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Dalal R, McGee RG, Riordan SM, Webster AC

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[Intervention Review]

Probiotics for people with hepatic encephalopathy

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ABSTRACT

Background

Hepatic encephalopathy is a disorder of brain function as a result of liver failure or portosystemic shunt or both. Both hepatic encephalopathy (clinically overt) and minimal hepatic encephalopathy (not clinically overt) significantly impair patient's quality of life and daily functioning, and represent a significant burden on healthcare resources. Probiotics are live micro-organisms, which when administered in adequate amounts, may confer a health benefit on the host.

Objectives

To determine the beneficial and harmful effects of probiotics in any dosage, compared with placebo or no intervention, or with any other treatment for people with any grade of acute or chronic hepatic encephalopathy. This review did not consider the primary prophylaxis of hepatic encephalopathy.

Search methods

We searched The Cochrane Hepato-Biliary Group Controlled Trials Register, CENTRAL, MEDLINE, Embase, Science Citation Index Expanded, conference proceedings, reference lists of included trials, and the World Health Organization International Clinical Trials Registry Platform until June 2016.

Selection criteria

We included randomised clinical trials that compared probiotics in any dosage with placebo or no intervention, or with any other treatment in people with hepatic encephalopathy.

Data collection and analysis

We used standard methodological procedures expected by The Cochrane Collaboration. We conducted random-effects model meta-analysis due to obvious heterogeneity of participants and interventions. We defined a P value of 0.05 or less as significant. We expressed dichotomous outcomes as risk ratio (RR) and continuous outcomes as mean difference (MD) with 95% confidence intervals (CI).

Main results

We included 21 trials with 1420 participants, of these, 14 were new trials. Fourteen trials compared a probiotic with placebo or no treatment, and seven trials compared a probiotic with lactulose. The trials used a variety of probiotics; the most commonly used group of probiotic was VSL#3, a proprietary name for a group of eight probiotics. Duration of administration ranged from 10 days to 180 days. Eight trials declared their funding source, of which six were independently funded and two were industry funded. The remaining 13 trials did not disclose their funding source. We classified 19 of the 21 trials at high risk of bias.

We found no effect on all-cause mortality when probiotics were compared with placebo or no treatment (7 trials; 404 participants; RR 0.58, 95% CI 0.23 to 1.44; low-quality evidence). No-recovery (as measured by incomplete resolution of symptoms) was lower for participants treated with probiotic (10 trials; 574 participants; RR 0.67, 95% CI 0.56 to 0.79; moderate-quality evidence). Adverse events were lower for participants treated with probiotic than with no intervention when considering the development of overt hepatic encephalopathy (10 trials; 585 participants; RR 0.29, 95% CI 0.16 to 0.51; low-quality evidence), but effects on hospitalisation and change of/or withdrawal from treatment were uncertain (hospitalisation: 3 trials, 163 participants; RR 0.67, 95% CI 0.11 to 4.00; very low-quality evidence; change of/or withdrawal from treatment: 9 trials, 551 participants; RR 0.70, 95% CI 0.46 to 1.07; very low-quality evidence). Probiotics may slightly improve quality of life compared with no intervention (3 trials; 115 participants; results not meta-analysed; low-quality evidence). Plasma ammonia concentration was lower for participants treated with probiotic (10 trials; 705 participants; MD -8.29 µmol/L, 95% CI -13.17 to -3.41; low-quality evidence). There were no reports of septicaemia attributable to probiotic in any trial.

When probiotics were compared with lactulose, the effects on all-cause mortality were uncertain (2 trials; 200 participants; RR 5.00, 95% CI 0.25 to 102.00; very low-quality evidence); lack of recovery (7 trials; 430 participants; RR 1.01, 95% CI 0.85 to 1.21; very low-quality evidence); adverse events considering the development of overt hepatic encephalopathy (6 trials; 420 participants; RR 1.17, 95% CI 0.63 to 2.17; very low-quality evidence); hospitalisation (1 trial; 80 participants; RR 0.33, 95% CI 0.04 to 3.07; very low-quality evidence); intolerance leading to discontinuation (3 trials; 220 participants; RR 0.35, 95% CI 0.08 to 1.43; very low-quality evidence); change of/or withdrawal from treatment (7 trials; 490 participants; RR 1.27, 95% CI 0.88 to 1.82; very low-quality evidence); quality of life (results not meta-analysed; 1 trial; 69 participants); and plasma ammonia concentration overall (6 trials; 325 participants; MD -2.93 µmol/L, 95% CI -9.36 to 3.50; very low-quality evidence). There were no reports of septicaemia attributable to probiotic in any trial.

Authors' conclusions

The majority of included trials suffered from a high risk of systematic error (‘bias’) and a high risk of random error (‘play of chance’). Accordingly, we consider the evidence to be of low quality. Compared with placebo or no intervention, probiotics probably improve recovery and may lead to improvements in the development of overt hepatic encephalopathy, quality of life, and plasma ammonia concentrations, but probiotics may lead to little or no difference in mortality. Whether probiotics are better than lactulose for hepatic encephalopathy is uncertain because the quality of the available evidence is very low. High-quality randomised clinical trials with standardised outcome collection and data reporting are needed to further clarify the true efficacy of probiotics.

PLAIN LANGUAGE SUMMARY

Probiotics for people with hepatic encephalopathy

Why the review is important

Hepatic encephalopathy is a disorder of brain function as a result of liver failure or portosystemic shunt or both. Both hepatic encephalopathy (clinically overt) and minimal hepatic encephalopathy (not clinically overt) significantly impair patient’s quality of life and daily functioning and represent a significant burden on healthcare resources. Probiotics are live micro-organisms, which when administered in adequate amounts may confer a health benefit on the host. We searched and summarised randomised trials about the benefits and harms of any probiotic in any dosage, compared with placebo or no intervention, or with any other treatment for people with any grade of acute or chronic hepatic encephalopathy.

Main findings

The evidence is current to June 2016. Of the 21 included trials including 1420 participants, 14 trials compared a probiotic with placebo or no treatment and seven trials compared a probiotic with lactulose. The treatment duration of the trials ranged from 10 days to 180 days.

Compared with placebo or no intervention, probiotics probably improve recovery and may lead to improvements in the development of overt hepatic encephalopathy, quality of life, and plasma ammonia concentrations, but may lead to little or no difference in mortality. Probiotics may slightly improve quality of life when compared with no intervention; however, this conclusion is based on three trials with low-quality evidence. Whether probiotics are better than lactulose for hepatic encephalopathy is uncertain because the quality of the available evidence was very low. There were no reports of septicaemia attributable to probiotic in any trial. There was no evidence of more adverse events with probiotics when compared to placebo or lactulose.

Funding

Eight trials declared their funding source, of which six were independently funded and two were industry funded. The remaining 13 trials did not disclose their funding source.

Limitations of the review

Many of the included trials suffered from a high risk of systematic error (‘bias’) and a high risk of random error (‘play of chance’). Accordingly, we consider the evidence to be of low quality.

Conclusions

Compared with placebo or no intervention, probiotics probably improve recovery and may lead to improvements in the development of overt hepatic encephalopathy, quality of life, and plasma ammonia concentrations, but probiotics may lead to little or no difference in mortality. Whether probiotics are better than lactulose for hepatic encephalopathy is uncertain because the quality of the available

evidence was very low. High-quality randomised clinical trials with standardised outcome collection and data reporting are needed to further clarify the true efficacy of probiotics.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Probiotic for people with hepatic encephalopathy

Probiotic versus placebo or no intervention for people with hepatic encephalopathy

Patient or population: people with hepatic encephalopathy
Setting: inpatients
Intervention: probiotic
Comparison: placebo/no intervention

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo/no intervention	Risk with probiotic				
All-cause mortality (follow-up: 2 weeks to 3 months)	Study population		RR 0.58 (0.23 to 1.44)	404 (7 RCTs)	⊕⊕⊖⊖ LOW [1,2]	
	51 per 1000	30 per 1000 (12 to 73)				
	Moderate					
	25 per 1000	14 per 1000 (6 to 36)				
No-recovery (incomplete resolution of clinical symptoms) (follow-up: 1 month to 3 months)	Study population		RR 0.67 (0.56 to 0.79)	574 (10 RCTs)	⊕⊕⊕⊖ MODERATE [2]	
	790 per 1000	529 per 1000 (442 to 624)				
	Moderate					
	877 per 1000	588 per 1000 (491 to 693)				
Adverse events - Overt hepatic encephalopathy (follow-up: 2 weeks to 3 months)	Study population		RR 0.29 (0.16 to 0.51)	585 (10 RCTs)	⊕⊕⊖⊖ LOW [1,2]	
	168 per 1000	49 per 1000 (27 to 86)				
	Moderate					
	169 per 1000	49 per 1000				

		(27 to 86)			
Adverse events - Change of/or withdrawal from treatment (follow-up: 1 month to 3 months)	Study population		RR 0.70 (0.46 to 1.07)	551 (9 RCTs)	⊕⊖⊖⊖ VERY LOW [1,2,3]
	204 per 1000	143 per 1000 (94 to 219)			
	Moderate				
	158 per 1000	111 per 1000 (73 to 169)			
Quality of life (follow-up: 1 month to 3 months)	—	—	—	115 (3 RCTs)	⊕⊕⊖⊖ LOW [1,2]
Plasma ammonia concentration (final and change scores) (µmol/L) (follow-up: 1 month to 6 months)	—	The mean plasma ammonia concentration (final and change scores) (µmol/L) in the intervention group was 8.29 fewer (13.17 fewer to 3.41 fewer).	—	705 (10 RCTs)	⊕⊕⊖⊖ LOW [2,3]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; **RCT:** randomised clinical trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[1]Downgraded one level for serious concerns or two levels for very serious concerns of imprecision (based on few events and wide confidence intervals).
[2]Downgraded one level for serious concerns or two levels for very serious concerns of trials judged as at high risk of bias (most studies at high risk of bias).
[3]Downgraded one level for serious concerns or two levels for very serious concerns of inconsistency of the outcomes in effects.

Summary of findings 2. Probiotics for people with hepatic encephalopathy

Probiotic versus lactulose for people with hepatic encephalopathy

Patient or population: people with hepatic encephalopathy

Setting: inpatients
Intervention: probiotic
Comparison: lactulose

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with lactulose	Risk with probiotic				
All-cause mortality (follow-up: 1 month to 2 months)	Study population		RR 5.00 (0.25 to 102.00)	200 (2 RCTs)	⊕⊖⊖⊖ VERY LOW [1,2]	
	0 per 1000	0 per 1000 (0 to 0)				
No-recovery (incomplete resolution of clinical symptoms) (follow-up: 1 month to 3 months)	Study population		RR 1.01 (0.85 to 1.21)	430 (7 RCTs)	⊕⊖⊖⊖ VERY LOW [2,3,4]	
	521 per 1000	526 per 1000 (443 to 630)				
	Moderate					
	500 per 1000	505 per 1000 (425 to 605)				
Adverse events - Overt hepatic encephalopathy (follow-up: 1 to 3 months)	Study population		RR 1.17 (0.63 to 2.17)	420 (6 RCTs)	⊕⊖⊖⊖ VERY LOW [2,3,4]	
	81 per 1000	95 per 1000 (51 to 177)				
	Moderate					
	60 per 1000	70 per 1000 (38 to 129)				
Adverse events - Change of/or withdrawal from treatment (follow-up: 1 month to 3 months)	Study population		RR 1.27 (0.88 to 1.82)	490 (7 RCTs)	⊕⊖⊖⊖ VERY LOW [,2,3,4]	
	160 per 1000	203 per 1000 (141 to 291)				
	Moderate					
	114 per 1000	145 per 1000 (101 to 208)				
Quality of life	It is uncertain whether probiotics improve quality of life because the available evidence is of very low quality.		—	69 (1 RCT)	⊕⊖⊖⊖	

(follow-up: 1 month to 3 months)					VERY LOW [1,2]
Plasma ammonia concentration (final and change scores) (µmol/L) (follow-up: 1 month to 3 months)	—	The mean plasma ammonia concentration (final and change scores) (µmol/L) in the intervention group was 2.93 fewer (9.36 fewer to 3.5 more).	—	325 (6 RCTs)	⊕⊖⊖⊖ VERY LOW [2,3,4]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; **RCT:** randomised clinical trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[1]Downgraded one for serious concerns or two levels for very serious concerns of imprecision (small samples, very few events, and wide confidence intervals).
[2]Downgraded one level for serious concerns or two levels for very serious concerns of trials judged as at high risk of bias (majority of studies at high risk of bias).
[3]Downgraded one level for serious imprecision (95% CI includes null effects).
[4]Downgraded one level for serious concerns or two levels for very serious concerns of inconsistency in results.

BACKGROUND

Description of the condition

Hepatic encephalopathy (also known as portosystemic encephalopathy) is a reversible neuropsychiatric disorder seen in the context of either acute or chronic liver failure or portosystemic shunting, or both (Ferenci 2002). Hepatic encephalopathy is characterised by complex cognitive dysfunction, which is independent of sleep dysfunction or problems with overall intelligence (Blei 2001). Minimal hepatic encephalopathy is a milder form of the same condition, which does not have obvious clinical signs (Stewart 2007; Bajaj 2011). The onset of hepatic encephalopathy indicates a poor prognostic outcome. It may also reduce quality of life and level of daily functioning (Groeneweg 1998; Arguedas 2003). The pathophysiology of hepatic encephalopathy is still uncertain, but the prevailing assumption is that different toxins, such as false neurotransmitters, natural benzodiazepines, short-chain fatty acids, and mercaptans enhance the negative effects of ammonia on the level of consciousness (Butterworth 1987; Blei 2001; Vaquero 2003). Current therapeutic options include intensive supportive care, identification and correction of the precipitating causes, tailored dietary restrictions, non-absorbable disaccharides, L-ornithine L-aspartate, and/or oral antibiotics (Riordan 1997; Blei 2001; Als-Nielsen 2003; Als-Nielsen 2004a; Als-Nielsen 2004b; Als-Nielsen 2004c; Jiang 2009).

Description of the intervention

Probiotics are live micro-organisms, which when administered in adequate amounts may confer a health benefit on the host (Schrezenmeir 2001). However, the dose needed to confer a health benefit is unknown for many conditions. Probiotics commonly come from two groups of bacteria, *Lactobacillus* or *Bifidobacterium*. Within each group, there are different species (e.g. *Lactobacillus acidophilus* and *Bifidobacterium bifidus*), and within each species, different strains (or varieties). A few common probiotics, such as *Saccharomyces boulardii*, are yeasts, which are different from bacteria. Therapeutic effects may be strain specific, and so caution must be exerted in generalising results from one species to another. While probiotics are generally considered safe, adverse events have been attributed to their use (Besselink 2008).

How the intervention might work

There is some evidence for an alteration in the composition of the gastrointestinal bacterial flora of people with liver disease (Rolfe 2000). Modulation of the gut microbiota is an important aspect of current therapy; the current conventional treatment option of the broad-spectrum antibiotic rifaxamin is minimally absorbed and targets gram-negative and gram-positive enteric bacteria. Similarly, in addition to the osmotic effect of lactulose, which encourages removal of toxic metabolic products such as ammonia, it is also known to have a bifidogenic effect (De Preter 2006; Bass 2010). Amongst other potential reasons, one rationale behind the use of probiotics for hepatic encephalopathy is to reduce the prevalence of harmful ammonia-producing bacteria in the gastrointestinal system. Probiotics are thought to reduce blood ammonia levels by several mechanisms including decreasing bacterial urease activity, decreasing ammonia absorption by decreasing pH, decreasing intestinal permeability, and improving nutritional status of gut epithelium (Poh 2012).

Why it is important to do this review

Hepatic encephalopathy significantly impairs patient's quality of life and daily functioning, job performance, and overall mortality (Groeneweg 1998; Arguedas 2003; Stinton 2013). Caring for and treating patients with hepatic encephalopathy is a significant burden on the healthcare system. In 2005, hepatic encephalopathy cost the US healthcare system an estimated USD 4676.7 million, increasing to USD 7244.7 million in 2009 (Stepanova 2012). Previous Cochrane Hepato-Biliary Group systematic reviews have only shown moderate, and in some cases no benefit for current or proposed therapies for hepatic encephalopathy, which include non-absorbable disaccharides, oral antibiotics, branched-chain amino acids, and dopamine (Als-Nielsen 2003; Als-Nielsen 2004a; Als-Nielsen 2004b; Als-Nielsen 2004c; Junker 2014; Gluud 2015). Based on a preliminary analysis, it is estimated that the literature on probiotics in hepatic encephalopathy has doubled since this systematic review was last published in 2011, hence this update will improve the evidence base on the use of probiotics in hepatic encephalopathy.

OBJECTIVES

To determine the beneficial and harmful effects of probiotics in any dosage, compared with placebo or no intervention or with any other treatment for people with any grade of acute or chronic hepatic encephalopathy. This review did not consider the primary prophylaxis of hepatic encephalopathy.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised trials that compared probiotics with placebo or no intervention, or with any other treatment for people with hepatic encephalopathy. We applied no restrictions on language of publication, publication date, or publication status. We excluded quasi-randomised trials.

Types of participants

Inclusion criteria

We included all people with any grade of acute or chronic hepatic encephalopathy in connection with acute and chronic liver disease as well as acute hepatic failure, no matter the aetiology of liver disease or factors precipitating the hepatic encephalopathy.

Exclusion criteria

We excluded trials with participants in whom a diagnosis of hepatic encephalopathy was not confirmed, that is where altered mental status or cognitive function was not confirmed by a standardised neuropsychological assessment. Where co-interventions such as medication were being administered, they had to be administered equally across the relevant intervention groups of the trial so that fair comparisons could be made.

Types of interventions

Any probiotic at any dose for any duration. Additional co-interventions were allowed if received by all trial intervention groups and deemed sufficiently similar across trial groups. Where synbiotics were used (a combination of a prebiotic and a probiotic;

a prebiotic is a substance that stimulates the growth of probiotics), the control group must have received a similar prebiotic to be included in the review, such that across trial groups the difference in intervention(s) was probiotic alone. For example, where probiotic and lactulose were compared to antibiotic plus lactulose, the comparison would have been probiotics versus antibiotic. If a trial compared probiotics and prebiotics versus prebiotics, the trial would have been considered a probiotic versus placebo trial, as the difference between the two groups would have been probiotic alone.

Types of outcome measures

We assessed all outcomes at time points reported by the authors, but, where possible, also summarised at one, two, three, six months, and one year.

Primary outcomes

1. All-cause mortality: number of participants dead.
2. Number of participants who did not recover from hepatic encephalopathy (defined as incomplete resolution of clinical symptoms). We considered an individual to be 'completely resolved' if he or she was not in a state of hepatic encephalopathy based on the trial's definition of hepatic encephalopathy used in the inclusion process.
3. Adverse events: number and type of adverse events, defined as participants with any untoward medical occurrence. We summarised adverse events that led to treatment discontinuation and those that did not lead to treatment discontinuation separately. We defined serious adverse events according to the International Conference on Harmonisation (ICH) guidelines (ICH-GCP 1997), as any event that led to death, was life-threatening, required inpatient hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability, and any important medical event that may have jeopardised the patient or required intervention to prevent it. We considered all other adverse events as non-serious.
4. Quality of life: as measured by the 36-Item Short Form Health Survey (SF-36) or other similar validated scales, such as the Sickness Impact Profile (SIP) (Brazier 1992; Ware 1994).

Secondary outcomes

1. Change of or withdrawal from treatment: number of participants who changed/withdrew from their allocated treatment regimen.
2. Sepsis: number of participants with one or more episodes of sepsis (confirmed by a positive blood culture).
3. Change in plasma ammonia concentration.
4. Duration of stay in hospital: measured in days.

Search methods for identification of studies

Electronic searches

For this update, we searched The Cochrane Hepato-Biliary Group Controlled Trials Register (Gluud 2016), The Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, MEDLINE Ovid, Embase Ovid, and Science Citation Index Expanded (Web of Science) (Royle 2003) all on the 14th of June 2016. The search strategies with the time spans of the searches are given in Appendix 1. The search filter for randomised trials in MEDLINE (OvidSP) was created by Lefebvre 2011, and the search filter for randomised trials in Embase (OvidSP) was created by Sharon 2006.

We also searched the World Health Organization International Clinical Trial Registry Platform (WHO ICTRP) (www.who.int/ictrp) for ongoing and unpublished trials up to June 2016 using an advanced search for the condition 'hepatic encephalopathy' and intervention 'probiotic', and using an advanced search for the condition 'hepatic encephalopathy'. As a quality check, we searched the ClinicalTrials.gov database (clinicaltrials.gov/ct2/home) in September 2016, even though ClinicalTrials.gov is included as one of the registers within the WHO ICTRP portal.

Searching other resources

We handsearched the proceedings of three relevant conferences:

1. American Association for the Study of Liver Disease (AASLD) from 2005 to 2014;
2. European Association for the Study of the Liver (EASL) from 2005 to 2014;
3. Digestive Diseases Week (DDW) from 2005 to 2014, using the keywords 'hepatic encephalopathy', 'probiotic', 'bifidobacterium', 'lactobacillus', and 'liver disease'.

We identified further trials through reference lists of relevant articles and by contacting content experts and authors of included trials. We applied no date or language restrictions. We translated non-English language articles using Google Translate (translate.google.com.au/). Mandarin translations were provided by Sunny Wu.

Data collection and analysis

Selection of studies

Working independently, three review authors conducted trial selection and data extraction. None of the review authors was blinded to journal or author names. Disagreements were resolved by consensus.

Data extraction and management

We extracted the following information using a standardised data extraction form.

- General information: author(s), title, source, contact address, year of trial, country of trial, language of publication, year of publication.
- Trial characteristics: design (randomised clinical trial), randomisation method, manner of recruitment, sampling method, duration of intervention period, length of follow-up, reason for and number of dropouts and withdrawals, adverse events.
- Participants: baseline characteristics of participants in treatment groups such as sex, age, prevalence of comorbidities (e.g. diabetes), inclusion and exclusion trial criteria.
- Trial setting: e.g. inpatient/outpatient department, emergency department.
- Detailed description of both the intervention and the comparison intervention, type, dose, and duration of probiotic(s).
- Outcomes: specific outcome reported, assessment instrument used, scoring range where appropriate.

- Any co-interventions.

We entered data into Review Manager 5 software and checked the data for accuracy (RevMan 2011).

Assessment of risk of bias in included studies

We followed the instructions given in the *Cochrane Handbook for Systematic Reviews of Intervention* (Higgins 2011) and the Cochrane Hepato-Biliary Group Module (Gluud 2016). Methodological quality was defined as the confidence that the design and the report of the randomised clinical trial would restrict bias in the comparison of the treatment groups (Moher 1998). According to empirical evidence (Schulz 1995; Moher 1998; Kjaergard 2001; Wood 2008; Lundh 2012; Savović 2012; Savović 2012a), we assessed the risk of bias of the trials using the following 'Risk of bias' domains.

Sequence generation

- Low risk of bias: the method used was either adequate (e.g. computer-generated random numbers, table of random numbers) or unlikely to introduce bias.
- Unclear risk of bias: there was insufficient information to assess whether the method used was likely to introduce confounding.
- High risk of bias: the method used was not best practise for randomisation.

Allocation concealment

- Low risk of bias: the method used (e.g. central allocation) was unlikely to induce bias on the final observed effect.
- Unclear risk of bias: there was insufficient information to assess whether the method used was likely to induce bias on the estimate of effect.
- High risk of bias: the method used (e.g. open random allocation schedule) was likely to induce bias on the final observed effect.

Blinding of participants

- Low risk of bias: blinding was performed adequately, or the outcome was not likely to be influenced by lack of blinding.
- Unclear risk of bias: there was insufficient information to assess whether the type of blinding used was likely to induce bias on the effect.
- High risk of bias: no blinding or incomplete blinding, and the outcome was likely to be influenced by lack of blinding.

Blinding of personnel

- Low risk of bias: blinding was performed adequately, or the outcome was not likely to be influenced by lack of blinding.
- Unclear risk of bias: there was insufficient information to assess whether the type of blinding used was likely to induce bias on the effect.
- High risk of bias: no blinding or incomplete blinding, and the outcome was likely to be influenced by lack of blinding.

Blinding of outcome assessors

- Low risk of bias: blinding was performed adequately, or the outcome measurement was not likely to be influenced by lack of blinding.
- Unclear risk of bias: there was insufficient information to assess whether the type of blinding used was likely to induce bias on the estimate of effect.
- High risk of bias: no blinding or incomplete blinding, and the outcome measurement was likely to be influenced by lack of blinding.

Incomplete outcome data

- Low risk of bias: the underlying reasons for missing data were unlikely to cause treatment effects to depart from plausible values, or appropriate methods were employed to handle missing data.
- Unclear risk of bias: there was insufficient information to assess whether the missing-data mechanism in combination with the method used to handle missing data was likely to induce bias on the estimate of effect.
- High risk of bias: the crude estimate of effects (e.g. complete-case estimate) was clearly biased due to the underlying reasons for missing data, and the methods used to handle missing data were unsatisfactory.

Selective outcome reporting

- Low risk of bias: the trial protocol was available, or the study author provided further information about prespecified outcomes and all of the trial's prespecified outcomes that were of interest in the review were reported or similar.
- Unclear risk of bias: there was insufficient information to assess whether the magnitude and direction of the observed effect were related to selective outcome reporting.
- High risk of bias: not all of the trial's prespecified primary outcomes were reported or similar.

Other bias

- Low risk of bias: the trial was independently funded, e.g. by a government organisation or university.
- Unclear risk of bias: the trial did not declare its funding source.
- High risk of bias: the trial was industry funded, e.g. by a pharmaceutical company, or an author was an employee of a pharmaceutical company.

We considered trials judged as being at low risk of bias in all of the specified individual domains as trials at low risk of bias. We considered trials judged as being at unclear risk of bias or high risk of bias in one or more of the specified individual domains as trials at high risk of bias. We contacted authors of the original reports to provide further details when any of the above information was unclear.

Measures of treatment effect

We conducted data analysis according to the guidelines presented in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and the Cochrane Hepato-Biliary Group Module (Gluud 2016).

For dichotomous data, we presented results as summary risk ratio (RR) with 95% confidence intervals (CI). For continuous data, we presented results as mean difference (MD) if outcomes were measured in the same way amongst trials.

Dealing with missing data

Data for all participants were analysed in the group to which they are allocated, regardless of whether or not they received the allocated intervention. If in the original reports participants were not analysed in the group to which they were randomised and there was sufficient information in the trial report, we attempted to restore these participants to the correct group, that is we conducted intention-to-treat analysis where it was possible to do so. Where data were missing, we sought clarification from the authors of the trial. If intention-to-treat analysis was not possible, we conducted available-case analysis or per-protocol analysis.

Assessment of heterogeneity

We assessed heterogeneity amongst trials, when appropriate, using the I^2 and Cochran Q statistics. Where we detected substantial heterogeneity (I^2 more than 50% or P less than 0.10), we explored this heterogeneity by prespecified subgroup analysis and sensitivity analysis.

Assessment of reporting biases

Where we suspected reporting bias, we attempted to contact trial authors to provide the missing outcome data. When missing data were thought to potentially introduce serious bias, the impact of including such trials in the overall assessment of results was explored by a sensitivity analysis. Where there were at least 10 trials, we also used funnel plot asymmetry to assess the existence of bias.

Data synthesis

We conducted statistical analysis with random-effects model meta-analyses using Review Manager 5 software (RevMan 2011). We used random-effects models for all analyses where trials examined the same intervention and the trials populations and methods were judged to be sufficiently similar. We originally planned to also conduct fixed-effect model meta-analysis, but abstained due to obvious heterogeneity of participants and intervention. We defined a P value of 0.05 or less as significant.

Subgroup analysis and investigation of heterogeneity

The following were priori subgroup analyses.

- Type of probiotic (by genus): *Lactobacillus*, *Bifidobacteria*, mixed, or unclear.
- Grade of hepatic encephalopathy: minimal compared to overt.
- Duration of therapy.
- MELD (Model for End-Stage Liver Disease) score.
- Co-interventions used.
- Trials with low risk of bias compared to trials with high risk of bias.

