ammonia scavenger	Mechanism of action
Sodium benzoate[a]	Conjugates with glycine to form hippurate, which is then eliminated in the urine. The glycine used in the hippurate synthesis is rapidly replenished from the endogenous pool of ammonia
Sodium phenylacetate[a]	Conjugates with glutamine to form phenylacetylglutamine (PAG) in the liver and kidneys, which is then eliminated in the urine. As glutamine is incorporated into PAG, more is synthesized by amidation of glutamic acid by ammonia through glutamine synthetase
Glycerol phenylbutyrate	Prodrug of sodium phenylbutyrate. Conjugates with glutamine to form PAG in the liver and kidneys, which is then eliminated in the urine. As glutamine is incorporated into PAG, more is synthesized by amidation of glutamic acid by ammonia through glutamine synthetase
Ornithine phenylacetate (OCR-002)	Reduces ammonia through two pathways: i) L-ornithine acts as a substrate for the synthesis of glutamine from ammonia in skeletal muscle, and ii) phenylacetate and glutamine combines to form phenylacetylglutamine, which is excreted in the urine
Spherical carbon microsphere adsorbent (AST-120)	Differs structurally from activated charcoal and exhibits superior adsorptive capacity of certain organic compounds (i.e. low molecular weight < 10 kDa) from the lumen of the lower gastrointestinal tract. It binds ammonia in the gut and facilitates its excretion
Polyethylene glycol (PEG)	A cathartic which causes rapid clearance of ammonia-synthesising gut bacterial from the gut lumen

Abbreviations: PAG: phenylacetylglutamine
[a] Include relatively high amounts of sodium

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A P P E N D I C E S

Appendix 1. Search strategies

Database	Date of search	Search strategy
The Cochrane Hepato-Biliary Group Controlled Trials Register	Date will be provided at the review stage	((disaccharid* or lactulos* or lactitol*) or (rifaximin* or xifaxan* or rifagut* Rcifax*) or (aminoglycoside* or neomycin or neo-fradin or neo-tab or mycifradin or myciguent or paromomycin or humatin) or (metronidazol* or elyzol or flagyl* or rozex or zidoval or metro* or protostat or noritate) or ((ornithin* and aspart*) or (LOLA or aksohep or analiv or biohep or hepamerz or hepalon or hepawin or livogard or livotop or longliv or lornit or orniliv or trisoliv or enervin or hepalex or hepatone or levijon or merzepa or ornamin or ornivit)) or (branched chain) or (((benzodiazepine receptor or GABA) and (antagonist* or blocking agent*)) or flumaze*il) or (dopa* or levodopa or bromocriptine) or (probiotic* or lactobacillus* or Bifidobacteri*) or (vanomycin or zink or naloxone)) and (encephalopath* or liver disease* or cirrho*)
Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library	Latest issue	#1 MeSH descriptor: [Disaccharides] explode all trees #2 MeSH descriptor: [Lactulose] explode all trees #3 (disaccharid* or lactulos* or lactitol*) #4 #1 or #2 or #3 #5 (rifaximin* or xifaxan* or rifagut* Rcifax*) #6 MeSH descriptor: [Aminoglycosides] explode all trees #7 (aminoglycoside* or neomycin or neofradin or neo-tab or mycifradin or myciguent or paromomycin or humatin) #8 #6 or #7 #9 MeSH descriptor: [Metronidazole] explode all trees #10 (metronidazol* or elyzol or flagyl* or rozex or zidoval or metro* or protostat or noritate) #11 #9 or #10 #12 MeSH descriptor: [Ornithine] explode

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(Continued)

		all trees #13 ornithin* #14 #12 or #13 #15 MeSH descriptor: [Aspartic Acid] explode all trees #16 aspart* #17 #15 or #16 #18 (#14 and #17) or (LOLA or aksohep or analiv or biohep or hepa-merz or hepalon or hepawin or livogard or livotop or longliv or lornit or orniliv or trisoliv or enervin or hepalex or hepatone or levijon or merzepa or ornamin or ornivit) #19 MeSH descriptor: [Amino Acids, Branched-Chain] explode all trees #20 branched chain #21 #19 or #20 #22 MeSH descriptor: [GABA Antagonists] explode all trees #23 MeSH descriptor: [Flumazenil] explode all trees #24 (((benzodiazepine receptor or GABA) and (antagonist* or blocking agent*)) or flumaze*il) #25 #22 or #23 or #24 #26 MeSH descriptor: [Dopamine Agents] explode all trees #27 MeSH descriptor: [Dopa Decarboxylase] explode all trees #28 MeSH descriptor: [Levodopa] explode all trees #29 MeSH descriptor: [Bromocriptine] explode all trees #30 (dopa* or levodopa or bromocriptine) #31 #26 or #27 #28 or #29 or #30 #32 MeSH descriptor: [Probiotics] explode all trees #33 MeSH descriptor: [Lactobacillus] explode all trees #34 MeSH descriptor: [Bifidobacterium] explode all trees #35 probiotic* or lactobacillus* or Bifidobacteri* #36 #32 or #33 or #34 or #35 #37 vanomycin or zink or naloxone #38 #4 or #5 or #8 or #11 or #18 or #21 or #25 or #31 or #36 or #37 #39 MeSH descriptor: [Hepatic En-