We assessed differences among subgroups by test of interaction (Altman 1996).

Sensitivity analysis

We carried out sensitivity analysis when we detected significant heterogeneity (I^2 more than 50% or P less than 0.10) to determine the source, that we sequentially removed trials from the analysis to determine which trial or trials were contributing to the heterogeneity.

'Summary of findings' tables

We used the GRADE system to evaluate the quality of the evidence for outcomes reported in the review, considering the within-study risk of bias (methodological quality), inconsistency, imprecision, indirectness, and publication bias (GRADEpro).

We defined the levels of evidence as 'high', 'moderate', 'low', or 'very low':

- High certainty: this research provides a very good indication of the likely effect; the likelihood that the effect will be substantially different is low.
- Moderate certainty: this research provides a good indication of the likely effect; the likelihood that the effect will be substantially different is moderate.
- Low certainty: this research provides some indication of the likely effect; however, the likelihood that the effect will be substantially different is high.
- Very low certainty: this research does not provide a reliable indication of the likely effect; the likelihood that the effect will be substantially different is very high.

RESULTS

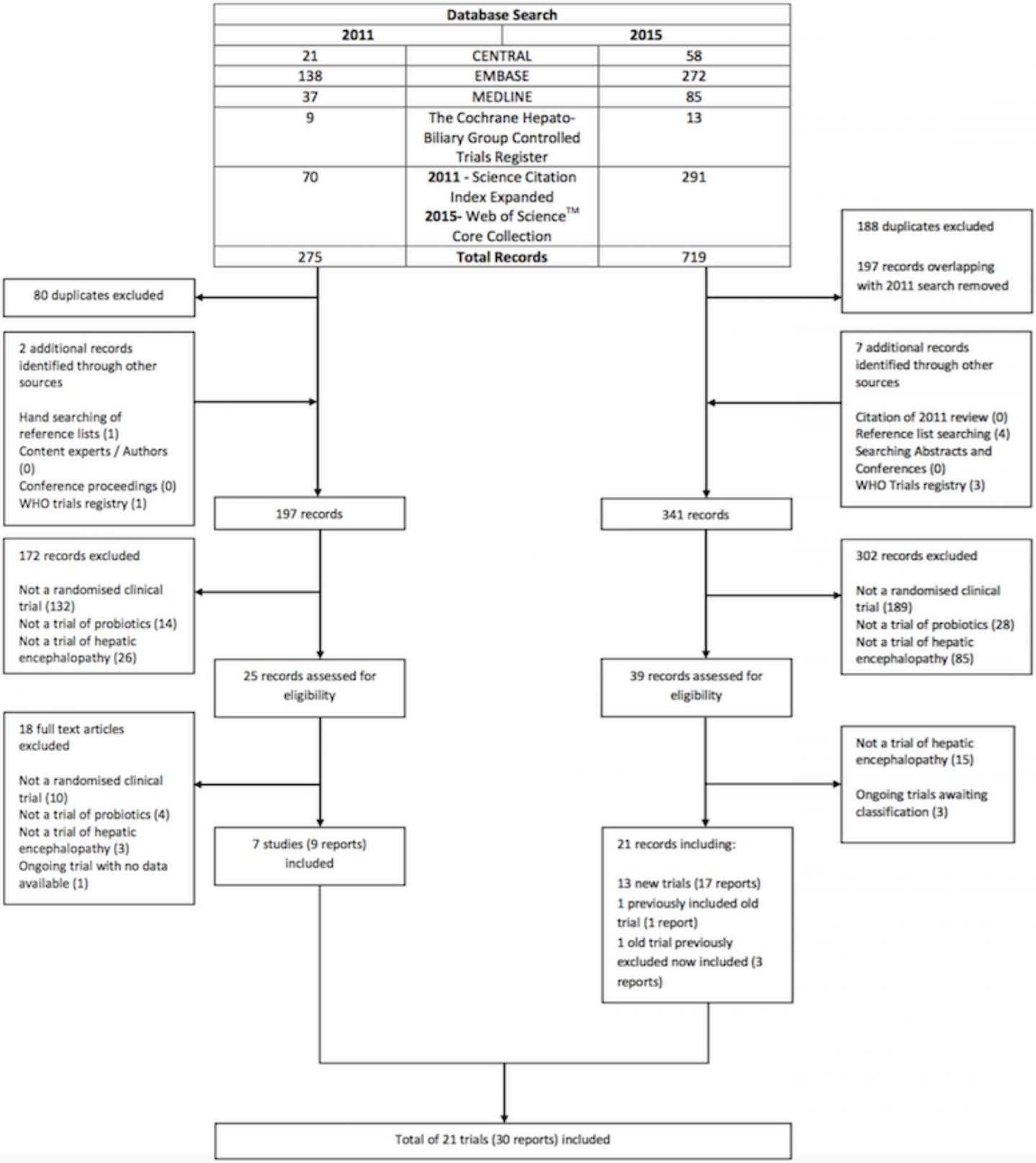
Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Results of the search

The process of identifying reports of randomised clinical trials for inclusion in the original review and in the review update is outlined in Figure 1.

Figure 1. Study flow diagram.



The original review published in 2011 included a total of seven trials reported in nine publications.

In this update, the electronic searches of the Cochrane Hepato-Biliary Group Controlled Trials Register (n = 13), the Cochrane Central Register of Controlled Trials (CENTRAL) (n = 58), MEDLINE (n = 85), Embase (n = 272), and Science Citation Index Expanded (n = 291) identified a total of 719 publications. We identified six additional trials from reference list (n = 4) and trials registry (n = 3) searching.

After excluding 188 duplicates and 197 records overlapping with the original search, 341 unique records remained. Of these, we excluded 302 after reviewing titles and abstracts, and of the remaining 39 records, which we assessed after reviewing their full texts, we excluded a further 15 records. Three of the 39 records were identified as ongoing trials (ACTRN12610001021066; IRCT201211012417N9; NCT01798329); therefore, the results were not available for use in the review; information about these trials is provided in Characteristics of studies awaiting classification.

Consequently, the review update contributed an additional 14 new trials reported in 20 publications.

Seventeen reports were of 13 new trials (Loguercio 1995; Qiao 2010; Saji 2011; Dhiman 2013a; Zhao 2013; Zhitai 2013; Ziada 2013; Bajaj 2014a; Lunia 2014; Mouli 2014; Sharma 2014; Shavakhi 2014; Vlachogiannakos 2014). Three reports were of one previously excluded trial now included after we obtained the manuscript from the author (Nair 2008).

A total of 30 reports (publications and abstracts) of 21 trials qualified for inclusion in the review (Figure 1).

Four of these 21 trials were available as an abstract across four different reports (Dhiman 2013a; Zhitai 2013; Lunia 2014; Vlachogiannakos 2014), whilst 17 of these 21 trials were published in 26 different reports.

Included studies

Of the 21 included trials, 14 trials compared a probiotic with placebo or no treatment in 785 participants (Liu 2004; Bajaj 2008; Nair 2008; Malaguarnera 2010; Qiao 2010; Pereg 2011; Saji 2011; Dhiman 2013a; Zhitai 2013; Bajaj 2014a; Lunia 2014; Sharma 2014; Shavakhi 2014; Vlachogiannakos 2014). Three trials compared a probiotic with lactulose in 200 participants (Loguercio 1987; Loguercio 1995; Mouli 2014). Four trials compared a probiotic both with placebo and with lactulose in 435 participants (Sharma 2008; Mittal 2009; Zhao 2013; Ziada 2013).

The probiotics used in each trial are in Table 1.

Seventeen trials enrolled participants with minimal hepatic encephalopathy (Liu 2004; Bajaj 2008; Nair 2008; Sharma 2008; Mittal 2009; Qiao 2010; Pereg 2011; Saji 2011; Dhiman 2013a; Zhao 2013; Ziada 2013; Bajaj 2014a; Lunia 2014; Mouli 2014; Sharma 2014; Shavakhi 2014; Vlachogiannakos 2014), and three trials enrolled participants with overt hepatic encephalopathy (grade I or II according to the West Haven criteria) (Loguercio 1987; Loguercio 1995; Malaguarnera 2010). The type of hepatic encephalopathy in one trial was unclear from the text (Zhitai 2013).

Excluded studies

We excluded a total of 320 newly identified and separate publications in the update. One previously excluded study was included after a manuscript containing further information was obtained from the author (Nair 2008).

Risk of bias in included studies

Reporting of trial methodology was incomplete for the majority of the domains, as summarised in Figure 2 and Figure 3. We classified most trials at a high risk of bias (with the exception of Bajaj 2014a and Nair 2008).

Figure 2. Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included trials.

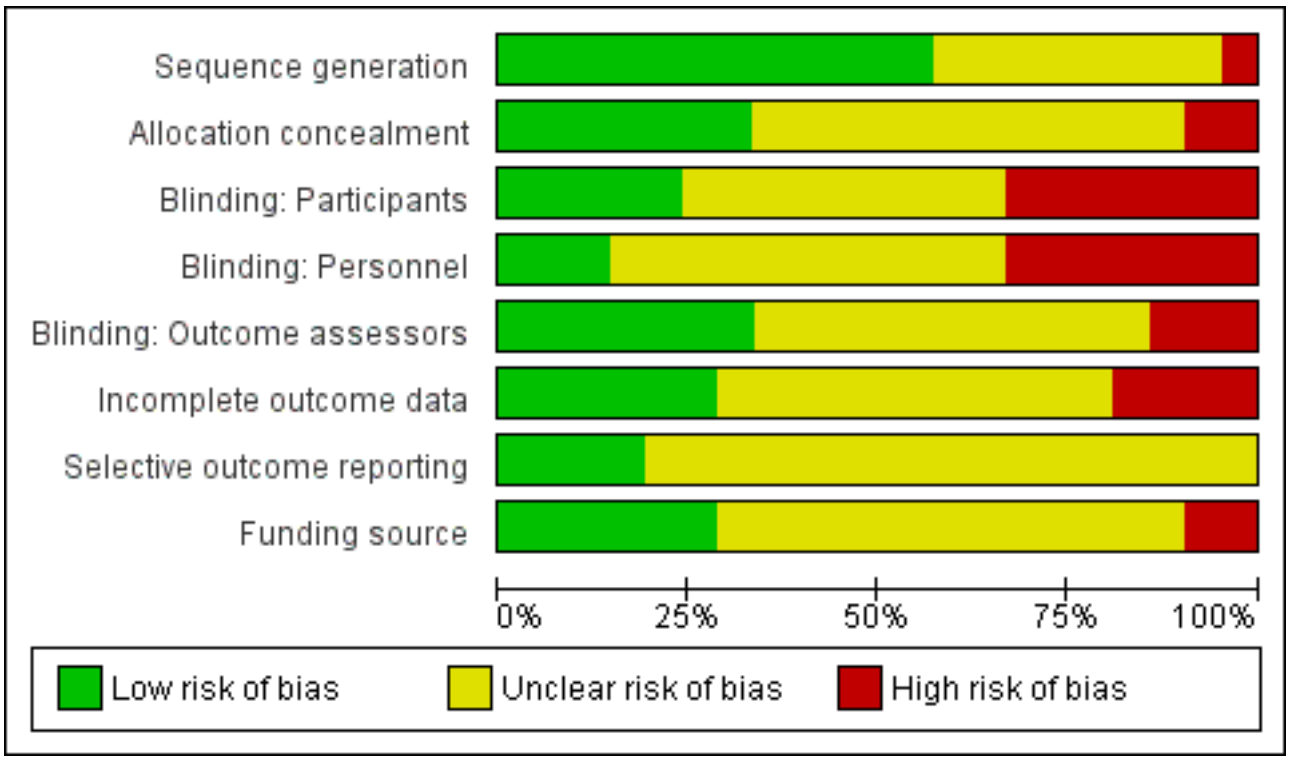


Figure 3. Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included trial.

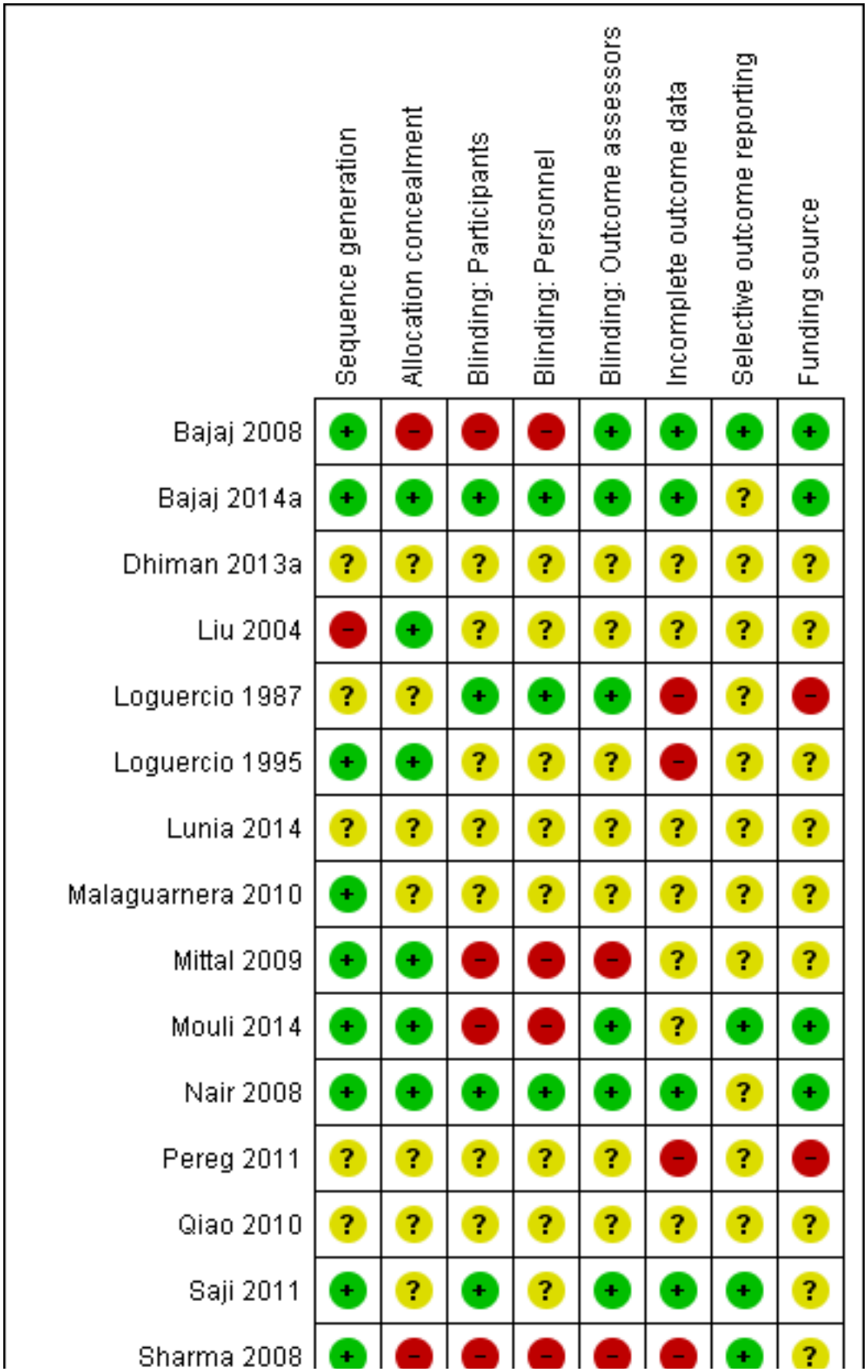
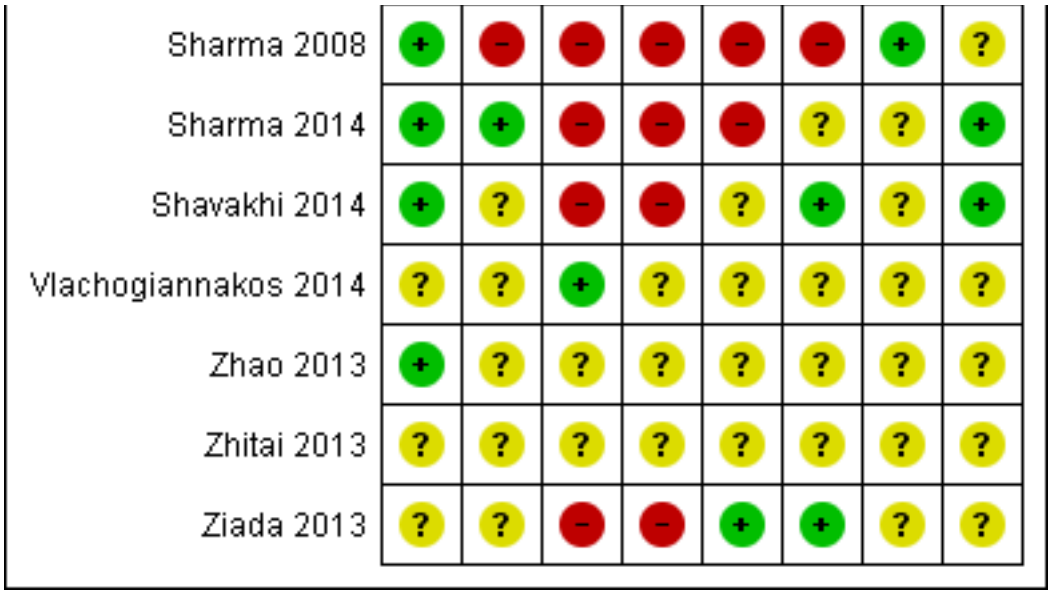


Figure 3. (Continued)



Allocation

Sequence generation was adequately performed in 12 trials (Loguercio 1995; Bajaj 2008; Nair 2008; Sharma 2008; Mittal 2009; Malaguarnera 2010; Saji 2011; Zhao 2013; Bajaj 2014a; Mouli 2014; Sharma 2014; Shavakhi 2014), inadequately performed in one trial (Liu 2004), and unclear in eight trials (Loguercio 1987; Qiao 2010; Pereg 2011; Dhiman 2013a; Zhitai 2013; Ziada 2013; Lunia 2014; Vlachogiannakos 2014).

Seven trials reported adequate allocation concealment (Loguercio 1995; Liu 2004; Nair 2008; Mittal 2009; Bajaj 2014a; Mouli 2014; Sharma 2014), two trials reported inadequate allocation concealment (Bajaj 2008; Sharma 2008), and 12 trials were unclear about their method of allocation concealment (Loguercio 1987; Malaguarnera 2010; Qiao 2010; Pereg 2011; Saji 2011; Dhiman 2013a; Zhao 2013; Zhitai 2013; Ziada 2013; Lunia 2014; Shavakhi 2014; Vlachogiannakos 2014).

Blinding

Three trials reported adequate blinding of participants, outcome assessors, and personnel (Loguercio 1987; Nair 2008; Bajaj 2014a). One trial reported adequate blinding of outcome assessors and participants, but was unclear regarding blinding of personnel (Saji 2011). Three trials reported adequate blinding of outcome assessors, but reported no blinding of participants and personnel (Bajaj 2008; Ziada 2013; Mouli 2014). One trial was unclear regarding blinding of outcome assessors, but reported no blinding of participants and personnel (Shavakhi 2014). One trial reported blinding of participants, but was unclear regarding blinding of personnel and outcome assessors (Vlachogiannakos 2014). Three trials did not blind participants, personnel, or outcome assessors (Sharma 2008; Mittal 2009; Sharma 2014). The remaining nine trials were unclear regarding the conduct of blinding (Loguercio 1995; Liu 2004; Malaguarnera 2010; Qiao 2010; Pereg 2011; Dhiman 2013a; Zhao 2013; Zhitai 2013; Lunia 2014).

Incomplete outcome data

Incomplete outcome data were adequately addressed in six trials (Bajaj 2008; Nair 2008; Saji 2011; Ziada 2013; Bajaj 2014a; Shavakhi 2014), inadequately addressed in four trials (Loguercio 1987; Loguercio 1995; Sharma 2008; Pereg 2011), and unclear in the remaining trials (Liu 2004; Mittal 2009; Malaguarnera 2010; Qiao 2010; Dhiman 2013a; Zhao 2013; Zhitai 2013; Lunia 2014; Mouli 2014; Sharma 2014; Vlachogiannakos 2014).

Selective reporting

Four trials were free of selective outcome reporting (Bajaj 2008; Sharma 2008; Saji 2011; Mouli 2014), while the remaining 17 trials were unclear (Loguercio 1987; Loguercio 1995; Liu 2004; Nair 2008; Mittal 2009; Malaguarnera 2010; Qiao 2010; Pereg 2011; Dhiman 2013a; Zhao 2013; Zhitai 2013; Ziada 2013; Bajaj 2014a; Lunia 2014; Sharma 2014; Shavakhi 2014; Vlachogiannakos 2014).

Other potential sources of bias

Eight trials declared their funding source (Loguercio 1987; Bajaj 2008; Nair 2008; Pereg 2011; Bajaj 2014a; Mouli 2014; Sharma 2014; Shavakhi 2014), of which six were independently funded (Bajaj 2008; Nair 2008; Bajaj 2014a; Mouli 2014; Sharma 2014; Shavakhi 2014), and two were industry funded (Loguercio 1987; Pereg 2011). The remaining trials did not disclose their funding source (Loguercio 1995; Liu 2004; Sharma 2008; Mittal 2009; Malaguarnera 2010; Qiao 2010; Saji 2011; Dhiman 2013a; Zhao 2013; Zhitai 2013; Ziada 2013; Lunia 2014; Vlachogiannakos 2014).

Effects of interventions

See: **Summary of findings for the main comparison** Probiotic for people with hepatic encephalopathy; **Summary of findings 2** Probiotics for people with hepatic encephalopathy

Probiotic versus placebo or no treatment

Primary outcomes

All-cause mortality

There were no significant differences in all-cause mortality (Analysis 1.1; 7 trials; 404 participants; RR 0.58, 95% CI 0.23 to 1.44; low quality of evidence).

Number of participants who did not recover from hepatic encephalopathy

No-recovery (as measured by incomplete resolution of symptoms) was significantly lower for participants treated with probiotic than with placebo or no intervention overall (Analysis 1.2; 10 trials; 574 participants; RR 0.67, 95% CI 0.56 to 0.79; moderate quality of evidence), at one month (Analysis 1.2 (Analysis 1.2.1); 4 trials; 228 participants; RR 0.75, 95% CI 0.58 to 0.96), and at three months (Analysis 1.2 (Analysis 1.2.3); 3 trials; 229 participants; RR 0.58, 95% CI 0.43 to 0.78), but not at two months (Analysis 1.2 (Analysis 1.2.2); 3 trials; 117 participants; RR 0.65, 95% CI 0.38 to 1.10).

Adverse events

Adverse events were lower for participants treated with probiotic than with placebo or no intervention when considering the development of overt hepatic encephalopathy (Analysis 1.3 (Analysis 1.3.1); 10 trials; 585 participants; RR 0.29, 95% CI 0.16 to 0.51; low quality of evidence), but there were no significant differences for hospitalisation (Analysis 1.3 (Analysis 1.3.3); 3 trials; 163 participants; RR 0.67, 95% CI 0.11 to 4.00; very low quality of evidence) or change of/or withdrawal from treatment (Analysis 1.3 (Analysis 1.3.5); 9 trials; 551 participants; RR 0.70, 95% CI 0.46 to 1.07; very low quality of evidence).

Quality of life

There were no significant differences in quality of life scores for participants treated with probiotic than with no intervention in the SF-36 Physical Functioning Scale (Analysis 1.4 (Analysis 1.4.1); 1 trial; 20 participants; MD 0.00, 95% CI -5.47 to 5.47; low quality of evidence) and the SF-36 Mental Health Scale (Analysis 1.4 (Analysis 1.4.2); 1 trial; 20 participants; MD -4.00, 95% CI -9.82 to 1.82; low quality of evidence). There was no significant difference in quality of life score for participants treated with probiotic than with no intervention in the Total Sickness Impact Profile (SIP) Score (Analysis 1.4 (Analysis 1.4.3); 2 trials; 95 participants; MD -3.66, 95% CI -7.75 to 0.44; low quality of evidence), but there were significant differences for change in SIP Psychological Score (Analysis 1.4 (Analysis 1.4.4); 2 trials; 95 participants; MD -3.54, 95% CI -4.95 to -2.12; low quality of evidence) and change in SIP Physical Score (Analysis 1.4 (Analysis 1.4.5); 2 trials; 95 participants; MD -2.94, 95% CI -4.44 to -1.44; low quality of evidence). A reduced SIP score indicates improved quality of life.

Secondary outcomes

Sepsis

There were no reports of septicaemia attributable to probiotic in any trial.

Change in plasma ammonia concentration

Plasma ammonia concentration was significantly lower for participants treated with probiotic than with no intervention overall (Analysis 1.5; 10 trials; 705 participants; MD -8.29 µmol/L, 95% CI -13.17 to -3.41; low quality of evidence), at one month (Analysis 1.5 (Analysis 1.5.1); 5 trials; 357 participants; MD -5.55 µmol/L, 95% CI -10.67 to -0.42), at three months (Analysis 1.5 (Analysis 1.5.3); 1 trial; 73 participants; MD -6.79 µmol/L, 95% CI -10.39 to -3.19), and at six months (Analysis 1.5 (Analysis 1.5.3); 1 trial; 64 participants; MD -31.08 µmol/L, 95% CI -40.50 to -21.66), but not at two months (Analysis 1.5 (Analysis 1.5.2); 4 trials; 211 participants; MD -5.11 µmol/L, 95% CI -14.56 to 4.34).

Duration of hospital stay: measured in days

No trials reported duration of hospital stay.

Subgroup analysis

We performed subgroup analyses for the outcomes no-recovery (Analysis 1.2) and plasma ammonia concentration (Analysis 1.5) using the prespecified subgroups (Subgroup analysis and investigation of heterogeneity). We could not perform subgroup analyses by MELD score, as most trials did not report this, or by risk of bias, as we judged most trials at high risk of bias.

No-recovery

We detected no significant differences for the following subgroup analyses: type of probiotic used, test for subgroup differences: Chi^2 = 0.74, df = 2 (P = 0.69); grade of hepatic encephalopathy, test for subgroup differences: Chi^2 = 3.56, df = 1 (P = 0.06); duration of therapy, test for subgroup differences: Chi^2 = 1.68, df = 2 (P = 0.43); co-interventions used, test for subgroup differences: Chi^2 = 3.57, df = 2 (P = 0.17) (Table 2).

Plasma ammonia

We detected no significant differences for the following subgroup analyses: type of probiotic used, test for subgroup differences: Chi^2 = 3.26, df = 3 (P = 0.35); grade of hepatic encephalopathy, test for subgroup differences: Chi^2 = 0.03, df = 1 (P = 0.85); duration of therapy, test for subgroup differences: Chi^2 = 1.09, df = 2 (P = 0.58); co-interventions used, test for subgroup differences: Chi^2 = 4.40, df = 2 (P = 0.11) (Table 2).

Quality of the evidence

In the analyses comparing probiotic versus placebo or no intervention (Summary of findings for the main comparison), we downgraded the quality of the evidence to 'moderate' for the outcome no-recovery because the included trials were at high risk of bias. Likewise, we downgraded the quality of the evidence for the outcomes adverse events -- overt hepatic encephalopathy and plasma ammonia concentration to low because the included trials were at high risk of bias and the results were inconsistent. We downgraded the quality of the evidence for the outcomes all-cause mortality and adverse events -- change of or withdrawal from treatment or both -- to very low because the included trials were at high risk of bias and the results were inconsistent or imprecise, or both.

Heterogeneity

Heterogeneity was demonstrated for the outcome no-recovery (Analysis 1.2) (Chi^2 = 17.48, df = 9 (P = 0.04); I^2 = 48%) and did not seem attributable to type of probiotic used, grade of hepatic encephalopathy, duration of therapy, or co-interventions

used. Heterogeneity was demonstrated for the outcome plasma ammonia concentration (Analysis 1.5) (Chi^2 = 47.32, df = 9 (P < 0.00001); I^2 = 81%) and did not seem attributable to type of probiotic used, grade of hepatic encephalopathy, duration of therapy, or co-interventions used (Table 2).

Probiotic versus lactulose

Primary outcomes

All-cause mortality

There were no significant differences in all-cause mortality (Analysis 2.1; 2 trials; 200 participants; RR 5.00, 95% CI 0.25 to 102.00; very low quality of evidence).

Number of participants who did not recover from hepatic encephalopathy

There was no significant difference in lack of recovery (Analysis 2.2; 7 trials; 430 participants; RR 1.01, 95% CI 0.85 to 1.21; very low quality of evidence).

Adverse events

There was no significant difference between participants treated with probiotic and those treated with lactulose for adverse events when considering the development of overt hepatic encephalopathy (Analysis 2.3 (Analysis 2.3.1); 6 trials; 420 participants; RR 1.17, 95% CI 0.63 to 2.17; very low quality of evidence), hospitalisation (Analysis 2.3 (Analysis 2.3.3); 1 trial; 80 participants; RR 0.33, 95% CI 0.04 to 3.07; very low quality of evidence), intolerance leading to discontinuation (Analysis 2.3 (Analysis 2.3.4); 3 trials; 220 participants; RR 0.35, 95% CI 0.08 to 1.43; very low quality of evidence), or change of/or withdrawal from treatment (Analysis 2.3 (Analysis 2.3.5); 7 trials; 490 participants; RR 1.27, 95% CI 0.88 to 1.82; very low quality of evidence).

Quality of life

There were no significant differences in quality of life scores between participants treated with probiotic and those treated with lactulose in change in Total SIP Score (Analysis 2.4 (Analysis 2.4.1); 1 trial; 69 participants; MD 0.65, 95% CI -1.13 to 2.43; very low quality of evidence); change in SIP Psychological Score (Analysis 2.4 (Analysis 2.4.2); 1 trial; 69 participants; MD 0.48, 95% CI -1.04 to 2.00; very low quality of evidence), or change in SIP Physical Score (Analysis 2.4 (Analysis 2.4.3); 1 trial; 69 participants; MD 0.38, 95% CI -0.61 to 1.37; very low quality of evidence).

Secondary outcomes

Sepsis

There were no reports of septicaemia attributable to probiotic in any trial.

Change in plasma ammonia concentration

There was no significant difference in plasma ammonia concentration overall (Analysis 2.5; 6 trials; 325 participants; MD -2.93 µmol/L, 95% CI -9.36 to 3.50; very low quality of evidence), at one month or less (Analysis 2.5 (Analysis 2.5.1); 5 trials; 248 participants; MD -4.30 µmol/L, 95% CI -13.17 to 4.56), or at three months (Analysis 2.5 (Analysis 2.5.2); 1 trial; 77 participants; MD 1.16 µmol/L, 95% CI -1.96 to 4.28).

Duration of hospital stay: measured in days

No trial reported duration of hospital stay.

Subgroup analysis

We performed subgroup analyses for the outcome plasma ammonia concentration (Analysis 2.5) using the prespecified subgroups (Subgroup analysis and investigation of heterogeneity). We did not perform subgroup analyses by MELD score as this was not reported in most trials, nor by risk of bias as the majority of the trials were at high risk of bias.

Plasma ammonia

We detected a significant difference for the subgroup analyses on grade of hepatic encephalopathy, test for subgroup differences: Chi^2 = 5.22, df = 1 (P = 0.02); I^2 = 80.9%. We detected no significant difference for the subgroup analyses on type of probiotic used, test for subgroup differences: Chi^2 = 5.60, df = 3 (P = 0.13) (Table 2).

Quality of the evidence

In the analyses comparing probiotic versus lactulose (Summary of findings 2), we downgraded the quality of the evidence to very low for all outcomes due to concerns that the included trials were at high risk of bias, the results were inconsistent or imprecise or both, and because a surrogate marker was used for clinically important outcomes.

Heterogeneity

Heterogeneity was demonstrated for the outcome plasma ammonia concentration (Analysis 2.5) (Chi^2 = 11.87, df = 4 (P = 0.02); I^2 = 66%). Heterogeneity seemed largely attributable to the grade of hepatic encephalopathy, and it did not seem attributable to the type of probiotic used (Table 2).

DISCUSSION

Summary of main results

We included 21 trials with a total of 1420 randomised participants. The trials used a variety of probiotics, although the most commonly used probiotic was VSL#3, a proprietary name for a group of eight probiotics. Duration of administration of the experimental intervention varied from 10 days to 180 days. We classified 19 of 21 trials as having a high risk of bias.

Probiotics may lead to little or no difference in mortality from any cause compared with no treatment. Probiotics probably improve recovery from hepatic encephalopathy (as measured by resolution of symptoms) compared with no treatment. Probiotics may prevent the development of overt hepatic encephalopathy compared with no treatment. The effects of probiotics on change of/or withdrawal from treatment is uncertain because the quality of the evidence was very low. Quality of life may slightly improve for patients treated with probiotic than with no intervention. Plasma ammonia concentration may decrease for patients treated with probiotic than with no intervention. No trial reported duration of hospital stay.

It is uncertain whether probiotics are better than lactulose for the management of hepatic encephalopathy, because the available evidence was of very low quality across all outcomes. There were no reports of septicaemia attributable to probiotic in any trial.

Overall completeness and applicability of evidence

The number of trials and randomised participants included in this review has substantially increased with this update. However, data from some trials were only available in abstract form; outcomes were often inconsistently reported; and most trials were at high risk of bias and included few participants. There is thus limited evidence for the use of probiotics as a treatment for people with hepatic encephalopathy. Overall, there is a large number of trials on probiotic use in cirrhosis (without confirmed diagnosis of hepatic encephalopathy). We have not considered trials of primary or secondary prevention using probiotics as prophylaxis against hepatic encephalopathy in the present review, which ought to be the subject of another systematic review. Also, trials on synbiotics should be considered for inclusion in the future alongside probiotics as a separate subgroup to illustrate comparative efficacy.

Quality of the evidence

Although compared to the original 2011 review the quantity of evidence has increased, the quality of evidence has lagged behind and is far from optimal. Although there may be emerging evidence for probiotic use, the quality of evidence for their use is low. Further randomised clinical trials with improved methodological quality and outcome data collection and data reporting are required to fully establish the role of probiotics in hepatic encephalopathy. The use of tools that quantify the statistical reliability of data across cumulative meta-analysis such as Trial Sequential Analysis, TSA 2011, ought to be included in future updates (Wetterslev 2008; Thorlund 2011). We also need to search data-bases of regulatory authorities for additional trials.

Potential biases in the review process

This systematic review with meta-analysis was undertaken with broad inclusion criteria to assess the totality of available evidence. Our literature search was comprehensive and did not exclude trials based on language of publication or publication status. We attempted to contact authors wherever trial data and methodology were unclear. All data extraction and analysis was undertaken by several authors working independently to minimise bias. Despite these strengths, there were some limitations: for example, we were not blinded to authorship during data extraction and 'Risk of bias' assessment. While we did attempt to contact study authors, we were not always certain that our messages were received, and we did not attempt to make any further contact if we received no response to our initial emails. As stated above, we might have missed trials by not searching databases of regulatory authorities, and we did not control risks of random errors.

Agreements and disagreements with other studies or reviews

A review published in 2011 discusses the effects of prebiotics, probiotics, and synbiotics in minimal hepatic encephalopathy (Shukla 2011a). As our review did not evaluate the combination of probiotics, prebiotics, and synbiotics, it is not possible to make direct comparisons between the reviews. Of note, the Shukla 2011a review was only able to locate two trials of probiotics including participants with minimal hepatic encephalopathy, compared to the five trials in the previous version of our review (McGee 2011), suggesting that we utilised a more sensitive search strategy.

A 2011 meta-analysis found improvement in “clinical and biochemical parameters in patients with minimal hepatic encephalopathy” and a “decrease the morbidity of clinical hepatic encephalopathy” (Tang 2011). However, that study used the time of Number Connection Test as a surrogate for clinical resolution of symptoms. In addition, they used a fixed-effect model, while we used the random-effects model in our review.

A 2012 review published a study, Holte 2012, with results largely similar to the initial 2011 publication of our systematic review and meta-analysis (McGee 2011).

A meta-analysis published in 2015 included nine randomised clinical trials comparing probiotic against placebo or no treatment (Zhao 2015). The authors concluded that probiotics were “associated with improvement of minimal hepatic encephalopathy, prophylaxis of overt hepatic encephalopathy, and reduction of SIP score and severe adverse events”, and our findings mirror these findings to some extent. They grouped serious adverse events as any of “minimal hepatic encephalopathy developing into overt hepatic encephalopathy, hospitalisations, infections, or unrelated emergency room (ER) visits”. However, we have separated these adverse events into subgroups, and found a significant difference favouring probiotics only for reducing the progression to overt hepatic encephalopathy, and not for the other serious adverse events. Furthermore, we have graded our findings to reflect the quality of the available evidence and the subsequent uncertainty around the results. In addition, due to the small sample sizes involved, random error or chance findings may partly explain the observed differences. Our review did not address the issue of prophylaxis of hepatic encephalopathy.

Another 2015 meta-analysis of probiotic use in hepatic encephalopathy included observational data as well as randomised clinical trials, but found only 14 studies, where we have included 21 randomised clinical trials (Saab 2015). Saab and colleagues found that when probiotics were compared with placebo, there was a significant improvement in minimal hepatic encephalopathy and decreased progression to overt hepatic encephalopathy, which is consistent with our findings. This study also reported no significant difference in improvement of minimal hepatic encephalopathy, hospitalisation rates, or progression to overt hepatic encephalopathy when probiotics were compared with lactulose, which is again consistent with our findings. However, the Saab study noted significantly decreased hospitalisation rates when probiotics were compared with placebo, which we did not. This is likely due to bias from their observational data and incomplete evidence synthesis.

AUTHORS' CONCLUSIONS

Implications for practice

Due to the very low overall quality of the evidence, there is limited evidence for the use of probiotics compared with lactulose. Compared with placebo or no intervention, probiotics probably improve recovery and may lead to improvements in the development of overt hepatic encephalopathy, quality of life, and

plasma ammonia concentrations, but may lead to little or no difference in mortality.

Implications for research

Hepatic encephalopathy has a poor clinical outcome and is a significant burden on the healthcare system. Current treatment options are of limited efficacy. Probiotics represent an inexpensive alternative option; however, their benefits and harms are still uncertain, and many fundamental questions concerning their use remain. First, the benefits and harms of probiotics must be assessed in randomised clinical trials with low risk of systematic errors ('bias') and low risk of random errors ('play of chance'). Moreover, it is unknown whether all probiotics are of equal effectiveness or what dose or duration of probiotic therapy is necessary for treatment. It is also unknown whether colonisation though multiple dosing is necessary for benefit or if a single dose of probiotic suffices (McGee 2010). Future research should take these factors into account and consider alternative study designs; for example, factorial trials would allow multiple comparisons to be made in one trial. Future trials should also adhere to the International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) consensus statement, which makes recommendations for trials in people with hepatic encephalopathy (Bajaj 2011), as well as guidelines for the nomenclature of hepatic encephalopathy (Vilstrup 2014; Allampati 2015). According to this new nomenclature, the term 'covert hepatic encephalopathy' is used to denote either 'minimal hepatic encephalopathy' or 'grade 1 hepatic encephalopathy' as per the West Haven criteria (Conn 1977). As the trials included in this review typically pre-date the development of this new nomenclature, we have continued to use the term 'minimal hepatic encephalopathy' where this has been historically applied by the original study authors to describe their study group, in order to precisely represent the participants enrolled in those particular studies. Furthermore, we have used the term ‘acute hepatic encephalopathy’ in our inclusion criteria as an inclusive term in order to select a broad range of studies. Any changes to the inclusion criteria based on the new nomenclature of ‘Type A hepatic encephalopathy’ should be considered for the next review update. The Human Microbiome Project is one important initiative that will likely contribute to a better understanding of the complex relationship between humans and microbes (Turnbaugh 2007).

The high response in the control groups of this review reflects the natural history of hepatic encephalopathy, with its spontaneously fluctuating nature and possibility for spontaneous remission. Future trials should take this into account when assessing the efficacy of interventions. It is also important that those conducting trials also account for the time of day in which assessments are made. Consideration should be given to the type of placebo used, for example inactivated probiotic. All trials should at a minimum assess important outcomes such as mortality, quality of life, and adverse events. Trials should also be designed according to Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Statement (www.spirit-statement.org/) and reported following the CONSORT Statement (www.consort-statement.org/).

Future systematic reviews on this topic ought to search also databases of regulatory authorities. Review authors should also use, for example, Trial Sequential Analysis to control risks of random errors.

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REFERENCES

References to studies included in this review

Bajaj 2008 *{published data only}*

Bajaj JS, Christensen KM, Hafeezullah M, Varma RR, Franco J, Hoffmann RG, et al. Randomized trial of probiotic yogurt in minimal hepatic encephalopathy - It helps to bug your patient. *Digestive Disease Week* 2007;**132**(4):A800.

* Bajaj JS, Saeian K, Christensen KM, Hafeezullah M, Varma RR, Franco J, et al. Probiotic yogurt for the treatment of minimal hepatic encephalopathy. *American Journal of Gastroenterology* 2008;**103**(7):1707-15.

McGee R. Request for clinical trial information [personal communication]. Email to: JS Bajaj 14 October 2010.

Bajaj 2014a *{published data only}*

Bajaj JS, Heuman D, Hylemon P, Sanyal A, Sterling R, Stravitz R, et al. Systems biology analysis of probiotic lactobacillus GG in cirrhotic patients with minimal hepatic encephalopathy: a randomized double-blind, placebo-controlled trial. Journal of Hepatology 2014; Vol. 1:S221. [0168-8278]

* Bajaj JS, Heuman DM, Hylemon PB, Sanyal AJ, Puri P, Sterling RK, et al. Randomised clinical trial: lactobacillus GG modulates gut microbiome, metabolome and endotoxemia in patients with cirrhosis. Alimentary Pharmacology & Therapeutics 2014; Vol. 39, issue 10:1113-25. [0269-2813]

Dhiman 2013a *{published data only}*

Dhiman R, Khatri A, Rana S, Chopra M, Thumburu K, Malhotra S, et al. Probiotic preparation in the treatment of MHE - A double-blind, randomized, placebo controlled study. Journal of Gastroenterology and Hepatology 2013; Vol. 28:401-2. [0815-9319]

Liu 2004 *{published data only}*

Liu Q, Duan ZP, Ha DK, Bengmark S, Kurtovic J, Riordan SM. Synbiotic modulation of gut flora: effect on minimal hepatic encephalopathy in patients with cirrhosis. *Hepatology (Baltimore, Md.)* 2004;**39**(5):1441-9.

Loguercio 1987 *{published data only}*

* Loguercio C, Del Vecchio Blanco C, Coltorti M. Enterococcus lactic acid bacteria strain SF68 and lactulose in hepatic encephalopathy: a controlled study. *Journal of International Medical Research* 1987;**15**(6):335-43.

McGee R. Request for clinical trial information [personal communication]. Email to: C Loguercio 15 October 2010.

Loguercio 1995 *{published data only}*

Loguercio C, Abbiati R, Rinaldi M, Romano A, Del Vecchio Blanco C, Coltorti M. Long-term effects of Enterococcus faecium SF68 versus lactulose in the treatment of patients with cirrhosis and grade 1-2 hepatic encephalopathy. Journal of Hepatology 1995; Vol. 23, issue 1:39-46. [0168-8278: (Print)]

Lunia 2014 *{published data only}*

Lunia MK, Sharma BC, Srivastav S, Sachdeva S. Efficacy of probiotics on minimal hepatic encephalopathy and improvement in small intestinal bacterial overgrowth and orocecal transit time in cirrhosis: a randomised controlled trial. Journal of Hepatology 2014; Vol. 1:S246. [0168-8278]

Malaguarnera 2010 *{published data only}*

Malaguarnera M, Gargante MP, Malaguarnera G, Salmeri M, Mastrojeni S, Rampello L, et al. Bifidobacterium combined with fructo-oligosaccharide versus lactulose in the treatment of patients with hepatic encephalopathy. *European Journal of Gastroenterology & Hepatology* 2010;**22**(2):199-206.

Mittal 2009 *{published data only}*

McGee R. Request for clinical trial information [personal communication]. Email to: BC Sharma 14 October 2010.

Mittal VV, Sharma BC, Sharma P, Sarin SK. A randomized controlled trial comparing lactulose, probiotics, and L-ornithine L-aspartate in treatment of minimal hepatic encephalopathy. European Journal of Gastroenterology & Hepatology 2011; Vol. 23, issue 8:725-32. [0954-691X]

* Mittal VV, Sharma P, Sharma B, Sarin SK. Treatment of minimal hepatic encephalopathy: a randomized controlled trial comparing lactulose, probiotics and L-ornithine L-aspartate with placebo. *Hepatology (Baltimore, Md.)* 2009;**4 (Suppl)**:471A.

Mouli 2014 *{published data only}*

Mouli VP, Benjamin J, Bhushan Singh M, Mani K, Garg SK, Saraya A, et al. Effect of probiotic VSL#3 in the treatment of minimal hepatic encephalopathy: a non-inferiority randomized controlled trial. Hepatology Research 2015; Vol. 45, issue 8:880-9. [1872-034X]

Nair 2008 *{published data only}*

Dalal R. Request for clinical trial information [personal communication]. Email to: RRS Nair 26 April 2015.

Nair RR. Early detection of hepatic encephalopathy in preclinical stage with evoked response studies: a randomised control trial. Neurology 2011; Vol. 76, issue 9:A222-3. [0028-3878]

Nair RRS, Abdurahiman P, Jose J, Sebastian S, Thomas V, Girija A. Brainstem evoked response audiometry versus visual evoked response in detecting minimal hepatic encephalopathy and to assess the response after treatment with probiotics - A randomized double blind placebo controlled study. *American Academy of Neurology* 2008;**70**(11):A50.

* Nair RRS, Jose J, Thomas V. BERA vs VEP in subclinical hepatic encephalopathy - A randomised control trial. Annals of Neurology 2009; Vol. 66:S28-9. [0364-5134]

Pereg 2011 *{published data only}*

Pereg D, Kotliroff A, Gadoth N, Hadary R, Lishner M, Kitay-Cohen Y. Probiotics for patients with compensated liver

cirrhosis: a double-blind placebo-controlled study. *Nutrition* 2011;**27**(2):177-81.

Qiao 2010 *{published data only}*

Qiao X-L. Clinical researches of bifid triple viable on the treatment of subclinical hepatic encephalopathy. Chinese Journal of Clinical Gastroenterology 2010; Vol. 22, issue 2:105-6.

Saji 2011 *{published data only}*

Saji S, Kumar S, Thomas V. A randomized double blind placebo controlled trial of probiotics in minimal hepatic encephalopathy. Tropical Gastroenterology 2011; Vol. 32, issue 2:128-32. [0250-636X]

Sharma 2008 *{published data only}*

McGee R. Request for clinical trial information [personal communication]. Email to: BC Sharma 14 October 2010.

Sharma P, Sharma BC, Puri V, Sarin SK. A randomized control trial of lactulose versus probiotics versus lactulose plus probiotics in the treatment of minimal hepatic encephalopathy of cirrhosis. 71st Annual Scientific Meeting of the American College of Gasroenterology, 2006 10 20-25, Las Vegas. American College of Gastroenterology, 2006; Vol. 101, issue 9:402.

* Sharma P, Sharma BC, Puri V, Sarin SK. An open-label randomized controlled trial of lactulose and probiotics in the treatment of minimal hepatic encephalopathy. *European Journal of Gastroenterology & Hepatology* 2008;**20**(6):506-11.

Sharma 2014 *{published data only}*

Pant S, Dwivedi M, Misra SP, Narang S, Sharma K. Minimal hepatic encephalopathy: effect of rifaximin, probiotics and L-ornithine L-aspartate. Indian Journal of Gastroenterology 2011; Vol. 1:A51. [0254-8860]

Pant S, Sharma K, Misra SP, Dwivedi M, Narang S, Mishra K, et al. Effect of rifaximin, probiotics and L-ornithine L-aspartate on minimal hepatic encephalopathy: a case control study. Indian Journal of Gastroenterology 2013; Vol. 1:A92. [0254-8860]

Sharma K, Pant S, Dwivedi M, Misra SP, Misra A, Narang S. Minimal hepatic encephalopathy: effect of rifaximin, probiotics and L-ornithine L-aspartate. Journal of Gastroenterology and Hepatology 2012; Vol. 27:275-6. [0815-9319]

* Sharma K, Pant S, Misra S, Dwivedi M, Misra A, Narang S, et al. Effect of rifaximin, probiotics, and l-ornithine l-aspartate on minimal hepatic encephalopathy: a randomized controlled trial. Saudi Journal of Gastroenterology 2014; Vol. 20, issue 4:225-32. [1319-3767]

Shavakhi 2014 *{published data only}*

Shavakhi A, Hashemi H, Tabesh E, Derakhshan Z, Farzamnia S, Meshkinfar S, et al. Multistrain probiotics and lactulose in the treatment of minimal hepatic encephalopathy. Journal of Research in Medical Sciences 2014; Vol. 19, issue 8:703-8. [1735-7136]

Vlachogiannakos 2014 *{published data only}*

Vlachogiannakos J, Vasianopoulou P, Via-zis N, Chroni M, Voulgaris T, Ladas SD, et al. The role of probiotics in the treatment of minimal hepatic encephalopathy. A prospective, randomized, placebo-controlled, double-blind study. Hepatology (Baltimore, Md.) 2014; Vol. 60, issue 4 Suppl:376A.

Vlachogiannakos J, Vasianopoulou P, Viazis N, Chroni M, Karamanolis D, Ladas SD. Reversal of minimal hepatic encephalopathy after a probiotic administration. A prospective, randomized, placebo-controlled, double-blind study. Journal of Hepatology 2016; Vol. 64, issue Suppl 2:S165. [1600-0641]

Zhao 2013 *{published data only}*

Zhao X-H, Feng Q, Zhang J, Jiang Y-F. A randomized-controlled trial to compare the effect of lactulose and probiotics on treatment of minimal hepatic encephalopathy. Practical Journal of Clinical Medicine 2013; Vol. 10, issue 4:61-3.

Zhitai 2013 *{published data only}*

Zhitai Z. Clinical application of probiotics in the treatment of hepatic encephalopathy. Journal of Gastroenterology and Hepatology 2013; Vol. 28:851. [0815-9319]

Ziada 2013 *{published data only}*

Ziada DH, Soliman HH, Yamany SA, Hamisa MF, Hasan AM. Can Lactobacillus acidophilus improve minimal hepatic encephalopathy? A neurometabolite study using magnetic resonance spectroscopy. Arab Journal of Gastroenterology 2013; Vol. 14, issue 3:116-22.

References to studies excluded from this review

Adams 2006 *{published data only}*

Adams LA, Angulo P. Treatment of non-alcoholic fatty liver disease. *Postgraduate Medical Journal* 2006;**82**(967):315-22.

Agrawal 2012 *{published data only}*

Agrawal M, Homel P, Badalov N, Mayer I, Rahmani R. Probiotics in minimal hepatic encephalopathy: a meta-analysis. *American Journal of Gastroenterology* 2012;**107**:S153-4.

Agrawal 2012a *{published data only}*

Agrawal A, Sharma BC, Sharma P, Sarin SK. Secondary prophylaxis of hepatic encephalopathy in cirrhosis: an open label, randomized controlled trial of lactulose, probiotics and no-therapy. Journal of Gastroenterology and Hepatology 2011; Vol. 26:7. [0815-9319]

Agrawal A, Sharma BC, Sharma P, Sarin SK. Secondary prophylaxis of hepatic encephalopathy in cirrhosis: an open-label, randomized controlled trial of lactulose, probiotics, and no therapy. American Journal of Gastroenterology 2012; Vol. 107, issue 7:1043-50. [0002-9270]

Agrawal A, Sharma P, Sharma B, Sarin S. Secondary prophylaxis of hepatic encephalopathy in cirrhosis: an open label, randomized controlled trial of lactulose, probiotics and no-therapy. American Journal of Gastroenterology 2010; Vol. 105:S105. [0002-9270]

NCT01178372. Secondary prophylaxis of hepatic encephalopathy in cirrhosis: an open label, randomized controlled trial of lactulose, probiotics and no-therapy.

apps.who.int/trialsearch/Trial.aspx?TrialID=NCT01178372 first recieved August 9 2010.

Al 2009 *{published data only}*

Al Sibae MR, McGuire BM. Current trends in the treatment of hepatic encephalopathy. *Therapeutics and Clinical Risk Management* 2009;**5**(1):617-26.

Albillos 2002 *{published data only}*

Albillos A, de la Hera A. Multifactorial gut barrier failure in cirrhosis and bacterial translocation: working out the role of probiotics and antioxidants. *Journal of Hepatology* 2002;**37**(4):523-6.

Alisi 2014 *{published data only}*

Alisi A, Bedogni G, Baviera G, Giorgio V, Porro E, Paris C, et al. Randomised clinical trial: the beneficial effects of VSL# 3 in obese children with non-alcoholic steatohepatitis. Alimentary Pharmacology & Therapeutics 2014; Vol. 39, issue 11:1276-85. [0269-2813]

Aller 2011 *{published data only}*

Aller R, De Luis DA, Izaola O, Conde R, Gonzalez Sagrado M, Primo D, et al. Effect of a probiotic on liver aminotransferases in nonalcoholic fatty liver disease patients: a double blind randomized clinical trial. European Review for Medical and Pharmacological Sciences 2011; Vol. 15, issue 9:1090-5.

Almeida 2006 *{published data only}*

Almeida J, Galhenage S, Yu J, Kurtovic J, Riordan SM. Gut flora and bacterial translocation in chronic liver disease. *World Journal of Gastroenterology* 2006;**12**(10):1493-502.

Arya 2010 *{published data only}*

Arya R, Gulati S, Deopujari S. Management of hepatic encephalopathy in children. *Postgraduate Medical Journal* 2010;**86**(1011):34-41.

Bai 2013 *{published data only}*

Bai M, Yang Z, Qi X, Fan D, Han G. L-ornithine-l-aspartate for hepatic encephalopathy in patients with cirrhosis: a meta-analysis of randomized controlled trials. *Journal of Gastroenterology and Hepatology* 2013;**28**:783-92.

Bajaj 2008a *{published data only}*

Bajaj J. Minimal hepatic encephalopathy matters in daily life. *World Journal of Gastroenterology* 2008;**14**(23):3609-15.

Bajaj 2008b *{published data only}*

Bajaj JS. Management options for minimal hepatic encephalopathy. *Expert Review of Gastroenterology & Hepatology* 2008;**2**(6):785-90.

Bajaj 2014 *{published data only}*

Bajaj JS. Commentary: Probing probiotics in cirrhosis - A template for future studies? Author's reply. *Alimentary Pharmacology & Therapeutics* 2014;**39**:1335-6.

Barclay 2011 *{published data only}*

Barclay AR, Beattie LM, Weaver LT, Wilson DC. Systematic review: medical and nutritional interventions for the management of intestinal failure and its resultant complications in children. *Alimentary Pharmacology & Therapeutics* 2011;**33**(2):175-84.

Barreto-Zuniga 2001 *{published data only}*

Barreto-Zuniga R, Naito Y, Li ZI, Zhang D, Yoshioka M, Ideo GM, et al. Anti-endotoxin capacity and reticulo-endothelial function in alcohol-related liver cirrhosis: a randomized pilot study comparing a probiotic preparation versus lactulose. *International Medical Journal* 2001;**8**(2):101-7.

Bass 2007 *{published data only}*

Bass NM. Emerging therapies for the management of hepatic encephalopathy. *Seminars in Liver Disease* 2007;**27**(Suppl 2):18-25.

Bengmark 2009a *{published data only}*

Bengmark S. Bio-ecological control of chronic liver disease and encephalopathy. *Metabolic Brain Disease* 2009;**24**:223-36.

Bengmark 2011 *{published data only}*

Bengmark S, Di Cocco P, Clemente K, Corona L, Angelico R, Manzia TM, et al. Bio-ecological control of chronic liver disease and encephalopathy. *Minerva Medica* 2011;**102**:309-19.

Bengmark 2013 *{published data only}*

Bengmark S. Gut microbiota, immune development and function. *Pharmacological Research* 2013;**69**:87-113.