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(Continued)

		cephalopathy] explode all trees #40 MeSH descriptor: [Liver Diseases] explode all trees #41 MeSH descriptor: [Fibrosis] explode all trees #42 (encephalopath* or liver disease* or cirrho*) #43 #39 or #40 or #41 or #42 #44 #38 and #43
MEDLINE Ovid	1946 to the date of the search	1. exp DISACCHARIDES/ 2. exp LACTULOSE/ 3. (disaccharid* or lactulos* or lactitol*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 4. 1 or 2 or 3 5. (rifaximin* or xifaxan* or rifagut* Rcifax*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 6. exp AMINOGLYCOSIDES/ 7. (aminoglycoside* or neomycin or neofradin or neo-tab or mycifradin or myciguent or paromomycin or humatin).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 8. 6 or 7 9. exp METRONIDAZOLE/ 10. (metronidazol* or elyzol or flagyl* or rozex or zidoval or metro* or protostat or noritate).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 11. 9 or 10

(Continued)

12. exp ORNITHINE/
13. ornithin*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
14. 12 or 13
15. exp Aspartic Acid/
16. aspart*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
17. 15 or 16
18. (14 and 17) or (LOLA or aksohep or analiv or biohep or hepa-merz or hepalon or hepawin or livogard or livotop or longliv or lornit or orniliv or trisoliv or enervin or hepalex or hepatone or levijon or merzepa or ornamin or ornivit).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
19. exp Amino Acids, Branched-Chain/
20. branched chain.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
21. 19 or 20
22. exp GABA Antagonists/
23. exp FLUMAZENIL/
24. (((benzodiazepine receptor or GABA) and (antagonist* or blocking agent*)) or flumaze*il).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplemen-

tary concept word, unique identifier, synonyms]

25. 22 or 23 or 24

26. exp Dopamine Agents/

27. exp Dopa Decarboxylase/

28. exp LEVODOPA/

29. exp BROMOCRIPTINE/

30. (dopa* or levodopa or bromocriptine).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

31. 26 or 27 or 28 or 29 or 30

32. exp PROBIOTICS/

33. exp LACTOBACILLUS/

34. exp BIFIDOBACTERIUM/

35. (probiotic* or lactobacillus* or Bifidobacteri*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

36. 32 or 33 or 34 or 35

37. (vanomycin or zink or naloxone).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

38. 4 or 5 or 8 or 11 or 18 or 21 or 25 or 31 or 36 or 37

39. exp Hepatic Encephalopathy/

40. exp Liver Diseases/

41. exp FIBROSIS/

42. (encephalopath* or liver disease* or cirrho*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

43. 39 or 40 or 41 or 42

44. 38 and 43

(Continued)

		45. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 46. 44 and 45
Embase Ovid	1974 to the date of search	1. exp disaccharide/ 2. exp lactulose/ 3. (disaccharid* or lactulos* or lactitol*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] 4. 1 or 2 or 3 5. exp rifaximin/ 6. (rifaximin* or xifaxan* or rifagut* Rcifax*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] 7. 5 or 6 8. exp aminoglycoside/ 9. (aminoglycoside* or neomycin or neofradin or neo-tab or mycifradin or myciguent or paromomycin or humatin).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] 10. 8 or 9 11. exp metronidazole/ 12. (metronidazol* or elyzol or flagyl* or rozex or zidoval or metro* or protostat or noritate).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] 13. 11 or 12 14. exp ornithine/ 15. ornithin*.mp. [mp=title, abstract, heading word, drug trade name, original title, de-

		vice manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] 16. 14 or 15 17. exp aspartic acid/ 18. aspart*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] 19. 17 or 18 20. (16 and 19) or (LOLA or aksohep or analiv or biohep or hepa-merz or hepalon or hepawin or livogard or livotop or longliv or lornit or orniliv or trisoliv or enervin or hepalex or hepatone or levijon or merzepa or ornamin or ornivit).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] 21. exp branched chain amino acid/ 22. branched chain.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] 23. 21 or 22 24. exp 4 aminobutyric acid receptor blocking agent/ 25. exp flumazenil/ 26. (((benzodiazepine receptor or GABA) and (antagonist* or blocking agent*)) or flumaze*il).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] 27. 24 or 25 or 26 28. exp dopamine receptor stimulating agent/ 29. exp aromatic levo amino acid decarboxylase/ 30. exp levodopa/ 31. exp bromocriptine/ 32. (dopa* or levodopa or bromocriptine).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufac-