Bismuth 2011 *{published data only}*

Bismuth M, Funakoshi N, Cadranel JF, Blanc P. Hepatic encephalopathy: from pathophysiology to therapeutic management. *European Journal of Gastroenterology & Hepatology* 2011;**23**(1):8-22.

Boca 2004 *{published data only}*

Boca M, Vyskocil M, Mikulecky M, Ebringer L, Kolibas E, Kratochvil'ova H, et al. Complex therapy of chronic hepatic encephalopathy completed with probiotic: comparison of two studies [Komplexna liecba chronickej hepatalnej encefalopatie doplnena probiotikom: Porovnanie dvoch studii]. *Casopis Lekaru Ceskych* 2004;**143**(5):324-8.

Bongaerts 2005 *{published data only}*

Bongaerts G, Severijnen R, Timmerman H. Effect of antibiotics, prebiotics and probiotics in treatment for hepatic encephalopathy. *Medical Hypotheses* 2005;**64**(1):64-8.

Cabre 2005 *{published data only}*

Cabre E, Gassull MA. Nutrition in liver disease. *Current Opinion in Clinical Nutrition and Metabolic Care* 2005;**8**(5):545-51.

Cash 2010 *{published data only}*

Cash WJ, McConville P, McDermott E, McCormick PA, Callender ME, McDougall NI. Current concepts in the assessment and treatment of hepatic encephalopathy. *QJM : Monthly Journal of the Association of Physicians* 2010;**103**(1):9-16.

Chadalavada 2010 *{published data only}*

Chadalavada R, Sappati Biyyani RS, Maxwell J, Mullen K. Nutrition in hepatic encephalopathy. *Nutrition in Clinical Practice* 2010;**25**(3):257-64.

Chauhan 2012 *{published data only}*

Chauhan SV, Chorawala MR. Probiotics, prebiotics and synbiotics. *International Journal of Pharmaceutical Sciences and Research* 2012;**3**:711-26.

Cheung 2012 *{published data only}*

Cheung K, Lee SS, Raman M. Prevalence and mechanisms of malnutrition in patients with advanced liver disease, and nutrition management strategies. *Clinical Gastroenterology and Hepatology* 2012;**10**:117-25.

Chikhacheva 2014 *{published data only}*

Chikhacheva EA, Seliverstov PV, Sitkin SI, Dobritsa VP, Radchenko VG. Tactics for the correction of intestinal microbiocenotic disorders in the combination therapy of patients with chronic liver diseases. *Terapevticheskii Arkhiv* 2014;**86**:52-7.

Ciorba 2012 *{published data only}*

Ciorba MA. A gastroenterologist's guide to probiotics. *Clinical Gastroenterology and Hepatology* 2012;**10**:960-8.

Colle 1989 *{published data only}*

Colle R, Ceschia T. Oral bacteriotherapy with Bifidobacterium bifidum and Lactobacillus acidophilus in cirrhotic patients [Batterioterapia orale con Bifidobacterium bifidum e Lactobacillus acidophilus nel cirrotico]. *Clinica Terapeutica* 1989;**131**(6):397-402.

Conn 1970 *{published data only}*

Conn HO, Floch MH. Effects of lactulose and Lactobacillus acidophilus on the fecal flora. *American Journal of Clinical Nutrition* 1970;**23**(12):1588-94.

Crittenden 2013 *{published data only}*

Crittenden NE, McClain C. Management of patients with moderate alcoholic liver disease. *Clinical Liver Disease* 2013;**2**:76-9.

Dai 2014 *{published data only}*

Dai G, Wu D, Lian J, Ma H, Jiang B. Clinical research on microecologic treatment combined enteral nutrition for hepatic encephalopathy. Zhonghua Liu Xing Bing Xue Za Zhi 2014; Vol. 35, issue 12:1392-5. [0254-6450]

Dasarathy 2003 *{published data only}*

Dasarathy S. Role of gut bacteria in the therapy of hepatic encephalopathy with lactulose and antibiotics. *Indian Journal of Gastroenterology* 2003;**22**(Suppl 2):S50-3.

Dbouk 2006 *{published data only}*

Dbouk N, McGuire BM. Hepatic encephalopathy: a review of its pathophysiology and treatment. *Current Treatment Options in Gastroenterology* 2006;**9**(6):464-74.

Demeter 2006 *{published data only}*

Demeter P. The possibilities of using probiotics in digestive diseases [A probiotikumok alkalmazasanak lehetosegei emesztoszervi betegsegekben]. *Lege Artis Medicine* 2006;**16**(1):41-7.

De Micco 2012 *{published data only}*

De Micco I, D'Aniello R, Sangermano M, Mandato C, Paolella G, Lenta S, et al. A systematic review of pediatric NAFLD therapy: year 2012. Digestive and Liver Disease 2012; Vol. 44:S288. [1590-8658]

Dhiman 2004 *{published data only}*

Dhiman RK, Chawla YK. Minimal hepatic encephalopathy: should we start treating it?. *Gastroenterology* 2004;**127**(6):1855-7.

Dhiman 2007 *{published data only}*

Dhiman RK. Minimal hepatic encephalopathy: has the time come to recognize and treat it?. *Bulletin, Postgraduate Institute of Medical Education and Research, Chandigarh* 2007;**41**(1):1-4.

Dhiman 2009 *{published data only}*

Dhiman RK, Chawla YK. Minimal hepatic encephalopathy. *Indian Journal of Gastroenterology* 2009;**28**(1):5-16.

Dhiman 2010 *{published data only}*

Dhiman RK, Saraswat VA, Sharma BK, Sarin SK, Chawla YK, Butterworth R, et al. Minimal hepatic encephalopathy: consensus statement of a working party of the Indian National Association for Study of the Liver. *Journal of Gastroenterology and Hepatology* 2010;**25**(6):1029-41.

Dhiman 2012 *{published data only}*

Dhiman RK, Rana BS, Garg A, Khattri A, Chopra M, Thumburu KK, et al. Efficacy and safety of a probiotic preparation in the secondary prophylaxis of hepatic encephalopathy in cirrhotic patients: interim results of a double blind, randomized, placebo controlled study. Hepatology (Baltimore, Md.) 2012; Vol. 56:255A. [0270-9139]

Dhiman 2013 *{published data only}*

Dhiman RK. Gut microbiota and hepatic encephalopathy. *Metabolic Brain Disease* 2013;**28**:321-6.

Dhiman 2014 *{published data only}*

Dhiman RK, Rana B, Agrawal S, Garg A, Chopra M, Thumburu KK, et al. Probiotic VSL#3 reduces liver disease severity and hospitalization in patients with cirrhosis: a randomized, controlled trial. Gastroenterology 2014; Vol. 147, issue 6:1327-37.e3.

Dhiman 2015 *{published data only}*

Dhiman RK. Hepatic encephalopathy. Journal of Clinical & Experimental Hepatology 2015; Vol. 5, issue S1:S1-2. [0973-6883]

Ding 2014 *{published data only}*

Ding X, Zhang F, Wang Y. Letter: probiotics vs. lactulose for minimal hepatic encephalopathy therapy. *Alimentary Pharmacology & Therapeutics* 2014;**39**:1000.

Ding 2014a *{published data only}*

Ding X, Zhang FC, Wang YJ. Probiotics versus lactulose for minimal hepatic encephalopathy therapy: a randomized controlled trial meta-analysis. Journal of Digestive Diseases 2014; Vol. 15:135. [1751-2972]

Doron 2005 *{published data only}*

Doron S, Snydman DR, Gorbach SL. Lactobacillus GG: bacteriology and clinical applications. *Gastroenterology Clinics of North America* 2005;**34**(3):483-98.

Druart 2014 *{published data only}*

Druart C, Alligier M, Salazar N, Neyrinck AM, Delzenne NM. Modulation of the gut microbiota by nutrients with prebiotic and probiotic properties. Advances in Nutrition 2014; Vol. 5, issue 5:624S-33S. [2161-8313]

Dylag 2014 *{published data only}*

Dylag K, Hubalewska-Mazgaj M, Surmiak M, Szmyd J, Brzozowski T. Probiotics in the mechanism of protection against gut inflammation and therapy of gastrointestinal disorders. *Current Pharmaceutical Design* 2014;**20**:1149-55.

EASL 2012 *{published data only}*

EASL. 47th Annual Meeting of the European Association for the Study of the Liver. *Journal of Hepatology* 2012;**56**(Suppl 2):S1-S614.

Eguchi 2011 *{published data only}*

Eguchi S, Takatsuki M, Hidaka M, Soyama A, Ichikawa T, Kanematsu T. Perioperative synbiotic treatment to prevent infectious complications in patients after elective living donor liver transplantation: a prospective randomized study. *American Journal of Surgery* 2011;**201**(4):498-502.

El-Nezami 2006 *{published data only}*

El-Nezami HS, Polychronaki NN, Ma J, Zhu HL, Ling WH, Salminen EK, et al. Probiotic supplementation reduces a biomarker for increased risk of liver cancer in young men from Southern China. American Journal of Clinical Nutrition 2006; Vol. 83, issue 5:1199-203. [0002-9165]

Eslamparast 2014 *{published data only}*

Eslamparast T, Poustchi H, Zamani F, Sharafkhah M, Malekzadeh R, Hekmatdoost A. Synbiotic supplementation in nonalcoholic fatty liver disease: a randomized, double-blind, placebo-controlled pilot study. American Journal of Clinical Nutrition 2014; Vol. 99, issue 3:535-42. [0002-9165]

Fan 2009 *{published data only}*

Fan N, Tian ZB, Kong XJ, Zhao QX, Wei LZ. Bifico improves intestinal macromolecular permeability in patients with liver cirrhosis. *World Chinese Journal of Digestology* 2009;**17**(36):3745-8.

Fan 2013 *{published data only}*

Fan JG, Cao HX. Role of diet and nutritional management in non-alcoholic fatty liver disease. *Journal of Gastroenterology and Hepatology* 2013;**28**:81-7.

Fehervari 2012 *{published data only}*

Fehervari I, Nemes B, Gorog D, Gerlei Z, Kobori L. Hepatic encephalopathy and liver transplantation. *Magyar Sebeszet* 2012;**65**:58-62.

Ferenci 2001 *{published data only}*

Ferenci P. Hepatic encephalopathy [Hepatische enzephalopathie]. *Deutsche Medizinische Wochenschrift* 2001;**126**(Suppl 1):S76-80.

Ferenci 2007 *{published data only}*

Ferenci P. Treatment options for hepatic encephalopathy: a review. *Seminars in Liver Disease* 2007;**27**(Suppl 2):10-7.

Feret 2010 *{published data only}*

Feret B, Barner B. Rifaximin: a nonabsorbable, broad-spectrum antibiotic for reduction in the risk for recurrence of overt hepatic encephalopathy. *Formulary* 2010;**45**(7):210-6.

Ferreira 2010 *{published data only}*

Ferreira LG, Anastacio LR, Correia M. The impact of nutrition on cirrhotic patients awaiting liver transplantation. *Current Opinion in Clinical Nutrition and Metabolic Care* 2010;**13**(5):554-61.

Festi 2014 *{published data only}*

Festi D, Schiumerini R, Eusebi LH, Marasco G, Taddia M, Colecchia A. Gut microbiota and metabolic syndrome. World Journal of Gastroenterology 2014; Vol. 20, issue 43:16079-94. [1007-9327]

Finney 2007 *{published data only}*

Finney M, Smullen J, Foster HA, Brokx S, Storey DM. Effects of low doses of lactitol on faecal microflora, pH, short chain fatty acids and gastrointestinal symptomology. *European Journal of Nutrition* 2007;**46**(6):307-14.

Floch 2015 *{published data only}*

Floch MH. Intestinal microbiota metabolism of a prebiotic to treat hepatic encephalopathy. Clinical Gastroenterology and Hepatology 2015; Vol. 13, issue 1:209. [1542-3565]

Fontana 2013 *{published data only}*

Fontana L, Bermudez-Brito M, Plaza-Diaz J, Munoz-Quezada S, Gil A. Sources, isolation, characterisation and evaluation of probiotics. *British Journal of Nutrition* 2013;**109**:S35-50.

Fooladi 2013 *{published data only}*

Fooladi AAI, Hosseini HM, Nourani MR, Khani S, Alavian SM. Probiotic as a novel treatment strategy against liver disease. *Hepatitis Monthly* 2013;**13**(2):e7521.

Foster 2010 *{published data only}*

Foster KJ, Lin S, Turck CJ. Current and emerging strategies for treating hepatic encephalopathy. *Critical Care Nursing Clinics of North America* 2010;**22**(3):341-50.

Fujita 2008 *{published data only}*

Fujita T. Probiotics for patients with liver cirrhosis. *Journal of Hepatology* 2008;**49**(6):1080-1.

Fuster 2007 *{published data only}*

Fuster GO, Gonzalez-Molero I. Probiotics and prebiotics in clinical practice. *Nutricion Hospitilaria* 2007;**22**:26-34.

Galhenage 2006 *{published data only}*

Galhenage S, Almeida J, Yu J, Kurtovic J, Segal I, Riordan SM. Modulation of intestinal flora for the treatment of hepatic encephalopathy in cirrhosis. In: Haussinger D, Kircheis G, Schliess F editor(s). Hepatic Encephalopathy and Nitrogen Metabolism. Dordrecht: Springer, 2006:539-50.

Ganguli 2013 *{published data only}*

Ganguli K, Meng D, Rautava S, Lu L, Walker WA, Nanthakumar N. Probiotics prevent necrotizing enterocolitis by modulating enterocyte genes that regulate innate immune-mediated inflammation. American Journal of Physiology. Gastrointestinal and Liver Physiology 2013; Vol. 304, issue 2:G132-41. [0193-1857]

Garcia 2012 *{published data only}*

Garcia JJ, Rodero GC, Calanas-Continente A. Importance of nutritional support in patients with hepatic encephalopathy. *Nutricion Hospitalaria* 2012;**27**:372-81.

Garcovich 2012 *{published data only}*

Garcovich M, Zocco MA, Roccarina D, Ponziani FR, Gasbarrini A. Prevention and treatment of hepatic encephalopathy: focusing on gut microbiota. *World Journal of Gastroenterology* 2012;**18**:6693-700.

Gareau 2014 *{published data only}*

Gareau MG. Microbiota-gut-brain axis and cognitive function. Advances in Experimental Medicine and Biology. Springer New York LLC, 2014; Vol. 817:357-71. [0065-2598]

Gluud 2013 *{published data only}*

Gluud LL, Dam G, Borre M, Les I, Cordoba J, Marchesini G, et al. Lactulose, rifaximin or branched chain amino acids for hepatic encephalopathy: what is the evidence?. *Metabolic Brain Disease* 2013;**28**:221-5.

Gomez-Hurtado 2014 *{published data only}*

Gomez-Hurtado I, Such J, Sanz Y, Frances R. Gut microbiota-related complications in cirrhosis. World Journal of Gastroenterology 2014; Vol. 20, issue 42:15624-31. [1007-9327]

Grat 2014 *{published data only}*

Grat M, Holowko W, Galecka M, Grat K, Szachta P, Lewandowski Z, et al. Gut microbiota in cirrhotic liver transplant candidates. Hepato-Gastroenterology 2014; Vol. 61, issue 134:1661-7. [0172-6390]

Gratz 2010 *{published data only}*

Gratz SW, Mykkanen H, El-Nezami HS. Probiotics and gut health: a special focus on liver diseases. *World Journal of Gastroenterology* 2010;**16**(4):403-10.

Greco 2007 *{published data only}*

Greco F, Barone G, Gargante MP, Malaguarnera M, Toscano MA. Bifidobacterium longum with fructo-oligosaccharide (FOS) treatment in minimal hepatic encephalopathy: a randomized, double-blind, placebo-controlled study. *Digestive Diseases and Sciences* 2007;**52**(11):3259-65.

Gu 2014 *{published data only}*

Gu L, Yan S, Li D, Wang J, Wang Q. Effect of glutamine combined with probiotics on intestinal mucosal barrier and liver function in patients with liver cirrhosis. Chinese Journal of Gastroenterology 2014; Vol. 19, issue 4:213-6. [1008-7125]

Guarner 2009 *{published data only}*

Guarner F, Khan AG, Garisch J, Eliakim R, Gangl A, Thomson A, et al. World Gastroenterology Organisation practice guideline: probiotics and prebiotics. *Arab Journal of Gastroenterology* 2009;**10**(1):33-42.

Guarner 2012 *{published data only}*

Guarner F, Khan AG, Garisch J, Eliakim R, Gangl A, Thomson A, et al. World Gastroenterology Organisation global guidelines: probiotics and prebiotics October 2011. *Journal of Clinical Gastroenterology* 2012;**46**:468-81.

Guerrero 2008 *{published data only}*

Guerrero HI, Torre DA, Vargas VF, Uribe M. Intestinal flora, probiotics, and cirrhosis. *Annals of Hepatology* 2008;**7**(2):120-4.

Gupta 2010 *{published data only}*

Gupta N, Kumar A, Sharma B, Sarin SK. Addition of probiotics to propranolol improves response for primary prophylaxis of variceal bleeding in patients with cirrhosis and large esophageal varices. Hepatology (Baltimore, Md.) 2010; Vol. 52:1064A. [0270-9139]

Gupta 2010a *{published data only}*

Gupta N, Sarin SK, Sharma BC, Garg V, Kumar A. Addition of probiotics to propranolol improves response for primary prophylaxis of variceal bleeding in patients with cirrhosis and large esophageal varices. Indian Journal of Gastroenterology 2010; Vol. 1:A45. [0254-8860]

Gupta 2013 *{published data only}*

Gupta N, Kumar A, Sharma P, Garg V, Sharma BC, Sarin SK. Effects of the adjunctive probiotic VSL#3 on portal haemodynamics in patients with cirrhosis and large varices: a randomized trial. Liver International 2013; Vol. 33, issue 8:1148-57. [1478-3223]

Hellinger 2002 *{published data only}*

Hellinger WC, Yao JD, Alvarez S, Blair JE, Cawley JJ, Paya CV, et al. A randomized, prospective, double-blinded evaluation of selective bowel decontamination in liver transplantation. Transplantation 2002; Vol. 73, issue 12:1904-9. [0041-1337]

Higashikawa 2010 *{published data only}*

Higashikawa F, Noda M, Awaya T, Nomura K, Oku H, Sugiyama M. Improvement of constipation and liver function by plant-derived lactic acid bacteria: a double-blind, randomized trial. *Nutrition* 2010;**26**(4):367-74.

Holte 2012 *{published data only}*

Holte K, Krag A, Gluud LL. Systematic review and meta-analysis of randomized trials on probiotics for hepatic encephalopathy. *Hepatology Research* 2012;**42**:1008-15.

Hotten 2003 *{published data only}*

Hotten P, Marotta F, Naito Y, Minelli E, Helmy A, Lighthouse J, et al. Effects of probiotics, lactitol and rifaximin on intestinal flora and fecal excretion of organic acids in cirrhotic patients. *Chinese Journal of Digestive Diseases* 2003;**4**(1):13-8.

Hutt 2011 *{published data only}*

Hutt P, Koll P, Stsepetova J, Alvarez B, Mandar R, Krogh-Andersen K, et al. Safety and persistence of orally administered human Lactobacillus sp. strains in healthy adults. *Beneficial Microbes* 2011;**2**:79-90.

Ianiro 2014 *{published data only}*

Ianiro G, Bibbo S, Gasbarrini A, Cammarota G. Therapeutic modulation of gut microbiota: current clinical applications and future perspectives. *Current Drug Targets* 2014;**15**:762-70.

Iannitti 2010 *{published data only}*

Iannitti T, Palmieri B. Therapeutical use of probiotic formulations in clinical practice. *Clinical Nutrition* 2010;**29**(6):701-25.

Imler 1971 *{published data only}*

Imler M, Kurtz D, Bockel R, Stahl J. Comparative study of portocaval encephalopathy treatment with lactulose, lactobacilli and antibiotics [Etude comparative du traitement de l'encephalopathie porto-cave par le lactulose, les bacilles lactiques et les antibiotiques]. *Therapeutique* 1971;**47**(3):237-48.

Ivanovic 2015 *{published data only}*

Ivanovic N, Minic R, Djuricic I, Dimitrijevic L, Sobajic S, Zivkovic I, et al. Brain and liver fatty acid composition changes upon consumption of Lactobacillus rhamnosus LA68. International Journal of Food Sciences and Nutrition 2015; Vol. 66, issue 1:93-7. [0963-7486]

Janczyk 2012 *{published data only}*

Janczyk W, Socha P. Non-alcoholic fatty liver disease in children. *Clinics and Research in Hepatology and Gastroenterology* 2012;**36**:297-300.

Jayakumar 2012 *{published data only}*

Jayakumar S, Tandon P, Bain V, Ma MM, Madsen K, Bailey RJ, et al. Probiotics do not reduce portal pressure in patients with decompensated cirrhosis. Hepatology (Baltimore, Md.) 2012; Vol. 56:744A. [0270-9139]

Jayakumar 2013 *{published data only}*

Jayakumar S, Carbonneau M, Hotte N, Befus AD, St. Laurent C, Owen R, et al. VSL#3 probiotic therapy does not reduce portal pressures in patients with decompensated cirrhosis. Liver International 2013; Vol. 33, issue 10:1470-7. [1478-3223]

Jeejeebhoy 2004 *{published data only}*

Jeejeebhoy KN. Enteral feeding. *Critical Care Medicine* 2004;**20**(2):110-3.

Jiang 2008 *{published data only}*

Jiang CY, Wang BE, Chen D. Protective effect of compound tongfu granule on intestinal mucosal barrier in patients with cirrhosis of decompensation stage. *Chinese Journal of Integrated Traditional and Western Medicine* 2008;**28**(9):784-7.

Jones 2013 *{published data only}*

Jones C, Badger SA, Regan M, Clements BW, Diamond T, Parks RW, et al. Modulation of gut barrier function in patients with obstructive jaundice using probiotic LP299v. European Journal of Gastroenterology & Hepatology 2013; Vol. 25, issue 12:1424-30. [0954-691X]

Jonkers 2007 *{published data only}*

Jonkers D, Stockbrugger R. Review article: probiotics in gastrointestinal and liver diseases. *Alimentary Pharmacology & Therapeutics* 2007;**26**:133-48.

Jover-Cobos 2014 *{published data only}*

Jover-Cobos M, Khetan V, Jalan R. Treatment of hyperammonemia in liver failure. *Current Opinion in Clinical Nutrition and Metabolic Care* 2014;**17**:105-10.

Jun 2013 *{published data only}*

Jun DW, Nam HH, Moon JH, Kim TY, Sohn JH, Koh DH. Randomized clinical trial: Effects of multi-species probiotics on small intestinal bacterial overgrowth in patients with chronic liver disease - a placebo controlled study. Hepatology (Baltimore, Md.) 2013; Vol. 58:867A. [0270-9139]

Jurado 2012 *{published data only}*

Jurado Garcia J, Costan Rodero G, Calanas-Continente A. Importance of nutritional support in patients with hepatic encephalopathy. Nutricion Hospitalaria 2012; Vol. 27, issue 2:372-81. [0212-1611]

Kachaamy 2011 *{published data only}*

Kachaamy T, Bajaj JS. Diet and cognition in chronic liver disease. *Current Opinion in Gastroenterology* 2011;**27**(2):174-9.

Kadayifci 2007 *{published data only}*

Kadayifci A, Merriman RB, Bass NM. Medical treatment of non-alcoholic steatohepatitis. *Clinics in Liver Disease* 2007;**11**(1):119-40.

Karczewski 2010 *{published data only}*

Karczewski J, Troost FJ, Konings I, Dekker J, Kleerebezem M, Brummer RJM, et al. Regulation of human epithelial tight junction proteins by Lactobacillus plantarum in vivo and protective effects on the epithelial barrier. *American Journal of Physiology. Gastrointestinal and Liver Physiology* 2010;**298**(6):G851-9.

Keeffe 2007 *{published data only}*

Keeffe EB. Hepatic encephalopathy. *Seminars in Liver Disease* 2007;**27**(Suppl 2):1-2.

Khungar 2012 *{published data only}*

Khungar V, Poordad F. Hepatic encephalopathy. *Clinics in Liver Disease* 2012;**16**:301-20.

Kirpich 2008 *{published data only}*

Kirpich IA, Solovieva NV, Leikhter SN, Shidakova NA, Lebedeva OV, Sidorov PI, et al. Probiotics restore bowel flora and improve liver enzymes in human alcohol-induced liver injury: a pilot study. Alcohol 2008; Vol. 42, issue 8:675-82.

Kitagawa 2015 *{published data only}*

Kitagawa K, Ishikawa H, Oda T, Saito H, Morishita N, Shimamoto K, et al. Development of combination therapy of bifidobacterium-based oral vaccine displaying HCV-NS3 with interferon-alpha. Molecular Therapy 2015; Vol. 23:S259. [1525-0016]

Koga 2013 *{published data only}*

Koga H, Tamiya Y, Mitsuyama K, Ishibashi M, Matsumoto S, Imaoka A, et al. Probiotics promote rapid-turnover protein production by restoring gut flora in patients with alcoholic liver cirrhosis. Hepatology International 2013; Vol. 7, issue 2:767-74. [1936-0533]

Kremer 1974 *{published data only}*

Kremer H. Intestine and liver-protective therapy [Darm- und Leberschutztherapie]. *Zeitschrift für Allgemeinmedizin* 1974;**50**(28):1252-5.

Kumashiro 2008 *{published data only}*

Kumashiro R. Treatment of minimal hepatic encephalopathy. *Hepatology Research* 2008;**38**(Suppl 1):S128-31.

Kwak 2014 *{published data only}*

Kwak DS, Jun DW, Seo JG, Chung WS, Park S-E, Lee KN, et al. Short-term probiotic therapy alleviates small intestinal bacterial overgrowth, but does not improve intestinal permeability in chronic liver disease. European Journal of Gastroenterology & Hepatology 2014; Vol. 26, issue 12:1353-9. [0954-691X]

Lata 2006 *{published data only}*

Lata J, Jurankova J, Pribramska V, Fric P, Senkyrik M, Dite P, et al. Effect of administration of Escherichia coli Nissle (Mutaflor) on intestinal colonisation, endo-toxemia, liver function and minimal hepatic encephalopathy in patients with liver cirrhosis [Vliv podani Escherichia coli Nissle (Mutaflor) na strevni osidleni, endotoxemii, funkcni stav jater a minimalni jaterni encefalopatii u nemocnych s jaterni cirhozou]. *Vnitrni Lekarstvi* 2006;**52**(3):215-9.

Lata 2007 *{published data only}*

Lata J, Novotny I, Pribramska V, Jurankova J, Fric P, Kroupa R, et al. The effect of probiotics on gut flora, level of endotoxin and Child-Pugh score in cirrhotic patients: results of a double-blind randomized study. *European Journal of Gastroenterology & Hepatology* 2007;**19**(12):1111-3.

Lata 2007a *{published data only}*

Lata J, Jurankova J, Fric P, Pribramska V. The effect of probiotics on gut flora, level of endotoxin and Child-Pugh score in cirrhotic patients - Results of double blind randomized study. Gastroenterology 2007; Vol. 132, issue 4:A797-8. [0016-5085]

Lata 2009 *{published data only}*

Lata J, Jurankova J, Pribramska V. The effects of probiotics on level of endotoxin in patients with liver disease - potential therapy of non alcoholic steatohepatitis?. *Journal of Diabetes* 2009;**1**(Suppl):A150.

Lata 2011 *{published data only}*

Lata J, Jurankova J, Kopacova M, Vitek P. Probiotics in hepatology. *World Journal of Gastroenterology* 2011;**17**:2890-6.

Leber 2012 *{published data only}*

Leber B, Spindelboeck W, Stadlbauer V. Infectious complications of acute and chronic liver disease. *Seminars in Respiratory & Critical Care Medicine* 2012;**33**:80-95.

Liboredo 2015 *{published data only}*

Liboredo JC, Abreu Ferrari MDL, Vilela EG, Lima AS, Toulson Davisson Correia MI. The effect of Saccharomyces boulardii in patients eligible for liver transplantation. Nutricion Hospitalaria 2015; Vol. 31, issue 2:778-84. [0212-1611]

Lien 2015 *{published data only}*

Lien T-H, Bu L-N, Wu J-F, Chen H-L, Chen A-C, Lai M-W, et al. Use of lactobacillus casei rhamnosus to prevent cholangitis in biliary atresia after Kasai operation. Journal of Pediatric Gastroenterology and Nutrition 2015; Vol. 60, issue 5:654-8. [0277-2116]

Lighthouse 2004 *{published data only}*

Lighthouse J, Naito Y, Helmy A, Hotten P, Fuji H, Min CH, et al. Endotoxinemia and benzodiazepine-like substances in compensated cirrhotic patients: a randomized study comparing the effect of rifaximine alone and in association with a symbiotic preparation. *Hepatology Research* 2004;**28**(3):155-60.

Liu 2006 *{published data only}*

Liu JS, Tian Y, Fu J, Zhang XH, Liu J, Lin J. Effects of probiotics agents treatment on the course of subclinical hepatic encephalopathy. Chinese Journal of Postgraduates of Medicine 2006; Vol. 29, issue 1C:12-4.

Liu 2009 *{published data only}*

Liu W. Effect of administration of Medilac-S probiotics on endo-toxemia and hepatic encephalopathy. Chinese Medicine of Factory and Mine 2009; Vol. 22, issue 3:296-7.

Liu 2010 *{published data only}*

Liu JE, Zhang Y, Zhang J, Dong PL, Chen M, Duan ZP. Probiotic yogurt effects on intestinal flora of patients with chronic liver disease. *Nursing Research* 2010;**59**(6):426-32.

Liu 2012 *{published data only}*

Liu J, Wu D, Ahmed A, Li X, Ma Y, Tang L, et al. Comparison of the gut microbe profiles and numbers between patients with liver cirrhosis and healthy individuals. *Current Microbiology* 2012;**65**:7-13.

Llorente 2015 *{published data only}*

Llorente C, Schnabl B. The gut microbiota and liver disease. Cellular and Molecular Gastroenterology and Hepatology 2015; Vol. 1, issue 3:275-84. [2352-345X]

Loguercio 2002 *{published data only}*

Loguercio C, De Simone T, Federico A, Terracciano F, Tuccillo C, Di Chicco M, et al. Gut-liver axis: a new point of attack to treat chronic liver damage?. *American Journal of Gastroenterology* 2002;**97**(8):2144-6.

Loguercio 2005 *{published data only}*

Loguercio C, Federico A, Tuccillo C, Terracciano F, D'Auria MV, De Simone C, et al. Beneficial effects of a probiotic VSL#3 on parameters of liver dysfunction in chronic liver diseases. *Journal of Clinical Gastroenterology* 2005;**39**(6):540-3.

Louvet 2015 *{published data only}*

Louvet A, Mathurin P. Alcoholic liver disease: Mechanisms of injury and targeted treatment. Nature Reviews. Gastroenterology & Hepatology 2015; Vol. 12, issue 4:231-42. [1759-5045]

Lu 2011 *{published data only}*

Lu H, Wu Z, Xu W, Yang J, Chen Y, Li L. Intestinal microbiota was assessed in cirrhotic patients with hepatitis B virus infection. Intestinal microbiota of HBV cirrhotic patients. *Microbial Ecology* 2011;**61**:693-703.

Luna 2010 *{published data only}*

Luna LEM, Fafutis-Morris M, Segura-Ortega JE, Delgado V, Zuniga-Partida V. Prebiotic vs symbiotic to decrease ammonium levels in cirrhotic patients with and without minimal hepatic encephalopathy. Hepatology (Baltimore, Md.) 2010; Vol. 52:919A. [0270-9139]

Lunia 2012 *{published data only}*

Lunia MK, Sachdeva S, Srivastava S, Sharma BC. An open label randomised controlled trial of probiotics for primary prophylaxis of hepatic encephalopathy in patients with cirrhosis. Journal of Gastroenterology and Hepatology 2012; Vol. 27:241. [0815-9319]

Lunia 2014a *{published data only}*

Lunia MK, Sharma BC, Sachdeva S, Srivastava S. An open label randomised controlled trial of probiotics for primary prophylaxis of hepatic encephalopathy in patients with cirrhosis. Journal of Hepatology 2013; Vol. 58:S35. [0168-8278]

Lunia MK, Sharma BC, Sharma P, Sachdeva S, Srivastava S. Probiotics prevent hepatic encephalopathy in patients with cirrhosis: a randomized controlled trial. Clinical Gastroenterology and Hepatology 2014; Vol. 12, issue 6:1003-8.e1. [1542-3565]

Luo 2011 *{published data only}*

Luo M, Li L, Lu CZ, Cao WK. Clinical efficacy and safety of lactulose for minimal hepatic encephalopathy: a meta-analysis. *European Journal of Gastroenterology & Hepatology* 2011;**23**:1250-7.

Ma 2013 *{published data only}*

Ma YY, Li L, Yu CH, Shen Z, Chen LH, Li YM. Effects of probiotics on nonalcoholic fatty liver disease: a meta-analysis. *World Journal of Gastroenterology* 2013;**19**:6911-8.

Machado 2012 *{published data only}*

Machado MV, Cortez-Pinto H. Gut microbiota and nonalcoholic fatty liver disease. *Annals of Hepatology* 2012;**11**:440-9.

Madsen 2008 *{published data only}*

Madsen K. Probiotics in critically ill patients. *Journal of Clinical Gastroenterology* 2008;**42**(8):S116-8.

Malaguarnera 2007 *{published data only}*

Malaguarnera M, Greco F, Barone G, Gargante MP, Malaguarnera M, Toscano MA. Bifidobacterium longum with fructo-oligosaccharide (FOS) treatment in minimal hepatic encephalopathy: a randomized, double-blind, placebo-controlled study. Digestive Diseases and Sciences 2007; Vol. 52, issue 11:3259-65. [CN-00609431]

Malaguarnera 2012 *{published data only}*

Malaguarnera M, Vacante M, Antic T, Giordano M, Chisari G, Acquaviva R, et al. Bifidobacterium longum with fructo-oligosaccharides in patients with non alcoholic steatohepatitis. Digestive Diseases and Sciences 2012; Vol. 57, issue 2:545-53. [0163-2116]

Marteau 2001 *{published data only}*

Marteau P. Prebiotics and probiotics for gastrointestinal health. *Clinical Nutrition* 2001;**20**:41-5.

Marteau 2002 *{published data only}*

Marteau P, Bourton-Ruault MC. Nutritional advantages of probiotics and prebiotics. *British Journal of Nutrition* 2002;**87**(Suppl 2):S153-7.

Marteu 2001 *{published data only}*

Marteu P. Prebiotics and probiotics for gastrointestinal health. *Clinical Nutrition* 2001;**20**(Suppl 1):41-5.

Michelfelder 2010 *{published data only}*

Michelfelder AJ, Lee KC, Bading EM. Integrative medicine and gastrointestinal disease. *Primary Care - Clinics in Office Practice* 2010;**37**(2):255-67.

Minemura 2015 *{published data only}*

Minemura M, Shimizu Y. Gut microbiota and liver diseases. World Journal of Gastroenterology 2015; Vol. 21, issue 6:1691-702. [1007-9327]

Mishra 2012 *{published data only}*

Mishra SK, Mishra P, Saxena M. Probiotics: an approach for better treatment. *Research Journal of Pharmaceutical, Biological and Chemical Sciences* 2012;**3**:1042-61.

Mohammad 2012 *{published data only}*

Mohammad RA, Regal RE, Alaniz C. Combination therapy for the treatment and prevention of hepatic encephalopathy. *Annals of Pharmacotherapy* 2012;**46**:1559-63.

Montagnese 2012 *{published data only}*

Montagnese S, Amodio P, Angeli P. What type of probiotic was used?. *European Journal of Gastroenterology & Hepatology* 2012;**24**:471-2.

Montgomery 2011 *{published data only}*

Montgomery JY, Bajaj JS. Advances in the evaluation and management of minimal hepatic encephalopathy. *Current Gastroenterology Reports* 2011;**13**(1):26-33.

Montrose 2005 *{published data only}*

Montrose DC, Floch MH. Probiotics used in human studies. *Journal of Clinical Gastroenterology* 2005;**39**(6):469-84.

Moreno-Luna 2011 *{published data only}*

Moreno-Luna LE, Fafutis-Morris M, Delgado Rizo V, Zuniga V, Segura-Ortega JE. Oral supplementation of symbiotic to decrease ammonium levels in cirrhotic patients with or without minimal hepatic encephalopathy. *Hepatology International* 2011;**5**(1):346.

Morgan 2007 *{published data only}*

Morgan MY, Blei A, Grungreiff K, Jalan R, Kircheis G, Marchesini G, et al. The treatment of hepatic encephalopathy. *Metabolic Brain Disease* 2007;**22**(3-4):389-405.

Mullen 2007 *{published data only}*

Mullen KD, Ferenci P, Bass NM, Leevy CB, Keeffe EB. An algorithm for the management of hepatic encephalopathy. *Seminars in Liver Disease* 2007;**27**(Suppl 2):32-47.

Nabavi 2014 *{published data only}*

Nabavi S, Rafraf M, Somi MH, Homayouni-Rad A, Asghari-Jafarabadi M. Effects of probiotic yogurt consumption on metabolic factors in individuals with nonalcoholic fatty liver disease. Journal of Dairy Science 2014; Vol. 97, issue 12:7386-93. [0022-0302]

Nazir 2010 *{published data only}*

Nazir S, Lau K, Sindram D, Martinie J, Asarian A, Iannitti D. Secondary prophylaxis of hepatic encephalopathy in cirrhosis: an open label, randomized controlled trial of lactulose, probiotics and no-therapy. *American Congress of Gastroenterology* 2010;**105**:282.

NCT01135628 *{published data only}*

NCT01135628. Hyperproteic and fiber-rich diet plus probiotics (lactobacillus reuteri) and nitazoxanide in the treatment of minimal hepatic encephalopathy. clinicaltrials.gov/ct2/show/NCT01135628 (first received 26 May 2010).

Olveira 2007 *{published data only}*

Olveira Fuster G, Gonzalez-Molero I. Probiotics and prebiotics in clinical practice. Nutricion Hospitalaria 2007; Vol. 22:26-34. [0212-1611]

Oshea 2010 *{published data only}*

Oshea RS, Dasarathy S, McCullough AJ. Alcoholic liver disease. *American Journal of Gastroenterology* 2010;**105**(1):14-32.

Pande 2009 *{published data only}*

Pande C, Kumar A, Sarin SK. Addition of probiotics to antibiotics does not improve its efficacy in prevention of spontaneous bacterial peritonitis: a double blind placebo-controlled randomized controlled trial. *Hepatology (Baltimore, Md.)* 2009;**50**(4 Suppl):454A.

Pande 2012 *{published data only}*

Pande C, Kumar A, Sarin SK. Addition of probiotics to norfloxacin does not improve efficacy in the prevention of spontaneous bacterial peritonitis: A double-blind placebo-controlled randomized-controlled trial. European Journal of Gastroenterology & Hepatology 2012; Vol. 24, issue 7:831-9. [0954-691X]

Paolella 2014 *{published data only}*

Paolella G, Mandato C, Pierri L, Poeta M, Di Stasi M, Vajro P. Gut-liver axis and probiotics: their role in non-alcoholic fatty liver disease. World Journal of Gastroenterology 2014; Vol. 20, issue 42:15518-31. [1007-9327]

Park 2007 *{published data only}*

Park J, Floch MH. Prebiotics, probiotics, and dietary fiber in gastrointestinal disease. *Gastroenterology Clinics of North America* 2007;**36**(1):47-63.

Patel 2015 *{published data only}*

Patel R, Dupont HL. New approaches for bacteriotherapy: prebiotics, new-generation probiotics, and synbiotics. Clinical Infectious Diseases 2015; Vol. 60:S108-21. [1058-4838]

Pawar 2012 *{published data only}*

Pawar R, Pardeshi M, Ghongane B. Study of effects of probiotic lactobacilli in preventing major complications in patients of liver cirrhosis. International Journal of Research in Pharmaceutical and Biomedical Sciences 2012; Vol. 3, issue 1:206-11.

Phongsamran 2010 *{published data only}*

Phongsamran PV, Kim JW, Cupo Abbott J, Rosenblatt A. Pharmacotherapy for hepatic encephalopathy. *Drugs* 2010;**70**(9):1131-48.

Plaza-Diaz 2014 *{published data only}*

Plaza-Diaz J, Gomez-Llorente C, Abadia-Molina F, Saez-Lara MJ, Campana-Martin L, Munoz-Quezada S, et al. Effects of Lactobacillus paracasei CNCM I-4034, Bifidobacterium breve CNCM I-4035 and Lactobacillus rhamnosus CNCM I-4036 on hepatic steatosis in zucker rats. PLoS ONE 2014; Vol. 9, issue 5:9. [1932-6203]

Poh 2012 *{published data only}*

Poh Z, Chang PEJ. A current review of the diagnostic and treatment strategies of hepatic encephalopathy. *International Journal of Hepatology* 2012;**2012**:480309.

Poustchi 2013 *{published data only}*

Poustchi H, Eslamparast T, Zamani F, Sharafkhah M, Eghtesad S, Malekzadeh R, et al. Effects of synbiotic supplementation on nonalcoholic fatty liver disease. Journal of Gastroenterology and Hepatology 2013; Vol. 28:850-1. [0815-9319]

Prakash 2013 *{published data only}*

Prakash RK, Kanna S, Mullen KD. Evolving concepts: the negative effect of minimal hepatic encephalopathy and role for prophylaxis in patients with cirrhosis. *Clinical Therapeutics* 2013;**35**:1458.

Quigley 2006 *{published data only}*

Quigley EMM, Quera R. Small intestinal bacterial overgrowth: roles of antibiotics, prebiotics, and probiotics. *Gastroentrology* 2006;**130**(2):S78-90.

Quigley 2013 *{published data only}*

Quigley EMM, Stanton C, Murphy EF. The gut microbiota and the liver. Pathophysiological and clinical implications. *Journal of Hepatology* 2013;**58**:1020-7.

Quigley 2014 *{published data only}*

Quigley EMM. Commentary: Probing probiotics in cirrhosis - A template for future studies?. *Alimentary Pharmacology & Therapeutics* 2014;**39**:1334-5.

Quigley 2014a *{published data only}*

Quigley EMM, Shanahan F. The future of probiotics for disorders of the brain-gut axis. *Advances in Experimental Medicine and Biology* 2014;**817**:417-32. [978-1-4939-0896-7; 978-1-4939-0897-4]

Rahimi 2012 *{published data only}*

Rahimi RS, Rockey DC. Complications of cirrhosis. *Current Opinion in Gastroenterology* 2012;**28**:223-9.

Rahimi 2013 *{published data only}*

Rahimi RS, Rockey DC. End-stage liver disease complications. *Current Opinion in Gastroenterology* 2013;**29**:257-63.

Rayes 2001 *{published data only}*

Rayes N, Brammer M, Hansen S, Mueller AR, Serke S, Seehofer D, et al. Early enteral supply of lactobacilli and fibre versus SBD - A prospective randomised trial in liver transplant recipients. Journal of Hepatology 2001; Vol. 34:199. [0168-8278]

Rayes 2002 *{published data only}*

Rayes N, Seehofer D, Hansen S, Boucsein K, Muller AR, Serke S, et al. Early enteral supply of Lactobacillus and fiber versus selective bowel decontamination: a controlled trial in liver transplant recipients. *Transplantation* 2002;**74**(1):123-8.

Rayes 2005 *{published data only}*

Rayes N, Seehofer D, Theruvath T, Schiller RA, Langrehr JM, Jonas S, et al. Supply of pre- and probiotics reduces bacterial infection rates after liver transplantation - A randomized, double-blind trial. American Journal of Transplantation 2005; Vol. 5, issue 1:125-30. [1600-6135]

Rayes 2012 *{published data only}*

Rayes N, Pilarski T, Stockmann M, Bengmark S, Neuhaus P, Seehofer D. Effect of pre- and probiotics on liver regeneration after resection: a randomised, double-blind pilot study. Beneficial Microbes 2012; Vol. 3, issue 3:237-44.

Read 1966 *{published data only}*

Read AE, McCarthy CF, Heaton KW, Laidlaw J. Lactobacillus acidophilus (Enpac) in treatment of hepatic encephalopathy. *British Medical Journal* 1966;**1**(5498):1267-9.

Reddy 2013 *{published data only}*

Reddy VS, Patole SK, Rao S. Role of probiotics in short bowel syndrome in infants and children - a systematic review. *Nutrients* 2013;**5**:679-99.

Rifatbegovic 2010 *{published data only}*

Rifatbegovic Z, Mesic D, Ljuca F, Zildzic M, Avdagic M, Grbic K, et al. Effect of probiotics on liver function after surgery resection for malignancy in the liver cirrhotic. Medicinski Arhiv 2010; Vol. 64, issue 4:208-11.

Riggio 2009 *{published data only}*

Riggio O, Ridola L. Emerging drugs for hepatic encephalopathy. *Expert Opinion on Emerging Drugs* 2009;**14**(3):537-49.

Rincon 2014 *{published data only}*

Rincon D, Vaquero J, Hernando A, Galindo E, Ripoll C, Puerto M, et al. Oral probiotic VSL#3 attenuates the circulatory disturbances of patients with cirrhosis and ascites. Liver International 2014; Vol. 34, issue 10:1504-12. [1478-3223]

Riordan 2007 *{published data only}*

Riordan SM, Skinner NA, McIver CJ, Liu Q, Bengmark S, Bihari D, et al. Synbiotic-associated improvement in liver function in cirrhotic patients: relation to changes in circulating cytokine messenger RNA and protein levels. *Microbial Ecology in Health and Disease* 2007;**19**(1):7-16.

Riordan 2010 *{published data only}*

Riordan SM, Williams R. Gut flora and hepatic encephalopathy in patients with cirrhosis. *New England Journal of Medicine* 2010;**362**(12):1140-2.

Rivkin 2011 *{published data only}*

Rivkin A, Gim S. Rifaximin: new therapeutic indication and future directions. *Clinical Therapeutics* 2011;**33**:812-27.

Romero-Gomez 2010 *{published data only}*

Romero-Gomez M. Pharmacotherapy of hepatic encephalopathy in cirrhosis. *Expert Opinion on Pharmacotherapy* 2010;**11**(8):1317-27.

Sanchez 2015 *{published data only}*

Sanchez E, Nieto JC, Boullosa A, Vidal S, Sancho FJ, Rossi G, et al. VSL#3 probiotic treatment decreases bacterial translocation in rats with carbon tetrachloride-induced cirrhosis. Liver International 2015; Vol. 35, issue 3:735-45. [1478-3223]

Scevola 1989 *{published data only}*

Scevola D, Zambelli A, Concia E, Perversi L, Candiani C. Lactitol and neomycin: monotherapy or combined therapy in the prevention and treatment of hepatic encephalopathy? [Lattitolo e neomicina: monoterapia o terapia combinata nella prevenzione e nel trattamento dell'encefalopatia epatica?]. *Clinica Terapeutica* 1989;**129**(2):105-11.

Schiano 2010 *{published data only}*

Schiano TD. Treatment options for hepatic encephalopathy. *Pharmacotherapy* 2010;**30**(5 pt 2):16S-21S.

Schuster-Wolff-Bühring 2010a *{published data only}*

Schuster-Wolff-Bühring R, Fischer L, Hinrichs J. Production and physiological action of the disaccharide lactulose. International Dairy Journal 2010; Vol. 20, issue 11:731-41. [0958-6946]

Schuster-Wolff-Bühring 2010b *{published data only}*

Schuster-Wolff-Bühring R, Fischer L, Hinrichs J. Production and physiological action of the disaccharide lactulose. *International Dairy Journal* 2010;**20**:731-41.

Segura-Ortega 2010 *{published data only}*

Segura-Ortega JE, Moreno-Luna LE, Delgado V, Zuniga-Partida V, Fafutis-Morris M. Decrease in ammonium levels and increase in the neutrophils phagocytic capacity in cirrhotic patients after the ingestion of agave inulin and a probiotic mixture of bifidobacterias and lactobillus. Hepatology (Baltimore, Md.) 2010; Vol. 52:917A. [0270-9139]

Shang 2013 *{published data only}*

Shang XJ. Effect of treatment with compound Lactobacillus acidophilus on complements and T lymphocyte subsets in patients with compensated liver cirrhosis. World Chinese Journal of Digestology 2013; Vol. 21, issue 24:2446-50. [1009-3079]

Sharma 2010 *{published data only}*

Sharma BC. Minimal hepatic encephalopathy. Hepatology International 2010; Vol. 4, issue 1:46. [1936-0533]

Sharma 2012 *{published data only}*

Sharma P, Sharma BC, Agrawal A, Sarin SK. Primary prophylaxis of overt hepatic encephalopathy in patients with cirrhosis: an open labelled randomized controlled trial of lactulose versus no lactulose. *Journal of Gastroenterology and Hepatology* 2012;**27**:1329-35.

Sharma 2013 *{published data only}*

Sharma P, Sharma BC. Disaccharides in the treatment of hepatic encephalopathy. *Metabolic Brain Disease* 2013;**28**:313-20.

Sharma 2014a *{published data only}*

Sharma M, Bhat S, Dutt K, Sharma P, Bhat JA. Randomized controlled trial of lactulose and lactulose plus probiotics in the treatment of minimal hepatic encephalopathy. Journal of Evidence Based Medicine and Healthcare 2014; Vol. 1, issue 9:1125-36.

Sharma 2014b *{published data only}*

Sharma P, Sharma BC. A survey of patterns of practice and perception of minimal hepatic encephalopathy: a nationwide survey in India. Saudi Journal of Gastroenterology 2014; Vol. 20, issue 5:304-8. [1319-3767]

Sharma 2015 *{published data only}*

Sharma BC, Maharshi S. Prevention of hepatic encephalopathy recurrence. Clinical Liver Disease 2015; Vol. 5, issue 3:64-7. [2046-2484]

Shawcross 2005 *{published data only}*

Shawcross D, Jalan R. Dispelling myths in the treatment of hepatic encephalopathy. *Lancet* 2005;**365**(9457):431-3.

Shen 2013 *{published data only}*

Shen Z, Ma L, Zhang W, Gao S. Curative effect observation of lactobacillus acidophilus complex combined fiberform in treatment of hepatic encephalopathy. Chinese Journal of Microecology 2013; Vol. 25:679-81.

Shen 2014 *{published data only}*

Shen Z, Ma L, Zhang WH. Effects of micro-ecological agents on intestinal flora and blood ammonia of patients with hepatic encephalopathy. *Chinese Journal of Nosocomiology* 2014;**10**:2505-7.

Sheth 2008 *{published data only}*

Sheth AA, Garcia-Tsao G. Probiotics and liver disease. *Journal of Clinical Gastroenterology* 2008;**42**(6):S80-4.

Shu 2008 *{published data only}*

Shu M, Che YG. Curative effects of bacillus licheniformis capsule on course of subclinical hepatic encephalopathy. Chinese Journal of General Practice 2008; Vol. 16:1119-20.

Shukla 2009 *{published data only}*

Shukla S, Leisner E, Guha S, Mehboob S. Effects of use of probiotics in minimal hepatic encephalopathy: a meta-analysis of randomized controlled trials. *American Journal of Gastroenterology* 2009;**104**:385.

Shukla 2010 *{published data only}*

Shukla S, Sampath PK, Shukla A, Guha S, Mehboob S. Comparison of probiotics and lactulose as treatment options in hepatic encephalopathy: a meta-analysis. *Gastroenterology* 2010;**1**:S818.

Shukla 2010a *{published data only}*

Shukla S, Sampath PK, Shukla A, Guha S, Mehboob S. Use of prebiotics, probiotics and synbiotics in treatment of minimal hepatic encephalopathy: a meta-analysis. *Gastroenterology* 2010;**1**:S777.

Shukla 2011 *{published data only}*

Shukla S, Shukla A, Mehboob S, Guha S. Meta-analysis: the effects of gut flora modulation using prebiotics, probiotics and synbiotics on minimal hepatic encephalopathy. *Alimentary Pharmacology & Therapeutics* 2011;**33**(6):662-71.

Solga 2003 *{published data only}*

Solga SF. Probiotics can treat hepatic encephalopathy. *Medical Hypotheses* 2003;**61**(2):307-13.

Soriano 2013 *{published data only}*

Soriano G, Guarner C. Probiotics in cirrhosis: do we expect too much?. *Liver International* 2013;**33**:1451-3.

Soriano 2013a *{published data only}*

Soriano G, Sanchez E, Guarner C. Probiotics in liver diseases. *Nutricion Hospitalaria* 2013;**28**:558-63.

Stadlbauer 2008 *{published data only}*

Stadlbauer V, Mookerjee RP, Hodges S, Wright GAK, Davies NA, Jalan R. Effect of probiotic treatment on deranged neutrophil function and cytokine responses in patients with compensated alcoholic cirrhosis. *Journal of Hepatology* 2008;**48**(6):945-51.

Stewart 2007 *{published data only}*

Stewart CA, Smith GE. Minimal hepatic encephalopathy. *Nature Clinical Practice. Gastroenterology & Hepatology* 2007;**4**(12):677-85.

Strasser 2011 *{published data only}*

Strasser SI, Vidot H. Nutritional considerations in end-stage liver disease. *Journal of Gastroenterology and Hepatology* 2011;**26**:1346-8.

Suk 2012 *{published data only}*

Suk KT, Sohn KM, Kim YD, Cheon GJ, Choi DH, Kim MY, et al. Effect of probiotics (cultured lactobacillus subtilis/ streptococcus faecium) in the treatment of alcoholic hepatitis: randomized controlled multicenter study. Hepatology (Baltimore, Md.) 2012; Vol. 56:590A. [0270-9139]

Sundaram 2009 *{published data only}*

Sundaram V, Shaikh OS. Hepatic encephalopathy: pathophysiology and emerging therapies. *Medical Clinics of North America* 2009;**93**(4):819-36.

Tang 2011 *{published data only}*

Tang SH, Wang KJ, Wu XJ, Zhang MM. Efficacy of probiotics in the treatment of minimal hepatic encephalopathy: a meta analysis. *World Chinese Journal of Digestology* 2011;**19**:2587-92.

Tapper 2015 *{published data only}*

Tapper EB, Jiang G, Patwardhan VR. Refining the ammonia hypothesis: a physiology-driven approach to the treatment of hepatic encephalopathy. Mayo Clinic Proceedings 2015; Vol. 90, issue 5:646-58. [0025-6196]

Tarantino 2015 *{published data only}*

Tarantino G, Finelli C. Systematic review on intervention with prebiotics/probiotics in patients with obesity-related nonalcoholic fatty liver disease. Future Microbiology 2015; Vol. 10, issue 5:889-902. [1746-0913]

Tarao 1995 *{published data only}*

Tarao K, Tamai S, Ito Y, Okawa S, Hayashi M. Effects of lactitol on fecal bacterial flora in patients with liver cirrhosis and hepatic encephalopathy. *Nippon Shokakibyo Gakkai Zasshi* 1995;**92**(7):1037-50.

Tojo 2014 *{published data only}*

Tojo R, Suarez A, Clemente MG, de los Reyes-Gavilan CG, Margolles A, Gueimonde M, et al. Intestinal microbiota in health and disease: role of bifidobacteria in gut homeostasis. World Journal of Gastroenterology 2014; Vol. 20, issue 41:15163-76. [1007-9327]

Toris 2011 *{published data only}*

Toris GT, Bikis CN, Tsourouflis GS, Theocharis SE. Hepatic encephalopathy: an updated approach from pathogenesis to treatment. *Medical Science Monitor* 2011;**17**(2):RA53-63.

Tsochatzis 2012 *{published data only}*

Tsochatzis EA, Bosch J, Burroughs AK. New therapeutic paradigm for patients with cirrhosis. *Hepatology (Baltimore, Md.)* 2012;**56**:1983-92.

Tsochatzis 2014 *{published data only}*

Tsochatzis EA, Bosch J, Burroughs AK. Future treatments of cirrhosis. *Expert Review of Gastroenterology & Hepatology* 2014;**8**:571-81.