		turer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
		33. 28 or 29 or 30 or 31 or 32
		34. exp probiotic agent/
		35. exp Lactobacillus/
		36. exp Bifidobacterium/
		37. (probiotic* or lactobacillus* or Bifidobacteri*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
		38. 34 or 35 or 36 or 37
		39. (vanomycin or zink or naloxone).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
		40. 4 or 7 or 10 or 13 or 20 or 23 or 27 or 33 or 38 or 39
		41. exp hepatic encephalopathy/
		42. exp liver disease/
		43. exp fibrosis/
		44. (encephalopath* or liver disease* or cirrho*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
		45. 41 or 42 or 43 or 44
		46. 40 and 45
		47. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
		48. 46 and 47
LILACS (Bireme)	1982 to the date of search	(disaccharid$ or lactulos$ or lactitol$) or (rifaximin$ or xifaxan$ or rifagut$ Rcifax$) or (aminoglycoside$ or neomycin or neofradin or neo-tab or mycifradin or myciguent or paromomycin or humatin) or (metronidazol$ or elyzol or flagyl$ or rozex or zidoval or metro$ or protostat or noritate) or ((ornithin$ and aspart$) or (LOLA

		or aksohep or analiv or biohep or hepa-merz or hepalon or hepawin or livogard or livotop or longliv or lornit or orniliv or trisoliv or enervin or hepalex or hepa-tone or levijon or merzepa or ornamin or ornivit)) or (branched chain) or (((benzo-diazepine receptor or GABA) and (antag-onist$ or blocking agent$)) or flumaze$il) or (dopa$ or levodopa or bromocriptine) or (probiotic$ or lactobacillus$ or Bifidobac-teri$) or (vanomycin or zink or naloxone) [Words] and (encephalopath$ or liver dis-ease$ or cirrho$) [Words]
Science Citation Index EXPANDED	1900 to the date of search	#15 #14 AND #13 #14 TS=(random* or blind* or placebo* or meta-analys*) #13 #12 AND #11 #12 TS=(encephalopath* or liver disease* or cirrho*) #11 #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1 #10 TS=(vanomycin or zink or naloxone) #9 TS=(probiotic* or lactobacillus* or Bifidobacteri*) #8 TS=(dopa* or levodopa or bromocriptine) #7 TS=(((benzodiazepine receptor or GABA) and (antagonist* or blocking agent*)) or flumaze*il) #6 TS=(branched chain) #5 TS=((ornithin* and aspart*) or (LOLA or aksohep or analiv or biohep or hepa-merz or hepalon or hepawin or livogard or livotop or longliv or lornit or orniliv or trisoliv or enervin or hepalex or hepatone or levijon or merzepa or ornamin or ornivit)) #4 TS=(metronidazol* or elyzol or flagyl* or rozex or zidoval or metro* or protostat or noritate) #3 TS=(aminoglycoside* or neomycin or neo-fradin or neo-tab or mycifradin or myciguent or paromomycin or humatin) #2 TS=(rifaximin* or xifaxan* or rifagut* Rcifax*) #1 TS=(disaccharid* or lactulos* or lactitol*)
Conference Proceedings Citation Index - Science (Web of Science)	1990 to the date of the search	#15 #14 AND #13 #14 TS=(random* or blind* or placebo* or

(Continued)

| | | meta-analys*)
 #13 #12 AND #11
 #12 TS=(encephalopath* or liver disease* or cirrho*)
 #11 #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
 #10 TS=(vanomycin or zink or naloxone)
 #9 TS=(probiotic* or lactobacillus* or Bifidobacteri*)
 #8 TS=(dopa* or levodopa or bromocriptine)
 #7 TS=(((benzodiazepine receptor or GABA) and (antagonist* or blocking agent*)) or flumaze*il)
 #6 TS=(branched chain)
 #5 TS=((ornithin* and aspart*) or (LOLA or aksohep or analiv or biohep or hepa-merz or hepalon or hepawin or livogard or livotop or longliv or lornit or orniliv or trisoliv or enervin or hepalex or hepatone or levijon or merzepa or ornamin or ornivit))
 #4 TS=(metronidazol* or elyzol or flagyl* or rozex or zidoval or metro* or protostat or noritate)
 #3 TS=(aminoglycoside* or neomycin or neo-fradin or neo-tab or mycifradin or myciguent or paromomycin or humatin)
 #2 TS=(rifaximin* or xifaxan* or rifagut* Rcifax*)
 #1 TS=(disaccharid* or lactulos* or lactitol*) |

CONTRIBUTIONS OF AUTHORS

PNB: participated in the critical revision of the protocol.

MYM: participated in the critical revision of the protocol.

HV: participated in the critical revision of the protocol.

SMN: participated in the critical revision of the protocol.

RC: participated in the critical revision of the protocol.

LLG: wrote the first protocol draft.

All protocol authors accepted the final version.

DECLARATIONS OF INTEREST

PNB: none

MYM: none

HV: none

SMN: none

RC: none

LLG: (i) investigator in trials (Norgine, Abbvie, Merck Intercept); (ii) speaker (Norgine, Eli Lilly, Alexion, VingMed); (iii) travel expenses, advisory board, and investigator (Novo Nordisk).

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External sources

- None, Other.

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