Upadhyay 2012 *{published data only}*

Upadhyay N, Moudgal V. Probiotics: a review. *Journal of Clinical Outcomes Management* 2012;**19**:76-84.

Usami 2011 *{published data only}*

Usami M, Miyoshi M, Kanbara Y, Aoyama M, Sakaki H, Shuno K, et al. Effects of perioperative synbiotic treatment on infectious complications, intestinal integrity, and fecal flora and organic acids in hepatic surgery with or without cirrhosis. Journal of Parenteral and Enteral Nutrition 2011; Vol. 35, issue 3:317-28. [0148-6071]

Valentini 2015 *{published data only}*

Valentini L, Pinto A, Bourdel-Marchasson I, Ostan R, Brigidi P, Turroni S, et al. Impact of personalized diet and probiotic supplementation on inflammation, nutritional parameters and intestinal microbiota - The "RISTOMED project": Randomized controlled trial in healthy older people. Clinical Nutrition 2015; Vol. 34, issue 4:593-602. [0261-5614]

Videhult 2015 *{published data only}*

Videhult FK, Ohlund I, Stenlund H, Hernell O, West CE. Probiotics during weaning: a follow-up study on effects on body composition and metabolic markers at school age. European Journal of Nutrition 2015; Vol. 54, issue 3:355-63. [1436-6207]

Vilstrup 2014 *{published data only}*

Vilstrup H, Amodio P, Bajaj J, Cordoba J, Ferenci P, Mullen KD, et al. Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. *Hepatology (Baltimore, Md.)* 2014;**60**:715-35.

Vilstrup 2014a *{published data only}*

Vilstrup H, Amodio P, Bajaj J, Ferenci P, Mullen KD, Weissenborn K, et al. Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases. Journal of Hepatology 2014; Vol. 61, issue 3:642-59. [0168-8278]

Vyas 2012 *{published data only}*

Vyas U, Ranganathan N. Probiotics, prebiotics, and synbiotics: gut and beyond. *Gastroenterology Research and Practice* 2012;**2012**:872716.

Waghray 2014 *{published data only}*

Waghray A, Waghray N, Kanna S, Mullen K. Optimal treatment of hepatic encephalopathy. *Minerva Gastroenterologica e Dietologica* 2014;**60**:55-70.

Waghray 2015 *{published data only}*

Waghray A, Waghray N, Mullen K. Management of covert hepatic encephalopathy. Journal of Clinical and Experimental Hepatology 2015; Vol. 5, issue S1:S75-81. [0973-6883]

Wang 2012 *{published data only}*

Wang XY, Qu CM, Liang SW, Cao YJ, Li LY, Zhong CQ, et al. Efficacy analysis on treatment of subclinical hepatic encephalopathy by live combined bacillus subtilis and enterococcus faecium enteric-coated capsules. Progress in Modern Biomedicine 2012; Vol. 12:6489-91.

Wang 2015 *{published data only}*

Wang WF, Cao JB, Xiong JH, Guo HB, Ma L, Chen LQ. Effect of probiotics in improvement of minimal hepatic encephalopathy in cirrhosis patients with hepatitis B virus. *Medical & Pharmaceutical Journal of Chinese People's Liberation Army* 2015;**2**:17-20.

Welliver 2012 *{published data only}*

Welliver M. Improving treatments for hepatic encephalopathy. *Gastroenterology Nursing* 2012;**35**:291-2.

Wong 2013a *{published data only}*

Wong VWS, Wong GLH, Chim AML, Chu WCW, Yeung DKW, Li KCT, et al. Treatment of nonalcoholic steatohepatitis with probiotics. A proof-of-concept study. Annals of Hepatology 2013; Vol. 12, issue 2:256-62. [1665-2681]

Woo 2012 *{published data only}*

Woo GA, O'Brien C. Long-term management of alcoholic liver disease. *Clinics in Liver Disease* 2012;**16**:763-81.

Wright 2007 *{published data only}*

Wright G, Jalan R. Management of hepatic encephalopathy in patients with cirrhosis. *Best Practice and Research in Clinical Gastroenterology* 2007;**21**(1):95-110.

Wu 2008 *{published data only}*

Wu WC, Zhao W, Li S. Small intestinal bacteria overgrowth decreases small intestinal motility in the NASH rats. *World Journal of Gastroenterology* 2008;**14**(2):313-7.

Xu 2012 *{published data only}*

Xu M, Wang B, Fu Y, Chen Y, Yang F, Lu H, et al. Changes of fecal Bifidobacterium species in adult patients with hepatitis B virus-induced chronic liver disease. *Microbial Ecology* 2012;**63**:304-13.

Xu 2014 *{published data only}*

Xu J, Ma R, Chen L-F, Zhao L-J, Chen K, Zhang R-B. Effects of probiotic therapy on hepatic encephalopathy in patients with liver cirrhosis: an updated meta-analysis of six randomized controlled trials. *Hepatobiliary & Pancreatic Diseases International* 2014;**13**:354-60.

Xu 2014a *{published data only}*

Xu M, Chang B, Mathews S, Gao B. New drug targets for alcoholic liver disease. Hepatology International 2014; Vol. 8, issue 2:475-80. [1936-0533]

Yakabe 2009 *{published data only}*

Yakabe T, Moore EL, Yokota S, Sui H, Nobuta Y, Fukao M, et al. Safety assessment of Lactobacillus brevis KB290 as a probiotic strain. *Food and Chemical Toxicology* 2009;**47**(10):2450-3.

Yao 2014 *{published data only}*

Yao XM, Qu JG, Lin AB, Li HW. Effect of probiotics on non-alcoholic fatty liver disease. Journal of International Pharmaceutical Research 2014; Vol. 41, issue 5:548-51. [1674-0440]

Yasutake 2012 *{published data only}*

Yasutake K, Kohjima M, Nakashima M, Kotoh K, Nakamuta M, Enjoji M. Nutrition therapy for liver diseases based on the status of nutritional intake. *Gastroenterology Research and Practice* 2012;**2012**:859697.

Zafirova 2010 *{published data only}*

Zafirova Z, O'Connor M. Hepatic encephalopathy: current management strategies and treatment, including management and monitoring of cerebral edema and intracranial hypertension in fulminant hepatic failure. *Current Opinion in Anaesthesiology* 2010;**23**(2):121-7.

Zamberlin 2012 *{published data only}*

Zamberlin S, Spehar ID, Kelava N, Samarzija D. Probiotic bacterium Lactobacillus rhamnosus: beneficial and adverse effects on human health. *Milchwissenschaft - Milk Science International* 2012;**67**:30-3.

Zhang 2014 *{published data only}*

Zhang M, Fang T, Zhang J, Yu C. Efficacy of probiotics in treating liver cirrhosis: a meta analysis. *Chinese Journal of Gastroenterology* 2014;**19**:25-31.

Zhao 2004 *{published data only}*

Zhao HY, Wang HJ, Lu Z, Xu SZ. Intestinal microflora in patients with liver cirrhosis. *Chinese Journal of Digestive Diseases* 2004;**5**(2):64-7.

Zucker 2014 *{published data only}*

Zucker D, Redulla R. Optimal medical management of minimal hepatic encephalopathy: a systematic review protocol. *JBI Database of Systematic Reviews and Implementation Reports* 2014;**12**(6):49-59. [2202-4433]

References to studies awaiting assessment

ACTRN12610001021066 *{published data only}*

ACTRN12610001021066. The effects of synbiotics, branched chain amino acids on hepatic encephalopathy. apps.who.int/trialsearch/Trial2.aspx?TrialID=ACTRN12610001021066 (irst recieved 22 November 2010).

IRCT201211012417N9 *{published data only}*

IRCT201211012417N9. Effects of probiotics on the level of consciousness in patients with hepatic encephalopathy. apps.who.int/trialsearch/Trial2.aspx?TrialID=IRCT201211012417N9 (first received 24 November 2012).

NCT01798329 *{published data only}*

NCT01798329. Minimal hepatic encephalopathy in childhood and young adult: epidemiological study and pilot interventional study. clinicaltrials.gov/ct2/show/NCT01798329 (first recieved 19 February 2013).

Additional references

Allampati 2015

Allampati S, Mullen KD. Nomenclature and definition of hepatic encephalopathy - An update. Clinical Liver Disease 2015; Vol. 5, issue 3:68-70. [2046-2484]

Als-Nielsen 2003

Als-Nielsen B, Koretz RL, Gluud LL, Gluud C. Branched-chain amino acids for hepatic encephalopathy. *Cochrane Database of Systematic Reviews* 2003, Issue 1. [DOI: 10.1002/14651858.CD001939]

Als-Nielsen 2004a

Als-Nielsen B, Gluud LL, Gluud C. Benzodiazepine receptor antagonists for hepatic encephalopathy. *Cochrane Database of Systematic Reviews* 2004, Issue 2. [DOI: 10.1002/14651858.CD002798.pub2]

Als-Nielsen 2004b

Als-Nielsen B, Gluud LL, Gluud C. Nonabsorbable disaccharides for hepatic encephalopathy. *Cochrane Database of Systematic Reviews* 2004, Issue 2. [DOI: 10.1002/14651858.CD003044.pub2]

Als-Nielsen 2004c

Als-Nielsen B, Gluud LL, Gluud C. Dopaminergic agonists for hepatic encephalopathy. *Cochrane Database of Systematic Reviews* 2004, Issue 4. [DOI: 10.1002/14651858.CD003047.pub2]

Altman 1996

Altman DG, Bland JM. Comparing several groups using analysis of variance. *BMJ (Clinical Research Ed.)* 1996;**312**:1472-3.

Arguedas 2003

Arguedas MR, DeLawrence TG, McGuire BM. Influence of hepatic encephalopathy on health-related quality of life in patients with cirrhosis. *Digestive Diseases and Sciences* 2003;**48**:1622-6.

Bajaj 2011

Bajaj JS, Cordoba J, Mullen KD, Amodio P, Shawcross DL, Butterworth RF, et al. Review article: the design of clinical trials in hepatic encephalopathy – an International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) consensus statement. *Alimentary Pharmacology & Therapeutics* 2011;**33**(7):739-47.

Bass 2010

Bass NM, Mullen KD, Sanyal A, Poordad F, Neff G, Leevy CB, et al. Rifaximin treatment in hepatic encephalopathy. New England Journal of Medicine 2010; Vol. 362, issue 12:1071-81. [0028-4793]

Besselink 2008

Besselink MGH, van Santvoort HC, Buskens E, Boermeester MA, van Goor H, Timmerman HM, et al. Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial. *Lancet* 2008;**371**(9613):651-9.

Blei 2001

Blei AT, Córdoba J. Hepatic encephalopathy. *American Journal of Gastroenterology* 2001;**96**:1968-76.

Brazier 1992

Brazier JE, Harper R, Jones NMB, O'Cathain A, Thomas KJ, Usherwood T, et al. Validating the SF-36® Health Survey Questionnaire: new outcome measure for primary care. *BMJ (Clinical Research Ed.)* 1992;**305**:160-4.

Butterworth 1987

Butterworth RF, Giguère JF, Michaud J, Lavoie J, Layrargues GP. Ammonia: key factor in the pathogenesis of hepatic encephalopathy. *Molecular and Chemical Neuropathology* 1987;**6**:1-12.

Conn 1977

Conn H, Leevy C, Vlahcevic Z, Rodgers J, Maddrey W, Seeff L, et al. Comparison of lactulose and neomycin in the treatment of chronic portal-systemic encephalopathy. A double blind controlled trial. Gastroenterology 1977; Vol. 72, issue 4 (Pt 1):573-83. [0016-5085]

De Preter 2006

De Preter V, Vanhoutte T, Huys G, Swings J, Rutgeerts P, Verbeke K. Effect of lactulose and Saccharomyces boulardii administration on the colonic urea-nitrogen metabolism and the bifidobacteria concentration in healthy human subjects. Alimentary Pharmacology & Therapeutics 2006; Vol. 23, issue 7:963-74. [0269-2813: (Print)]

Ferenci 2002

Ferenci P, Lockwood A, Mullen K, Tarter R, Weissenborn K, Blei AT. Hepatic encephalopathy - Definition, nomenclature, diagnosis, and quantification: final report of the Working Party at the 11th World Congress of Gastroenterology, Vienna, 1998. *Hepatology (Baltimore, Md.)* 2002;**35**:716-21.

Gluud 2015

Gluud LL, Dam G, Les I, Córdoba J, Marchesini G, Borre M, et al. Branched-chain amino acids for people with hepatic encephalopathy. *Cochrane Database of Systematic Reviews* 2015, Issue 9. [DOI: 10.1002/14651858.CD001939.pub3]

Gluud 2016

Gluud C, Nikolova D, Klingenberg SL. Cochrane Hepato-Biliary Group. About Cochrane (Cochrane Review Groups (CRGs)) 2016, Issue 5. Art. No.: LIVER.

GRADEpro [Computer program]

Brozek J, Oxman A, Schünemann H. GRADEpro. Version 3.2 for Windows. Grade Working Group 2004-2007, 2008.

Groeneweg 1998

Groeneweg M, Quero JC, De Bruijn I, Hartmann IJC, Essink-bot M, Hop WCJ, et al. Subclinical hepatic encephalopathy impairs daily functioning. *Hepatology (Baltimore, Md.)* 1998;**28**:45-9.

Higgins 2011

Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

ICH-GCP 1997

International Conference on Harmonisation Expert Working Group. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use. ICH harmonised tripartite guideline. Guideline for good clinical practice CFR & ICH Guidelines. Vol. **1**, Philadelphia (PA): Barnett International/PAREXEL, 1997.

Jiang 2009

Jiang Q, Jiang XH, Zheng MH, Chen YP. l ornithine l aspartate in the management of hepatic encephalopathy: a meta analysis. *Journal of Gastroenterology and Hepatology* 2009;**24**(1):9-14.

Junker 2014

Junker AE, Als-Nielsen B, Gluud C, Gluud LL. Dopamine agents for hepatic encephalopathy. *Cochrane Database of Systematic Reviews* 2014, Issue 2. [DOI: 10.1002/14651858.CD003047.pub3]

Kjaergard 2001

Kjaergard LL, Villumsen J, Gluud C. Reported methodologic quality and discrepancies between large and small randomized trials in meta-analyses. *Annals of Internal Medicine* 2001;**135**(11):982-9.

Lefebvre 2011

Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Lundh 2012

Lundh A, Sismondo S, Lexchin J, Busuioc OA, Bero L. Industry sponsorship and research outcome. *Cochrane Database of Systematic Reviews* 2012, Issue 12. [DOI: 10.1002/14651858.MR000033.pub2]

McGee 2010

McGee R, O'Connor PM, Russell D, Dempsey EM, Ryan AC, Ross PR, et al. Prolonged faecal excretion following a single dose of probiotic in low birth weight infants. *Acta Paediatrica* 2010;**99**(10):1587-8.

Moher 1998

Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses?. *Lancet* 1998;**352**:609-13.

RevMan 2011 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Riordan 1997

Riordan SM, Williams R. Treatment of hepatic encephalopathy. *New England Journal of Medicine* 1997;**337**:473.

Rolfe 2000

Rolfe RD. The role of probiotic cultures in the control of gastrointestinal health. *Journal of Nutrition* 2000;**130**:396.

Royle 2003

Royle P, Milne R. Literature searching for randomized controlled trials used in Cochrane reviews: rapid versus exhaustive searches. *International Journal of Technology Assessment in Health Care* 2003;**19**(4):591-603.

Saab 2015

Saab S, Suraweera D, Au J, Saab EG, Alper TS, Tong MJ. Probiotics are helpful in hepatic encephalopathy: a meta-analysis of randomized trials. Liver International 2015 Nov 12 [Epub ahead of print]. [1478-3231]

Savović 2012

Savović J, Jones HE, Altman DG, Harris RJ, Jüni P, Pildal J, et al. Influence of reported study design characteristics on intervention effect estimates from randomized, controlled trials. *Health Technology Assessment* 2012;**16**(35):1-82.

Savović 2012a

Savović J, Jones HE, Altman DG, Harris RJ, Jüni P, Pildal J, et al. Influence of reported study design characteristics on intervention effect estimates from randomized, controlled trials. *Annals of Internal Medicine* 2012;**157**(6):429-38.

Schrezenmeir 2001

Schrezenmeir J, de Vrese M. Probiotics, prebiotics, and synbiotics - approaching a definition. *American Journal of Clinical Nutrition* 2001;**73**:361S.

Schulz 1995

Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;**273**(5):408-12.

Sharon 2006

Sharon SLW, Wilczynski NL, Haynes RB. Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. *Journal of the Medical Library Association* 2006;**94**:41-7.

Shukla 2011a

Shukla S, Shukla A, Mehboob S, Guha S. Meta analysis: the effects of gut flora modulation using prebiotics, probiotics and synbiotics on minimal hepatic encephalopathy. *Alimentary Pharmacology & Therapeutics* 2011;**33**:662-71.

Stepanova 2012

Stepanova M, Mishra A, Venkatesan C, Younossi ZM. In-hospital mortality and economic burden associated with hepatic encephalopathy in the United States from 2005 to 2009. Clinical Gastroenterology and Hepatology 2012; Vol. 10, issue 9:1034-41.e1. [1542-3565]

Stinton 2013

Stinton LM, Jayakumar S. Minimal hepatic encephalopathy. *Canadian Journal of Gastroenterology* 2013;**27**(10):572-4. [0835-7900]

Thorlund 2011

Thorlund K, Engstrøm J, Wetterslev J, Brok J, Imberger G, Gluud C. User manual for Trial Sequential Analysis (TSA). ctu.dk/tsa/files/tsa_manual.pdf 2011 (accessed 13 June 2016).

TSA 2011 [Computer program]

Copenhagen Trial Unit. TSA - Trial Sequential Analysis. Version 0.9 Beta. Copenhagen: Copenhagen Trial Unit, 2011.

Turnbaugh 2007

Turnbaugh PJ, Ley RE, Hamady M, Fraser-Liggett CM, Knight R, Gordon JI. The human microbiome project. *Nature* 2007;**449**(7164):804-10.

Vaquero 2003

Vaquero J, Chung C, Cahill ME, Blei AT. Pathogenesis of hepatic encephalopathy in acute liver failure. *Seminars in Liver Disease* 2003;**23**:259-69.

Ware 1994

Ware JE, Kosinski M, Keller SK. SF-36® Physical and Mental Health Summary Scales: A User's Manual. Boston: The Health Institute, 1994.

Wetterslev 2008

Wetterslev J, Thorlund K, Brok J, Gluud C. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. Journal of Clinical Epidemiology 2008; Vol. 61, issue 1:64-75. [0895-4356]

Wood 2008

Wood L, Egger M, Gluud LL, Schulz KF, Jüni P, Altman GD, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. *BMJ (Clinical Research Ed.)* 2008;**336**:601-5.

Zhao 2015

Zhao LN, Yu T, Lan SY, Hou JT, Zhang ZZ, Wang SS, et al. Probiotics can improve the clinical outcomes of hepatic encephalopathy: An update meta-analysis. Clinics and Research in Hepatology and Gastroenterology 2015; Vol. 39, issue 6:674-82. [2210-7401]

References to other published versions of this review

McGee 2011

McGee RG, Bakens A, Wiley K, Riordan SM, Webster AC. Probiotics for patients with hepatic encephalopathy. *Cochrane Database of Systematic Reviews* 2011, Issue 11. [DOI: 10.1002/14651858.CD008716.pub2; 1361-6137]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bajaj 2008

Methods	Design: a prospective randomised trial with open allocation A 2:1 randomisation to the treatment arm was performed Trial duration: 60 days Treatment duration: 60 days
Participants	Setting: outpatient single tertiary centre trial Country: USA Age range (years): 44 to 60 Total numbers randomised (group A/group B): 25 (17/8) Sex (M/F): not stated Language: English Stage/severity of hepatic encephalopathy: Child-Pugh score A/B/C: 22/3/0. Cause of hepatic encephalopathy: non-alcoholic aetiology of cirrhosis. Inclusions: non-alcoholic participants with cirrhosis with minimal hepatic encephalopathy. Defined by no alcohol intake within 3 months of the trial and a non-alcoholic aetiology of cirrhosis.

Bajaj 2008 *(Continued)*

	Exclusions: • Alcohol use within 3 months. • Alcoholic aetiology of cirrhosis. • Current psychoactive medication use. • On current therapy for prevention or treatment of overt hepatic encephalopathy. • Lack of English fluency. • History of overt hepatic encephalopathy. • Antibiotic use within 6 weeks of the trial. • Diabetes mellitus.
Interventions	Treatment group (A) probiotic yogurt: 1. *Streptococcus thermophilus* (log 9 CFU/g on Day 0) for 60 days. 2. *Lactobacillus bulgaricus* (log 8.7 CFU/g on Day 0) for 60 days. 3. *Lactobacillus acidophilus* and *Lactobacillus casei* (log 5.9 CFU/g on Day 0) for 60 days. 4. *Bifidobacteria* (log 5.2 CFU/g on Day 0) for 60 days. Participants received 12 ounces of yogurt a day. The specific probiotic used in this yogurt was Yo-Fast 88 manufactured by Chr-Hansen Inc in Denmark. Yogurt is manufactured by CC Jersey Crème, Spring Valley, Wisconsin. Control group (B): no treatment.
Outcomes	1. Minimal hepatic encephalopathy reversal. 2. Overt hepatic encephalopathy development. 3. Adherence. 4. Child-Pugh score. 5. MELD score. 6. SF-36 score. 7. Venous ammonia. 8. IL-6 and TNF-alpha levels.
Notes	Contacted Professor JS Bajaj on 14 October 2010, who provided additional information. Funding source: "The General Clinical Research Center at the Medical College of Wisconsin sponsored by the NIH supported this study". This study declared the funding source and was deemed to be independently funded.

Risk of bias

Bias	Authors' judgement	Support for judgement
Sequence generation	Low risk	Adequate sequence generation. A 2:1 randomisation was performed using a random numbers table.
Allocation concealment	High risk	The treatment allocation was not concealed from the principal investigator.
Blinding Participants	High risk	Participants knew whether they were in the treatment group or the control group.
Blinding Personnel	High risk	The investigator knew whether a participant was included in the treatment group or the control group.
Blinding Outcome assessors	Low risk	The outcome scorer was blinded.

Bajaj 2008 *(Continued)*

Incomplete outcome data All outcomes	Low risk	3 out of 17 participants in the treatment group dropped out: 1 died from sepsis unrelated to the trial on day 67 but did not come to his first visit, and 2 did not like the taste and dropped out on days 13 and 17, respectively. 2 out of 8 participants in the control group dropped out; they developed OHE on days 22 and 35. Primary analysis used an intention-to-treat approach.
Selective outcome reporting	Low risk	All outcomes mentioned in the methods (minimal hepatic encephalopathy reversal, overt hepatic encephalopathy development, and adherence) were described in the results at baseline, after 30 days, and after 60 days. Personal communication with the author revealed no other outcomes were assessed.
Funding source	Low risk	The General Clinical Research Center at the Medical College of Wisconsin sponsored by the NIH supported this study.

Bajaj 2014a

Methods	Design: a parallel randomised trial Trial duration: 8 weeks Treatment duration: 8 weeks
Participants	Setting: outpatient clinic setting Country: USA Age range (years): inclusion criteria 18 to 65 years; mean age (SD) in treatment group 56.3 +/- 9.0, placebo group 58.4 +/- 4.3; range not specified Total numbers randomised (treatment group/placebo group): 37 (18/19) Sex (M/F): 25/12 Language: English Stage/severity of hepatic encephalopathy: minimal hepatic encephalopathy, MELD score (mean +/- SD of intervention, control group: 8.6 +/- 2.2, 8.3 +/- 2.0) Cause of hepatic encephalopathy: cirrhosis due to HCV, HCV + alcohol, alcohol, NASH, and other causes Inclusions: "Patients with cirrhosis defined as having histological evidence or evidence with radiology and endoscopy of cirrhosis whose disease had been stable for 6 months without specific treatment changes, and were between the age range 18–65 were included." Exclusions: "We excluded patients with an unclear diagnosis of cirrhosis, those who had consumed alcohol within 6 months, those with an upper gastrointestinal bleeding episode or need to be on systemic antibiotics within 6 weeks, those on current or past specific treatment for HE, with hepatocellular cancer, with yogurt/probiotic consumption within 2 weeks, those with inflammatory bowel disease, history of pancreatitis, psychoactive medication use (apart from chronic anti-depressants), with a recent absolute neutrophil count <500/mm^3 and those with liver transplant."
Interventions	*Lactobacillus* GG AT strain 53103, 3 batches of LGG and placebo were used. Each LGG batch had > 50 billion CFU/g (51, 61, and 53, respectively), without any other organisms. No live organisms were detected in the placebo batches.
Outcomes	1. Detection of LGG in stool. 2. Serum and urine metabolomics.

Bajaj 2014a *(Continued)*

	3. Cognition and QoL. 4. Adverse events and serious adverse event.
Notes	This study was carried out under the IND mechanism of Center for Biologics Evaluation and Research (CBER) of the Food and Drug Administration (FDA) (IND number BB13870). Contacted Professor JS Bajaj on 14 March 2015, who provided additional information. Funding source: "JSB received funding from NCCAM, NIH grant U01AT004428 for this trial. No other personal or funding interests exist. Writing and preparation of this paper was performed by the authors". This study declared the funding source and was deemed to be independently funded.

Risk of bias

Bias	Authors' judgement	Support for judgement
Sequence generation	Low risk	"Subjects were then randomised into placebo or LGG for 4 weeks using blocks of 4 created by the VCU Investigational Pharmacy using a random sequence generator."
Allocation concealment	Low risk	Treatment allocation only available to investigational pharmacy staff.
Blinding Participants	Low risk	Participants were blinded.
Blinding Personnel	Low risk	Personnel were blinded.
Blinding Outcome assessors	Low risk	Outcome assessors were blinded.
Incomplete outcome data All outcomes	Low risk	"Thirty-seven patients were randomised. Two patients withdrew consent within the first month due to logistic reasons without any adverse events (both LGG group). One additional patient had to be scheduled for a splenic arterial embolisation for which he would need antibiotics and narcotics (LGG group) and was withdrawn before receiving medication. Four patients withdrew due to infections or other contraindications to continuation of the study [one broke her wrist and needed antibiotics (placebo), one had an asymptomatic urinary tract infection based on urine collected before randomisation with methicillin-sensitive Staphylococcus aureus (placebo), two were found to have dental issues within a week of randomisation that needed antibiotics (one placebo and one LGG)]"
Selective outcome reporting	Unclear risk	"Blood was collected for MELD score, ammonia, serum albumin and pre-albumin, and the dietician met with them to confirm continued adherence on the prescribed diet. If there were no adverse events requiring discontinuation, the subjects were re-prescribed their medication for another 4 weeks. The end-of-drug visit was carried out 4 weeks later (8 weeks after drug initiation) where all procedures including physical examination, cognitive testing, HRQOL evaluation, dietary assessment, sample (blood, urine, stool) collection and evaluation of adherence and adverse events were performed." Only information at the end of 8 weeks was reported.
Funding source	Low risk	"JSB received funding from NCCAM, NIH grant U01AT004428 for this trial. No other personal or funding interests exist. Writing and preparation of this paper was performed by the authors."

Dhiman 2013a

Methods	Design: randomised parallel trial/double-blind, randomised, placebo-controlled study Trial duration: 16 weeks Treatment duration: 16 weeks
Participants	Setting: unspecified Country: India Age range (years): 45.5 to 52.5 Total numbers randomised: 80 Sex (M/F): 71/9 Language: unspecified Stage/severity of hepatic encephalopathy: minimal hepatic encephalopathy Cause of hepatic encephalopathy: unspecified Inclusions: cirrhotics with MHE Exclusions: unspecified
Interventions	40 participants received probiotic (1 sachet of VSL#3 (CD Pharma India Pvt. Ltd, New Delhi), at a dose of 900 billion bacteria daily, and 40 participants received placebo.
Outcomes	1. Reversal of MHE. 2. Figure connection test-A. 3. Digit symbol test. 4. Plasma IL-6. 5. Plasma oxindole. 6. Plasma ammonia. 7. MCS of SF-36 HRQOL. 8. Adverse events/serious adverse event.
Notes	Clinical Trials Registry - India /2008/091/000268 Contacted Professor RK Dhiman on 22 December 2014. Awaiting additional information from author. Funding source: abstract only, unable to assess funding source

Risk of bias

Bias	Authors' judgement	Support for judgement
Sequence generation	Unclear risk	Abstract only, unable to assess
Allocation concealment	Unclear risk	Abstract only, unable to assess
Blinding Participants	Unclear risk	Abstract only, unable to assess
Blinding Personnel	Unclear risk	Abstract only, unable to assess
Blinding	Unclear risk	Abstract only, unable to assess

Dhiman 2013a *(Continued)*

Outcome assessors		
Incomplete outcome data All outcomes	Unclear risk	Abstract only, unable to assess
Selective outcome reporting	Unclear risk	Abstract only, unable to assess
Funding source	Unclear risk	Abstract only, unable to assess

Liu 2004

Methods	Design: a parallel-group randomised trial Study duration: unknown Treatment duration: 30 days
Participants	Setting: outpatient Country: China Age range (years): 43 to 69 Total numbers randomised (group A/group B/group C): 55 (20/20/15) Group C was not relevant to our analysis. Sex (M/F): 53/2 Language: English Stage/severity of hepatic encephalopathy: Child-Pugh score A/B+C: 8/47 Cause of hepatic encephalopathy: people with cirrhosis and hepatic encephalopathy without known precipitants of hepatic encephalopathy such as renal impairment, alcohol-related hepatic encephalopathy, complicating hepatocellular carcinoma, etc. Inclusions: • Cirrhotic patients with minimal hepatic encephalopathy, without over hepatic encephalopathy. • People who had been abstinent from alcohol for at least 2 months, as corroborated by family members or caregivers or both. Exclusions: • Histological features of alcoholic hepatitis. • A history within the previous 6 weeks of factors including infection, treatment with antibiotics, lactulose or immunomodulatory drugs, and gastrointestinal haemorrhage. • Other causes of reversible hepatic functional decompensation such as drug-related hepatotoxicity and choledocholithiasis. • Other known precipitants of hepatic encephalopathy, including renal impairment, electrolyte imbalance, and complicating hepatocellular carcinoma.
Interventions	Treatment group (A) Oral supplementation with a synbiotic preparation containing *Pediacoccus pentosaceus*, *Leuconostoc mesenteroides*, *Lactobacillus paracasei*, and *Lactobacillus plantarum* (each probiotic at 10^{10} CFUs/day, total dose of probiotics in a day: 4 x 10^{10} CFUs) plus 10 g of bioactive fermentable fibre (2.5 g beta glucan, 2.5 g inulin, 2.5 g pectin, 2.5 g resistant starch) for 30 days. Treatment group (B) 10 g of bioactive fermentable fibre (2.5 g beta glucan, 2.5 g inulin, 2.5 g pectin, 2.5 g resistant starch) for 30 days. Control group (C) Placebo (non-fermentable fibre) for 30 days.
Outcomes	1. Faecal pH.

Liu 2004 *(Continued)*

2. Venous ammonia levels.
3. Serum endotoxin levels.
4. Minimal hepatic encephalopathy status.
5. Child-Pugh score.
6. Adverse events.
7. Overt hepatic encephalopathy development.

Notes	Contacted Dr Q Liu on 15 October 2010, received no response. Funding source: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Sequence generation	High risk	1 sachet was randomly drawn from a pool for each participant, which is equivalent to drawing lots. We feel that this does not represent best practise for randomisation, and so have judged this category as high risk of bias according to our predefined criteria.
Allocation concealment	Low risk	Sachets were coded and contents unknown to investigators when drawn.
Blinding Participants	Unclear risk	Not stated for participants
Blinding Personnel	Unclear risk	Which sachets (A, B, or C) contained the synbiotic, fermentable fibre or non-fermentable fibre preparations was unknown to the investigators until after the study had been completed and results had been analysed.
Blinding Outcome assessors	Unclear risk	Not stated for outcome assessors
Incomplete outcome data All outcomes	Unclear risk	Unclear from the study
Selective outcome reporting	Unclear risk	Unclear from the study
Funding source	Unclear risk	Not stated

Loguercio 1987

Methods	Design: a parallel-group randomised trial Study duration: 23 days Treatment duration: 10 days
Participants	Setting: outpatient Country: Italy Age range (years): 25 to 68 Total numbers randomised (group A/group B): 40 (20/20) Sex (M/F): 26/14 Language: English Stage/severity of hepatic encephalopathy: grade I or II Cause of hepatic encephalopathy: alcohol, hepatitis, cirrhosis Inclusions: cirrhotic patients with non-advanced hepatic encephalopathy (grade I or II).

Loguercio 1987 *(Continued)*

	Exclusions: • HE degree > 2. • Alcohol use at the moment of the study. • Mental disorders or benzodiazepine use or both. • Non-compliance.
Interventions	Treatment group (A) *Enterococcus* lactic acid bacteria strain SF68 (2 capsules, each containing 75 x 10^6 CFUs, 3 times daily, for 10 days). Bioflorin is a trade name of Giuliani and is distributed by Gipharmex SpA, Italy. Control group (B) 30 mL lactulose 4 times daily, for 10 days.
Outcomes	1. Mental state. 2. Bowel function. 3. Presence/absence abdominal pain. 4. Blood ammonia level. 5. Presence/absence meteorism. 6. Reitan's test (Number Connection Test). 7. Adverse events.
Notes	Additional information on 'Risk of bias' criteria provided by the author. Contacted Professor C Loguercio on 15 October 2010. Funding source: "Gipharmex (Milan, Italy) supported this study". This study declared the funding source and was deemed to be industry funded.

Risk of bias

Bias	Authors' judgement	Support for judgement
Sequence generation	Unclear risk	Participants were randomly assigned to a treatment group. No further information about randomisation
Allocation concealment	Unclear risk	Information not provided
Blinding Participants	Low risk	Participants were blinded.
Blinding Personnel	Low risk	Personnel were blinded.
Blinding Outcome assessors	Low risk	The outcome scorer was blinded.
Incomplete outcome data All outcomes	High risk	All participants completed the treatment period. 5 participants given lactulose and 4 given *Enterococcus* SF68 did not arrive for post-treatment follow-up. On day 15, 2 participants given lactulose were withdrawn from the study because of marked hyperammonaemia and a worsening of hepatic encephalopathy.
Selective outcome reporting	Unclear risk	Unclear from study
Funding source	High risk	Gipharmex (Milan, Italy) supported this study.

Loguercio 1995

Methods	Design: randomised parallel trial Trial duration: 18 weeks Treatment duration: 3 periods of 4 weeks
Participants	Setting: outpatient setting Country: Italy Age range (years): 41 to 76 Total numbers randomised: 40 Sex (M/F): 26/14 Language: unspecified Stage/severity of hepatic encephalopathy: grade 1 to 2 hepatic encephalopathy Cause of hepatic encephalopathy: alcoholic/other: 21/19 Inclusions: "Forty patients with cirrhosis, with low grade 1-2 hepatic encephalopathy of the chronic recurrent type and ammonia plasma levels above 59 uM (normal values: < 44 uM) were considered suitable for the study." Exclusions: "Exclusion criteria in the selection of patients included the presence of one of these pathologies: grade 3-4 hepatic encephalopathy, ascites that needed treatment with furosemide, alcohol abuse or recent abstinence (<6 months), liver tumour, and hepatorenal syndrome. We also excluded patients with severe sight disorders, colour blindness, alterations of the eye fundus and disorders of the anterior segment."
Interventions	Participants entered a 15-day run-in period. 1 group of participants took, after main meals, 2 capsules containing a total of 150 million *Enterococcus faecium* strain SF68 3 times a day for 4 weeks; the participants in the lactulose treatment branch ingested, after main meals, 30 mL (20 g) oral lactulose 3 times a day for the same time span. The treatment was repeated for three 4-week periods, each separated by a 2-week wash-out interval. During the 2-week wash-out period participants were treated as during the run-in period.
Outcomes	1. Arterial ammonia concentration. 2. NCT score. 3. Mental state. 4. Encephalopathy Global Score. 5. Flash evoked visual potentials.
Notes	Contacted Professor C Loguercio on 7 June 2015, received no response. Funding source: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Sequence generation	Low risk	"After the basal evaluation, the patients enrolled in the study were assigned to one of two treatments according the Broc Plan computerised randomisation scheme (kindly provided by the Biometrics Division of Bracco SPA)."
Allocation concealment	Low risk	Computer randomisation was provided by external providers.
Blinding	Unclear risk	Unclear from the study

Loguercio 1995 *(Continued)*

Participants		
Blinding Personnel	Unclear risk	Unclear from the study
Blinding Outcome assessors	Unclear risk	Unclear from the study
Incomplete outcome data All outcomes	High risk	21 participants were initially randomised to SF68 and 19 to lactulose group. "Seven patients in the lactulose group interrupted the treatment: one because of diarrhoea and fever during the second period, two because of drug intolerance with diarrhoea (one during the second period and one during the third period), and four because of deterioration of the neurological state (one during the first period, two during the first wash-out period, and one during the second period). Therefore, only 14 patients treated with SF68 and 11 treated with lactulose completed the study."
Selective outcome reporting	Unclear risk	Unclear from the study
Funding source	Unclear risk	Unclear from the study

Lunia 2014

Methods	Design: parallel randomised trial Trial duration: mean follow-up of group 1 participants was 38.6 ± 8.80 weeks and group 2 participants was 34.3 ± 9.8 weeks Treatment duration: 3 months
Participants	Setting: unspecified Country: India Age range (years): range unspecified, mean (SD): 46.6 (13.1) Total numbers randomised: 81 Sex (M/F): 47/28 Language: unspecified Stage/severity of hepatic encephalopathy: minimal hepatic encephalopathy Cause of hepatic encephalopathy: unspecified in abstract Inclusions: unspecified in abstract Exclusions: unspecified in abstract
Interventions	Cirrhotic patients with MHE were divided into: group 1 (probiotics, n = 42, VSL#3) and group 2 (control, n = 39).
Outcomes	All participants underwent psychometric tests, critical flicker frequency, glucose hydrogen breath test for SIBO and lactulose hydrogen breath test for OCTT. Primary endpoint was reversal of MHE. Mortality. Arterial ammonia.

Lunia 2014 *(Continued)*

	Small intestinal bowel overgrowth. Orocaecal transit time.
Notes	Contacted Dr Manish Lunia on 22 December 2014. Awaiting additional information from author. Funding source: abstract only, unable to assess funding source

Risk of bias

Bias	Authors' judgement	Support for judgement
Sequence generation	Unclear risk	Abstract only, unable to assess
Allocation concealment	Unclear risk	Abstract only, unable to assess
Blinding Participants	Unclear risk	Abstract only, unable to assess
Blinding Personnel	Unclear risk	Abstract only, unable to assess
Blinding Outcome assessors	Unclear risk	Abstract only, unable to assess
Incomplete outcome data All outcomes	Unclear risk	Abstract only, unable to assess
Selective outcome reporting	Unclear risk	Abstract only, unable to assess
Funding source	Unclear risk	Abstract only, unable to assess

Malaguarnera 2010

Methods	Design: a double-blind, parallel-group randomised trial Study duration: 2004 to 2007 Treatment duration: 60 days
Participants	Setting: inpatient Country: Italy Age range (years): not stated Total numbers randomised (group A/group B): 125 (63/62) Sex (M/F): 62/63 Language: English Stage/severity of hepatic encephalopathy: Child-Pugh score A/B/C: 46/59/20 Cause of hepatic encephalopathy: chronic hepatitis and cryptogenic cirrhosis with spontaneous hepatic encephalopathy Inclusions: • Chronic hepatitis with spontaneous manifest hepatic encephalopathy (mental state grade I or II according to the West Haven criteria) and a Number Collection Test-A performance time > 30 seconds. • Hyperammonaemia (venous ammonia concentration > 50 mmol/L). • Co-operative, hospitalised, adult patients with liver cirrhosis diagnosed by clinical, histological, and ultrasonographic findings (reduced dimensions of the liver as well as splenomegaly) and oesophageal varices (stages II or III) observed by endoscopy.

Malaguarnera 2010 *(Continued)*

	Exclusions: • Major complications of portal hypertension, such as gastrointestinal blood loss, hepatorenal syndrome, or bacterial peritonitis. • Acute superimposed liver injury. • Other neurological disease and metabolic disorders such as alcoholism, diabetes mellitus, unbalanced heart failure and/or respiratory failure or end-stage renal disease. • Severe hepatic encephalopathy (mental state grade III to IV). • Administration of anti-hepatic encephalopathy medications such as neomycin, branched-chain amino acids. • Any additional precipitating factors such as high protein intake (additional high-protein meals), constipation, or intake of psychostimulants, sedatives, antidepressants, benzodiazepines or benzodiazepines antagonists (flumazenil). • Fever, sepsis, or shock were also excluded to avoid variations caused by body temperature.
Interventions	Treatment group (A) *Bifidobacterium* (subtype not stated) + (FOS) fructo-oligosaccharides for 60 days (dose not stated). Control group (B) Lactulose for 60 days (dose not stated). Note: FOS and lactulose were considered comparable because they are both complex carbohydrates, which are indigestible to humans but digestible to bacteria. We were unable to locate any efficacy data comparing FOS to lactulose in people with hepatic encephalopathy.
Outcomes	1. Trail Making Test. 2. Cognitive functions. 3. Grade of hepatic encephalopathy. 4. Child-Pugh score.
Notes	Contacted Dr M Malaguarnera on 15 October 2010, received no response. Funding source: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Sequence generation	Low risk	Randomisation was based on a computer-generated list.
Allocation concealment	Unclear risk	Unclear from study
Blinding Participants	Unclear risk	Stated it was a double-blind trial, but not for whom.
Blinding Personnel	Unclear risk	Stated it was a double-blind trial, but not for whom.
Blinding Outcome assessors	Unclear risk	Not stated for outcome assessors
Incomplete outcome data All outcomes	Unclear risk	Unclear from study
Selective outcome reporting	Unclear risk	Unclear from study
Funding source	Unclear risk	Not stated

Mittal 2009

Methods	Design: a parallel randomised trial Study duration: October 2007 to October 2009 Treatment duration: 3 months
Participants	Setting: outpatient Country: India Age range (years): 32 to 54 Total numbers randomised (group A/group B/group C/group D): 160 (40/40/40/40) We did not use group B and D in our analysis, as these were not useful to compare to probiotics. Sex (M/F): 123/37 Language: English Stage/severity of hepatic encephalopathy: not stated Cause of hepatic encephalopathy: cirrhosis due to alcoholic liver disease, hepatitis B, hepatitis C, or other causes Inclusions: people with cirrhosis who have minimal hepatic encephalopathy, diagnosed by 2 or more abnormal (+2SD from the mean) psychometric tests. Exclusions: • Overt HE based on detailed neurological examination or history of overt HE in past 6 weeks. • Recent history (< 6 wk) of gastrointestinal bleed. • Active ongoing infection. • Renal impairment with serum creatinine > 1.5 mg %. • Electrolyte impairment (serum sodium < 130 or > 150 meq/dL, serum potassium < 3.0 or > 5.5 meq/dL). • Recent alcohol use (< 6 wk) as reported by the person, recent use of antibiotic, lactulose, or LOLA (< 6 wk), use of psychotropic drugs in last 6 weeks. • TIPS, shunt surgery. • Hepatocellular carcinoma. • Severe comorbidity such as congestive heart failure, pulmonary disease, neurological and psychiatric problems impairing quality of life, or poor vision precluding neuropsychiatric assessment.
Interventions	Control group (A) No treatment. Treatment group (B) 30 mL to 60 mL lactulose twice daily for 3 months. Treatment group (C) VSL#3 (containing *Streptococcus thermophilus*, *Bifidobacterium breve*, *Bifidobacterium longum*, *Bifidobacterium infantis*, *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Lactobacillus paracasei*, *Lactobacillus bulgaricus*) 110 billion CFUs twice daily for 3 months. Treatment group (D) 6 g (LOLA) L-ornithine L-aspartate 3 times daily for 3 months.
Outcomes	1. Minimal hepatic encephalopathy recovery. 2. Minimal hepatic encephalopathy improvement. 3. Arterial ammonia level. 4. Development of overt hepatic encephalopathy. 5. Sickness Impact Profile Score (quality of life).
Notes	Author provided additional information on 'Risk of bias' criteria. Contacted Professor BC Sharma on 14 October 2010. Author provided unpublished data.

Mittal 2009 *(Continued)*

	Funding source: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Sequence generation	Low risk	Participants were randomised to 1 of the treatment groups using computer-generated random tables.
Allocation concealment	Low risk	"The sequences were concealed until a decision to enrol a patient was taken after assessment for eligibility and after receiving informed consent."
Blinding Participants	High risk	Different way of administering for every treatment, therefore participants knew which treatment they had received.
Blinding Personnel	High risk	Compliance was assessed primarily using pill and bottle count, therefore blinding was not possible.
Blinding Outcome assessors	High risk	Compliance was assessed primarily using pill and bottle count, therefore blinding was not possible.
Incomplete outcome data All outcomes	Unclear risk	11 participants were lost to follow-up, 3 from group A, 1 from group B, 3 from group C, and 4 from group D. During treatment, 7 participants had to be admitted to the hospital for causes other than overt hepatic encephalopathy. Of these 7 participants, 2 participants died, 1 each in group A and D. Primary analysis used an intention-to-treat approach, probably with imputation.
Selective outcome reporting	Unclear risk	Unclear from the trial
Funding source	Unclear risk	Not stated

Mouli 2014

Methods	Design: randomised controlled trial Trial duration: 2 months Treatment duration: 2 months
Participants	Setting: tertiary care medical centre Country: India Age range (years): range unspecified, mean (SD): lactulose group 44.2 (10.4); probiotic group 39.6 (11.4) Total numbers randomised: 120 Sex (M/F): 110/10 Language: English Stage/severity of hepatic encephalopathy: minimal hepatic encephalopathy; CTP (A/B/C): probiotics group (14/24/22); lactulose group (15/30/15) Cause of hepatic encephalopathy: alcoholic/viral/other: probiotics group (24/24/12); lactulose group (21/24/15)

Mouli 2014 *(Continued)*

	Inclusions: The inclusion criterion was the diagnosis of MHE in people with cirrhosis aged between 15 and 80 years. Exclusions: "The exclusion criteria were: history of overt HE in the past 6 weeks; history of intake of lactulose or probiotics or antibiotics within the past 6 weeks; presence of any other neurological or psychiatric diseases; history of undergoing shunt surgery or transjugular intrahepatic portosystemic shunt for portal hypertension; currently on medications which were likely to interfere with psychometric performance; history of alcohol intake during the past 6 weeks; history of gastrointestinal bleeding or spontaneous bacterial peritonitis in the past 6 weeks; presence of hepatocellular carcinoma, renal failure or portal vein thrombosis; presence of significant co-morbidities such as diabetes, congestive heart failure, chronic respiratory disease, chronic kidney disease or malignancy; and visual impairment and refusal for consent."
Interventions	Participants were randomised to receive either lactulose (Lark Laboratories; Rajasthan, India) or probiotics (VSL#3; Sun Pharmaceutical, Mumbai, India) for a period of 2 months. Lactulose was given at a dose of 30 to 60 mL/day orally to ensure 2 to 3 soft stools per day. VSL#3 was given at a dose of 4 capsules (2 twice a day) per day, amounting to a total of 450 billion CFU/day; each capsule contained 112.5 billion viable lyophilised bacteria of 4 strains of *Lactobacillus* (*L acidophilus* DSM 24735, *L plantarum* DSM 24730, *L paracasei* DSM 24733, *L delbrueckii* subsp. *bulgaricus* DSM 24734), 3 strains of *Bifidobacterium* (*B longum* DSM 24736, *B breve* DSM 24732, *B infantis* DSM 24737), and 1 strain of *Streptococcus* (*S thermophilus* DSM 24731).
Outcomes	The primary outcome measure was improvement of MHE, which was defined as the normalisation of the prior abnormal neuropsychometric/neurophysiological tests. The secondary outcome measure was change in venous ammonia level with study intervention. The study endpoints were: (i) completion of 2 months of treatment; (ii) development of overt HE; and (iii) death.
Notes	Trial ID: NCT01008293 Contacted Dr VP Mouli on 14 March 2015, received no response. Funding source: "We thank the Indian Council of Medical Research (ICMR) for providing a research grant and CD Pharmaceuticals India for providing probiotic VSL#3 and lactulose". This study declared the funding source and was deemed to be independently funded.

Risk of bias

Bias	Authors' judgement	Support for judgement
Sequence generation	Low risk	"Block randomization was used to allocate the patients to lactulose and probiotics groups. The random numbers were generated using Stata software (StataCorp, College Station, TX, USA)."
Allocation concealment	Low risk	"Allocation of the patients to receive the study intervention drugs was done by using the sequentially numbered, opaque, sealed envelope method. The envelopes were prepared by a statistician not associated with the conduct of the study, and were opened sequentially only after the patient's name, age and sex were written on them by a person not associated with the study."
Blinding Participants	High risk	The study was limited by being an open-label trial with a relatively small sample size with a short period of intervention. Blinding was not possible due to the differences in physical state between the drugs.
Blinding Personnel	High risk	The study was limited by being an open-label trial with a relatively small sample size with a short period of intervention. Blinding was not possible due to the differences in physical state between the drugs.
Blinding Outcome assessors	Low risk	The objective nature of the tests for MHE would likely limit the effect of bias on MHE recovery outcomes and venous ammonia.

Mouli 2014 *(Continued)*

Incomplete outcome data All outcomes	Unclear risk	"60 patients each were randomized into the lactulose and probiotics groups. Four patients were dropouts and 19 were lost to follow up, two patients died and 22 developed overt encephalopathy, and hence discontinued with the trial drugs due to different management protocols for overt HE. At the end of intervention (i.e. at 2 months), 40 patients in the lactulose group and 33 patients in the probiotics group were taken for analysis who had completed the study medications."
Selective outcome reporting	Low risk	Outcomes were reported as per protocol found registered at ClinicalTrials.gov identifier NCT01008293.
Funding source	Low risk	"We thank the Indian Council of Medical Research (ICMR) for providing a research grant and CD Pharmaceuticals India for providing probiotic VSL#3 and lactulose".

Nair 2008

Methods	Design: randomised controlled trial Trial duration: September 2006 to March 2007 (7 months) Treatment duration: 4 weeks
Participants	Setting: Study was conducted in Department of Neurology, Medical College Calicut, in collaboration with Department of Gastroenterology. Country: India Age range (years): range unspecified, mean 49.5 ± 8.05 SD Total numbers randomised: 40 Sex (M/F): M:F ratio 1:0.05 Language: English Stage/severity of hepatic encephalopathy: MHE (Child A 14, Child B 26) Cause of hepatic encephalopathy: alcohol 29, cryptogenic 10, HBV-related 1 Inclusions: • Cirrhosis diagnosed by clinical/USG/biopsy. • Minimal hepatic encephalopathy diagnosed by Number Connection Test-A and evoked response tests - auditory and visual. Exclusions: • Clinically evident hepatic encephalopathy. • Neurological diseases. • Alcohol-free period of less than 2 months. • Coexistent gastrointestinal haemorrhage. • Renal impairment and electrolyte disturbances. • Severe visual or auditory abnormalities.
Interventions	Group A was given probiotic preparation in a dose of 1-gram sachet containing not less than 1.25 billion cells of *Lactobacillus acidophilus*, *Lactobacillus rhamnosus*, *Bifidobacterium longum*, and *Saccha-*

Nair 2008 *(Continued)*

	romyces boulardii 3 times daily after meals, and group B was given placebo powder in identically looking sachet in a similar dose.
Outcomes	Number Connection Test-A, arterial ammonia, auditory evoked response tests, visual evoked response tests
Notes	Contacted Dr R Nair on 22 December 2014, full manuscript provided, awaiting additional information from author. Funding source: "Sachets of drug as well as placebo were supplied by Aristo pharmaceuticals Pvt. Ltd. No financial aid of any form was received from any source for the purpose of conducting this trial". This study declared the funding source and was deemed to be independently funded.

Risk of bias

Bias	Authors' judgement	Support for judgement
Sequence generation	Low risk	Randomisation was done using random table allocation.
Allocation concealment	Low risk	Treatment allocation was concealed from individual who did the allocation.
Blinding Participants	Low risk	"The patients, examiners and investigators were blinded as to who is receiving the drug and who receives placebo".
Blinding Personnel	Low risk	"The patients, examiners and investigators were blinded as to who is receiving the drug and who receives placebo".
Blinding Outcome assessors	Low risk	"The patients, examiners and investigators were blinded as to who is receiving the drug and who receives placebo".
Incomplete outcome data All outcomes	Low risk	1 dropout in group A and 2 dropouts in group B; "There were 3 drop outs (Group A - 1, Group B - 2) – one in group A was lost to follow up, so was one in group B. Second patient in Group B decided to withdraw from study due to personal reasons."
Selective outcome reporting	Unclear risk	Unable to assess
Funding source	Low risk	Sachets of drug as well as placebo were supplied by Aristo Pharmaceuticals Pvt. Ltd. No financial aid of any form was received from any source for the purpose of conducting this trial.

Pereg 2011

Methods	Design: a parallel randomised trial Study duration: unclear Treatment duration: 6 months
Participants	Setting: outpatient Country: Israel Age range (years): 53 to 74 Total numbers randomised (group A/group B): 40 (20/20) Sex (M/F): unclear Language: English

Pereg 2011 *(Continued)*

	Stage/severity of hepatic encephalopathy: minimal hepatic encephalopathy Cause of hepatic encephalopathy: cirrhosis due to alcoholic liver disease, hepatitis B, hepatitis C, or other causes Inclusions: people with liver cirrhosis and at least 1 major complication of cirrhosis in the past, clinical evidence of portal hypertension, or decreased hepatic synthetic function. Exclusions: • Any sign of decompensation from any precipitant including gastrointestinal bleeding, infections, acute renal failure, electrolyte impairment, or hepatocellular carcinoma. • Those chronically treated with antibiotics or lactulose. • People with alcoholic cirrhosis, for whom alcohol abstinence for at least 2 months prior to enrolment could not be confirmed.
Interventions	Control group (A) Wheat-based non-fermentable fiber placebo. Treatment group (B) *Lactobacillus acidophilus*, *Lactobacillus bulgaricus*, *Bifidobacterium bifidum*, and *Streptococcus thermophilus* (Bio Plus, Supherb, Israel), each at a daily dose of 2 x 10^{10} CFUs.
Outcomes	1. Plasma ammonia. 2. Adverse events.
Notes	The study was registered in ClinicalTrials.gov (ID: NCT00312910). Funding source: "Supported by Supherb Ltd, Israel". This study declared the funding source and was deemed to be industry funded.

Risk of bias

Bias	Authors' judgement	Support for judgement
Sequence generation	Unclear risk	Not stated
Allocation concealment	Unclear risk	Not stated
Blinding Participants	Unclear risk	Only stated in the title that the trial was double-blinded - no specific details provided on who was blinded or how blinding was conducted.
Blinding Personnel	Unclear risk	Only stated in the title that the trial was double-blinded - no specific details provided on who was blinded or how blinding was conducted.
Blinding Outcome assessors	Unclear risk	Only stated in the title that the trial was double-blinded - no specific details provided on who was blinded or how blinding was conducted.
Incomplete outcome data All outcomes	High risk	Four participants "dropped out", no further details provided.
Selective outcome reporting	Unclear risk	Unclear from the trial
Funding source	High risk	Supported by Supherb Ltd, Israel.

Qiao 2010

Methods	Design: randomised controlled trial Trial duration: There was a follow-up every 1to 2 weeks until treatment ended in which the incidence of hepatic encephalopathy was recorded. Treatment duration: Treatment lasted for 24 weeks, and there was a follow-up every 1 to 2 weeks until treatment ended in which the incidence of hepatic encephalopathy was recorded.
Participants	Setting: Laiyang Central Hospital, Yantai Country: China Age range (years): age range from 37 to 70, average age was 53.4 Total numbers randomised: 64 Sex (M/F): of the 64 participants, 51 were male and 13 were female Language: Mandarin Stage/severity of hepatic encephalopathy: diagnosed with subclinical hepatic encephalopathy (SHE) and recruited for this study after intelligence testing Cause of hepatic encephalopathy: 54 cases were cirrhosis from hepatitis B, 6 cases were alcoholic cirrhosis, 1 case was primary biliary cirrhosis, 1 case was Budd-Chiari syndrome, and 2 cases were of unknown cause. Inclusions: "Inclusion criteria: between August 2004 and August 2008, of all the patients diagnosed with cirrhosis, 64 of them we diagnosed with SHE and recruited for this study after intelligence testing. Cirrhosis diagnosis was based on history, clinical assessment, laboratory findings, ultrasound, and CT scan investigations." Exclusions: "Exclusion criteria: 1. Currently or previously diagnosed with hepatic encephalopathy. 2. Patients with psychological or neurological disease. 3. Use of any sedatives or CNS depressants in the past 4 weeks. 4. Any GI bleeding, electrolyte/acid-base disturbances in the past 2 weeks. 5. Patients with alcoholic cirrhosis and continue to drink alcohol."
Interventions	Control group was given compound vitamin B tablets, 2 tablets each time, 3 times a day. Treatment group was given bifid triple viable, 2 tablets each time, 3 times a day.
Outcomes	Outcome measurements: Blood ammonium, ALT, and NCT were measured 1 day before treatment and again 1 day after treatment. NCT used the NCT-A version, where the patient orders the numbers 1 to 25 and the time it takes to complete the test is recorded, including time spent correcting any mistakes. NCT was measured in seconds; longer time to complete indicates abnormality.
Notes	We could not find author contact details. Funding source: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Sequence generation	Unclear risk	Unclear from the trial
Allocation concealment	Unclear risk	Unclear from the trial
Blinding	Unclear risk	Unclear from the trial

Qiao 2010 *(Continued)*

Participants		
Blinding Personnel	Unclear risk	Unclear from the trial
Blinding Outcome assessors	Unclear risk	Unclear from the trial
Incomplete outcome data All outcomes	Unclear risk	Unclear from the trial
Selective outcome reporting	Unclear risk	Unclear from the trial
Funding source	Unclear risk	Unclear from the trial

Saji 2011

Methods	Design: a parallel randomised trial/randomised double-blind, placebo-controlled trial Trial duration: 4 weeks Treatment duration: 4 weeks
Participants	Setting: unclear Country: India Age range (years): range unclear, mean age (SD) treatment group/placebo group: 50.6 (5.81)/52.15 (0.18) Total numbers randomised: total (probiotic/placebo): 43 (21/22) Sex (M/F): 37/3 excluding dropouts Language: unspecified Stage/severity of hepatic encephalopathy: stable cirrhotics in Child's grade A and B (diagnosed clinically, by ultrasonography or biopsy) with minimal hepatic encephalopathy diagnosed by NCT and evoked responses Cause of hepatic encephalopathy: Aetiology of cirrhosis was alcohol in the majority of participants (34/40). Other causes included hepatitis B in 2 participants, hepatitis C in 1 participant, and cryptogenic in 3 participants. Inclusions: Stable cirrhotics in Child's grade A and B (diagnosed clinically, by ultrasonography or biopsy) and having minimal hepatic encephalopathy as per the NCT-A and evoked responses (auditory and visual) were included. Exclusions: "Those with clinically evident hepatic encephalopathy, neurological disease, alcohol free period of less than 2 months, coexistent gastrointestinal hemorrhage, renal impairment, electrolyte disturbances and those with severe visual or auditory abnormalities were excluded from the study."
Interventions	Group A received probiotic preparation in a dose of 1-gram sachet containing not less than 1.25 billion spores of *Lactobacillus acidophilus*, *Lactobacillus rhamnosus*, *Bifidobacterium longum*, and *Saccharomyces boulardii*, 3 times daily after meals. Group B received placebo powder in identical-looking sachet 3 times daily after meals. The duration of treatment was 4 weeks.

Saji 2011 *(Continued)*

Outcomes	At the end of 4 weeks, participants' symptoms were recorded and a thorough examination was done for any features of overt encephalopathy. Investigations were done to reassess the Child's score. Arterial ammonia, NCT –A, and evoked responses were repeated.
Notes	Both sachets of probiotics and placebo were supplied by Aristo Pharmaceuticals Pvt. Ltd Mumbai. Contacted Dr S Saji on 14 March 2015, awaiting additional information from author. Funding source: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Sequence generation	Low risk	"Randomization was done using random table allocation."
Allocation concealment	Unclear risk	Unclear from study
Blinding Participants	Low risk	"Group B received placebo powder in identical looking sachet".
Blinding Personnel	Unclear risk	"The patients were randomized to two groups and the drugs were administered in a double blind fashion."
Blinding Outcome assessors	Low risk	Unclear from study, although the objective nature of the tests for MHE would likely limit the effect of bias on MHE recovery outcomes and venous ammonia.
Incomplete outcome data All outcomes	Low risk	"There were 3 drop-outs, one in the probiotic group and two in the placebo group." "The data reported are only for the intent-to-treat population."
Selective outcome reporting	Low risk	"At the end of 4 weeks patients symptoms were recorded and a thorough examination was done for any features of overt encephalopathy. Investigations were done to reassess the Child's score. Arterial ammonia, number connection test–A and evoked responses were repeated." All of the above outcomes except the Child's score were reported.
Funding source	Unclear risk	"Sachets of probiotics as well as placebo were supplied by Aristo pharmaceuticals Pvt. Ltd Mumbai."

Sharma 2008

Methods	Design: open-label randomised trial Treatment duration: 1 month Time period: February 2005 to August 2006
Participants	Setting: India Age range (years): 30 to 54 Total numbers randomised (group A/group B/group C): 105 (35/35/35) Sex (M/F): 79/26 Language: English Stage/severity of hepatic encephalopathy: Child-Pugh score A/B/C: 36/39/30 Cause of hepatic encephalopathy: cirrhosis due to alcohol consumption, chronic hepatitis, and cryptogenic cirrhosis.

Sharma 2008 *(Continued)*

	Inclusions: cirrhotic patients with minimal hepatic encephalopathy without overt encephalopathy. Exclusions: • The presence of overt hepatic encephalopathy or history of hepatic encephalopathy. • History of taking lactulose or any antibiotics. • Alcohol intake. • Gastrointestinal haemorrhage or spontaneous bacterial peritonitis during the past 6 weeks. • Earlier transjugular intrahepatic portosystemic shunt or shunt surgery. • Significant comorbid illness such as heart failure, respiratory failure, or renal failure. • Any neurologic diseases such as Alzheimer's disease, Parkinson's disease, and non-hepatic metabolic encephalopathies. • Colour blindness and mature cataract, diabetic retinopathy, and people on psychoactive drugs such as antidepressants or sedatives.
Interventions	Control group (A) 30 mL to 60 mL lactulose/day for 1 month. Treatment group (B) 1 capsule (containing *Enterococcus faecalis*, *Clostridium butyricum*, *Bacillus mesentericus*, Lactic acid *Bacillus*) 3 times daily for 1 month, dose not stated. Treatment group (C) 30 mL to 60 mL lactulose plus probiotics daily for 1 month.
Outcomes	1. Venous ammonia level. 2. Child-Pugh score. 3. Minimal hepatic encephalopathy recovery.
Notes	Additional information provided by the author. Contacted Professor BC Sharma on 14 October 2010.

Risk of bias

Bias	Authors' judgement	Support for judgement
Sequence generation	Low risk	Participants were randomised according to a computer-generated randomisation chart.
Allocation concealment	High risk	Trial personnel were able to view the allocation sequence.
Blinding Participants	High risk	The trial was not blinded.
Blinding Personnel	High risk	The trial was not blinded.
Blinding Outcome assessors	High risk	The trial was not blinded.
Incomplete outcome data All outcomes	High risk	13 participants in the control group and 5 participants in the lactulose plus probiotic group were lost to follow-up. Reasons are unclear.
Selective outcome reporting	Low risk	All outcomes reported in the methods (psychometric tests outcomes, P300 auditory event-related potential, venous ammonia level, and Child-Pugh classification) were measured and discussed on baseline and after 1 month. Personal communication with the author revealed that no other outcomes were assessed.

Sharma 2008 *(Continued)*

Funding source	Unclear risk	Not stated

Sharma 2014

Methods	Design: a randomised parallel study Trial duration: 2 months Treatment duration: Duration of the treatment was 2 months ± 3 days, or unless the participant developed overt encephalopathy, expired, or was lost to follow-up.
Participants	Setting: Department of Gastroenterology at a teaching hospital Country: India Age range (years): range unspecified, mean (SD): 39.1 (12.8) Total numbers randomised: 124 Sex (M/F): 77/47 Language: unspecified Stage/severity of hepatic encephalopathy: minimal hepatic encephalopathy by psychometric tests (NCT-A, FCT-A, and DST) and critical flicker frequency (CFF); CTP A/B/C: 35/52/37 Cause of hepatic encephalopathy: anti-HCV positive/HBsAg positive/history of ethanol: 17/30/34 Inclusions: A total of 317 cirrhotics were screened; 111 were excluded, and the remaining 206 cirrhotics were screened for MHE using NPTs or CFF test or both. Exclusions: The exclusion criteria included: • People with overt HE or a history of overt HE in the past 6 weeks. • History of alcohol intake during past 6 weeks. • History of antibiotic or lactulose or probiotics use within the past 3 weeks. • Gastrointestinal bleed in the past 6 weeks. • History of recent use of drugs (< 6 weeks) affecting psychometric performance such as antidepressants, antiepileptic, sedatives, psychotropic drugs. • Spontaneous bacterial peritonitis or other infection in the past 7 days. • Renal insufficiency with creatinine > 1.5 mg/dL. • Electrolyte imbalance. • Hepatocellular carcinoma. • Significant comorbid illness, such as heart, respiratory, or renal failure; and any neurological disease that could interfere with intellect or motor performance of the person such as Alzheimer's or Parkinson's disease, respectively, or non-hepatic metabolic encephalopathies. • Previous transjugular intrahepatic portosystemic shunt or shunt surgery. • People who restarted alcohol consumption during follow-up. • Inability to do psychometric tests due to poor vision, or those having colour blindness. • People not having a fair knowledge of numbers and not having been to school for at least 2 years. • Women who were pregnant.
Interventions	After the diagnosis of MHE was made, the participants were randomised into 4 groups: DRUG 1 (l-ornithine l-aspartate (LOLA), 2 sachets 3 g each thrice a day) n = 31, DRUG 2 (tab rifaximin 400 mg thrice a day) n = 31, DRUG 3 (cap Velgut (5 billion CFUs of *Bifidobacterium breve*, *Bifidobacterium longum*, *Bifidobacterium infantis*, *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Lactobacillus casei*, *Lacto-*

Sharma 2014 *(Continued)*

	bacillus rhamnosus, *Streptococcus thermophilus*, *Saccharomyces boulardii*)1 capsule twice a day) n = 32, and DRUG 4 (placebo twice a day) n = 30.
Outcomes	1. Death. 2. Recovery from MHE. 3. Overt HE. 4. CFF.
Notes	Contacted Dr K Sharma on 14 March 2015, received no response. Funding source: "Source of Support: Nil, Conflict of Interest: None declared". This study declared the funding source and was deemed to be independently funded.

Risk of bias

Bias	Authors' judgement	Support for judgement
Sequence generation	Low risk	"the block randomization method was utilized for random allocation of drugs."
Allocation concealment	Low risk	"The sequence remained concealed from the investigator and the generator of the random blocks did not participate in screening, enrolment, or drug delivery."
Blinding Participants	High risk	The study was not blinded.
Blinding Personnel	High risk	The study was not blinded.
Blinding Outcome assessors	High risk	The study was not blinded.
Incomplete outcome data All outcomes	Unclear risk	A total of 20 participants could not be followed up to the end of the study: 10 were lost to follow-up, 6 went into overt HE, and 4 expired. Of the total 10 participants lost to follow-up, the most were in the LOLA group (4 cases) followed by the placebo group (3 cases). The largest number of deteriorations in clinical state, i.e. development of overt HE, occurred in the placebo group (3 cases). Of the total 4 deaths, 2 were in the placebo group and 1 each was in the rifaximin and Velgut groups. There were no deaths in the LOLA group.
Selective outcome reporting	Unclear risk	"Maximal number of deteriorations in clinical state, that is, development of overt HE among patients occurred in the placebo (3 cases) group." Overt HE development was not well reported.
Funding source	Low risk	"Source of Support: Nil, Conflict of Interest: None declared."

Shavakhi 2014

Methods	Design: randomised parallel trial + non-randomised cohort study Trial duration: 10 weeks Treatment duration: 2 weeks

Shavakhi 2014 *(Continued)*

Participants	Setting: The study was conducted on adults with MHE referred consecutively to the gastroenterology clinic of a university hospital in Isfahan city (Iran) between June and October 2012. Country: Iran Age range (years): range not given, mean age (SD) 38.4 (9.6) years Total numbers randomised: total (Gp-LPr/Gp-L): 46 (23/23) Sex (M/F): 48/12 Language: unspecified Stage/severity of hepatic encephalopathy: minimal hepatic encephalopathy; Child-Pugh score A/B/C: 8/37/14 (data missing for 1 participant) Cause of hepatic encephalopathy: viral/autoimmune/other: 44/11/5 Inclusions: The study was conducted on adults with MHE referred consecutively to the gastroenterology clinic of a university hospital in Isfahan city (Iran) between June and October 2012. Cirrhosis was diagnosed histologically (unless biopsy was contraindicated) and on clinical and radiological grounds. Diagnosis of MHE was based on the Conn's modification of the Parsons-Smith classification (grade 1 and above). Exclusions: People with overt HE, known brain lesions, active gastrointestinal bleeding, active ongoing infection, renal impairment (serum creatinine > 2 mg/dL), electrolyte abnormalities (serum sodium < 130 or > 150 meq/dL, serum potassium < 3.0 or > 5.5 meq/dL), and those who had received HE treatments such as lactulose and antibiotics or consumed benzodiazepines, narcotics, opioids, or alcohol in the preceding 8 weeks were not included in the trial.
Interventions	Participants were randomised into 2 groups: lactulose + probiotic (Gp-LPr) and lactulose + placebo (Gp-L). Another non-randomised group of participants who received probiotic alone (Gp-Pr) were included separately for further comparisons; this group received neither placebo nor lactulose. All participants received routine treatment for cirrhosis, including diuretics, β-blockers, endoscopic treatment, and a salt-restricted diet but not protein-restricted diet in those with ascites. For Gp-LPr and Gp-L, lactulose syrup was administered as 30 to 60 mL/day in divided doses for a stool frequency of 2 to 3 soft defecations per day. For Gp-LPr and Gp-Pr, a multistrain probiotics compound, Balance (Protexin Co., Somerset, UK), was administered twice daily after meal. Balance capsules contain 7 bacteria species including *Lactobacillus* strains (*L casei*, *L rhamnosus*, *L acidophilus*, and *L bulgaricus*), *Bifidobacterium* strains (*B breve* and *B longum*), and *Streptococcus thermophilus*. Total viable count is 1 × 108 CFU per capsule. Other ingredients are fructo-oligosaccharides as prebiotic, magnesium stearate, and hydroxypropyl methyl cellulose. These interventions were continued for 14 consecutive days, and compliance was assessed with pill and bottle count.
Outcomes	Primary endpoint was improvement in MHE status, which was assessed by applying the PHES at baseline, 14 days after start of the intervention (14th day), and then at 8 weeks' follow-up (10th week). The PHES is a set of neuropsychological tests including the Line-Tracing Test, Digit Symbol Test, Serial Dotting Test, and Number Connection Test. These tests are used in the diagnosis and grading of MHE and examine visual perception, visuospatial orientation, visual construction, motor speed and accuracy, concentration, attention, and memory. Participants could achieve between +6 and −18 points. Secondary outcomes were development of overt HE, admission to hospital for any other complication of cirrhosis, or death.
Notes	The study was also registered at Iranian Registry of Clinical Trials (IRCT201211012417N9). Contacted Dr A Shavakhi on 14 March 2015, received no response. Funding source: "Source of Support: Isfahan University of Medical Sciences, Potential competing interests: None declared". This study declared the funding source and was deemed to be independently funded.

Shavakhi 2014 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Sequence generation	Low risk	"Using a table of random numbers generated by random allocation software, patients were randomized into two groups".
Allocation concealment	Unclear risk	Unclear from study
Blinding Participants	High risk	"Because we could not provide an appropriate placebo for lactulose, our study was not completely randomized and double blinded, which could affect our results."
Blinding Personnel	High risk	"Because we could not provide an appropriate placebo for lactulose, our study was not completely randomized and double blinded, which could affect our results."
Blinding Outcome assessors	Unclear risk	Although the trial was not blinded, the objective nature of the tests for MHE would likely limit the effect of bias on MHE recovery outcomes.
Incomplete outcome data All outcomes	Low risk	"After randomization, two patients from the Gp-L, four patients from the Gp-LPr, and three patients from the Gp-Pr declined to receive intervention. Finally, 60 adult patients with cirrhosis (80% male, mean age 38.4 ± 9.6 years) started the trial and completed the intervention." "During the follow-up period, one patient from each of the Gp-LPr and Gp-L was lost to follow-up."
Selective outcome reporting	Unclear risk	The outcomes to be measured were not clearly specified in trial as registered at Iranian Registry of Clinical Trials (trial number IRCT201211012417N9).
Funding source	Low risk	"Source of Support: Isfahan University of Medical Sciences, Potential competing interests: None declared."

Vlachogiannakos 2014

Methods	Design: a randomised parallel trial Trial duration: 12 weeks Treatment duration: 12 weeks
Participants	Setting: unspecified Country: Greece Age range (years): range unspecified, mean (SD): 59 (10) Total numbers randomised: 72 Sex (M/F): 62/10 Language: unspecified Stage/severity of hepatic encephalopathy: minimal hepatic encephalopathy; "Mean (SD) Child-Pugh score: 6.4 (1.6), 46% Child-Pugh A, mean (SD) MELD score: 11.9 (3.6)" Cause of hepatic encephalopathy: 58% alcoholic cirrhosis

Vlachogiannakos 2014 *(Continued)*

	Inclusions: "In a period of 18 months, we screened 142 consecutive patients without overt HE for MHE using both, psychometric (number connection test, NCT) and neurophysiological (brainstem auditory evoked potentials, BAEP) modalities." Exclusions: unclear from abstract
Interventions	72 participants were equally randomised into *Lactobacillus plantarum* 299v at a dose of 1010 units per sachet (Lp299v) or identical placebo, given twice a day for a period of 12 weeks.
Outcomes	1. Development of overt HE. 2. Adherence to treatment. 3. MHE reversal. 4. Psychometric test score (NCT, BAEP). 5. Serum fasting ammonia.
Notes	Contaced Dr J Vlachogiannakos on 22 December 2014, received no response. Funding source: abstract only, unable to assess

Risk of bias

Bias	Authors' judgement	Support for judgement
Sequence generation	Unclear risk	Abstract only, unable to assess
Allocation concealment	Unclear risk	Abstract only, unable to assess
Blinding Participants	Low risk	"identical placebo" used
Blinding Personnel	Unclear risk	Abstract only, unable to assess
Blinding Outcome assessors	Unclear risk	Abstract only, unable to assess
Incomplete outcome data All outcomes	Unclear risk	Abstract only, unable to assess
Selective outcome reporting	Unclear risk	Abstract only, unable to assess
Funding source	Unclear risk	Abstract only, unable to assess

Zhao 2013

Methods	Design: randomised controlled trial Trial duration: 1 month Treatment duration: 1 month
Participants	Setting: hospital gastroenterology clinic Country: China

Zhao 2013 *(Continued)*

Age range (years): range unspecified, mean (SD): control group 41.15 (11.85), lactulose group 43.85 (11.10), probiotic group 44.25 (11.85)

Total numbers randomised: 120

Sex (M/F): 92/28

Language: Chinese language/s, with psychometric testing language adjusted to suit population

Stage/severity of hepatic encephalopathy: minimal hepatic encephalopathy; CTP A/B/C: 50/39/31

Cause of hepatic encephalopathy: chronic hepatitis B

Inclusions:

- Compliance with chronic hepatitis B prevention and treatment guidelines.
- Diagnosed with MHE based on psychometric testing.

Exclusions:

- Clinical symptoms of HE.
- Clinical symptoms of HE in last 6 weeks.
- History of upper GI bleeding in the last 6 weeks.
- Active infection.
- Renal impairment and creatinine greater than 133 μM/L.
- Electrolyte abnormality (Na+ < 130 mM/L or > 150 mM/L; K+ < 3 mM/L or > 5.5 mM/L).
- People with alcoholic cirrhosis.
- Recently taking antibiotics, probiotics, or aspartate/ornithine.
- Took psychotropic drugs in the last 6 weeks.
- TIPS shunt.
- Surgery.
- Liver tumours.
- Serious systemic disease such as heart failure, pulmonary disease, neurological and psychiatric illness.
- Visual impairment.
- Impairment on intelligence tests.

Interventions	Standard treatment of liver cirrhosis (control) compared to both lactulose (twice daily, 30 to 60 mL with soft stools 2 to 3 times daily) and probiotic (110 million CFU twice daily for 1 month) groups.
Outcomes	1. All-cause mortality. 2. MHE improvement. 3. Arterial ammonia level. 4. Adverse effects. 5. Change of/withdrawal from treatment.
Notes	We found no contact details. Funding source: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Sequence generation	Low risk	Randomised table used.
Allocation concealment	Unclear risk	Unclear from study

Zhao 2013 *(Continued)*

Blinding Participants	Unclear risk	Unclear from study
Blinding Personnel	Unclear risk	Unclear from study
Blinding Outcome assessors	Unclear risk	Unclear from study
Incomplete outcome data All outcomes	Unclear risk	Unclear from study
Selective outcome reporting	Unclear risk	Unclear from study
Funding source	Unclear risk	Unclear from study

Zhitai 2013

Methods	Design: unclear from abstract Trial duration: unclear from abstract Treatment duration: unclear from abstract
Participants	Setting: unclear from abstract Country: China Age range (years): unclear from abstract Total numbers randomised: 30 Sex (M/F): unclear from abstract Language: unclear from abstract Stage/severity of hepatic encephalopathy: hepatic encephalopathy (excluding clinical IV stage) Cause of hepatic encephalopathy: unclear from abstract Inclusions: unclear from abstract Exclusions: unclear from abstract
Interventions	Treatment group: routine liver protection against hepatic coma therapy, oral or nasal feeding of live *Bacillus cereus* capsules Control group: conventional liver protection against hepatic coma therapy, oral or nasal feeding of lactulose
Outcomes	1. Resolution of hepatic encephalopathy. 2. Blood ammonia levels.
Notes	We found no contact details. Funding source: abstract only, unable to assess

Zhitai 2013 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Sequence generation	Unclear risk	Abstract only, unable to assess
Allocation concealment	Unclear risk	Abstract only, unable to assess
Blinding Participants	Unclear risk	Abstract only, unable to assess
Blinding Personnel	Unclear risk	Abstract only, unable to assess
Blinding Outcome assessors	Unclear risk	Abstract only, unable to assess
Incomplete outcome data All outcomes	Unclear risk	Abstract only, unable to assess
Selective outcome reporting	Unclear risk	Abstract only, unable to assess
Funding source	Unclear risk	Abstract only, unable to assess

Ziada 2013

Methods	Design: randomised parallel trial Trial duration: 1 month Treatment duration: 1 month
Participants	Setting: outpatient clinic and inpatient wards Country: Egypt Age range (years): range unclear, group A/B /C mean (SD): 48.8 (8.2)/50.3 (7.8)/51.2 (7.5) Total numbers randomised: 90 Sex (M/F): 55/20 (excluding attrition) Language: unspecified Stage/severity of hepatic encephalopathy: minimal hepatic encephalopathy screened by NCT-A, DST, and SDT; Child A/B/C: 8/41/26 Cause of hepatic encephalopathy: unspecified Inclusions: All cirrhotic patients attending the Tropical Medicine and Infectious Disease outpatient clinic and inpatient wards from March 2010 to January 2012 were encouraged to join this prospective randomised trial. Exclusions: The exclusion criteria were the presence of overt HE, alcohol intake, gastrointestinal haemorrhage or spontaneous bacterial peritonitis during the past 6 weeks, previous shunt surgery and associated heart, respiratory, or renal failure as well as history of any neurologic or metabolic encephalopathies. People on psychoactive drugs such as antidepressants or sedatives were excluded.

Ziada 2013 *(Continued)*

Interventions	Group A received lactulose (30 to 60 mL/day); group B received a probiotic (1 capsule containing 10^6 *Lactobacillus acidophilus* 3 times/day); and group C was the control.
Outcomes	1. Psychometric tests (normalisation, persistence of abnormality in 1 psychometric test, no improvement). 2. Gut microecology study. 3. Ammonia level. 4. Brain metabolites using MRS.
Notes	Contacted Dr DH Ziada on 14 March 2015, received no response. Funding source: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Sequence generation	Unclear risk	"Patients were allocated by simple randomisation to three parallel equal groups of 30 patients each."
Allocation concealment	Unclear risk	Unclear from study
Blinding Participants	High risk	"This study was designed as overtime open-label randomised controlled trial testing the role of a probiotic in comparison with lactulose or no therapy in MHE patients."
Blinding Personnel	High risk	"This study was designed as overtime open-label randomised controlled trial testing the role of a probiotic in comparison with lactulose or no therapy in MHE patients."
Blinding Outcome assessors	Low risk	Although the trial was not blinded, the objective nature of the tests for MHE would likely limit the effect of bias on MHE recovery outcomes.
Incomplete outcome data All outcomes	Low risk	Group A: 30 allocated to lactulose, 30 received lactulose, 2 lost to follow-up, 2 discontinued therapy, 2 overt encephalopathy, 24 participants analysed. Group B: 30 allocated to probiotics, 30 received probiotics, 2 lost to follow-up, 1 discontinued therapy, 1 overt encephalopathy, 26 participants analysed. Group C: 30 allocated, 0 lost to follow-up, 5 overt encephalopathy, 25 analysed.
Selective outcome reporting	Unclear risk	Unable to assess
Funding source	Unclear risk	"The authors declared that there is no conflict of interest".

ALT = alanine aminotransferase; BAEP = brainstem auditory evoked potentials; CFF = critical flicker frequency; CFU = colony forming unit; CNS = central nervous system; CT = computed tomography; CTP = Child-Turcotte-Pugh; DST = digit symbol test; FCT = figure connection test; GI = gastrointestinal; HBV = hepatitis B virus; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HE = hepatic encephalopathy; HRQOL = health-related quality of life; IL-6 = interleukin 6; LOLA = L-ornithine-L-aspartate; MCS = Mental Component summary; MELD = Model for End-Stage Liver Disease; MHE = minimal hepatic encephalopathy; MRS = Magnetic resonance spectroscopy; NASH = non-alcoholic steatohepatitis;
NCT = Number Connection Test; NIH = National Institutes of Health; NPT = neuropsychological testing; OCTT = orocaecal transit time; OHE = overt hepatic encephalopathy; PHES = psychometric hepatic encephalopathy score; QOL= quality of life; SD = standard deviation; SDT = serial dotting test; SF-36 = 36-Item Short Form Health Survey; SIBO = small intestinal bacterial overgrowth; TIPS = transjugular intrahepatic portosystemic shunt; TNF alpha = tumour necrosis factor-alpha; USG = ultrasonography

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Adams 2006	No hepatic encephalopathy patients involved
Agrawal 2012	Not a randomised trial
Agrawal 2012a	Hepatic encephalopathy not used as participant selection criteria
Al 2009	Not a randomised trial
Albillos 2002	No hepatic encephalopathy patients involved
Alisi 2014	No hepatic encephalopathy patients involved
Aller 2011	No hepatic encephalopathy patients involved
Almeida 2006	Not a randomised trial
Arya 2010	Not a randomised trial
Bai 2013	Not a randomised trial
Bajaj 2008a	Not a randomised trial
Bajaj 2008b	Not a randomised trial
Bajaj 2014	Not a randomised trial
Barclay 2011	Not a randomised trial
Barreto-Zuniga 2001	No hepatic encephalopathy patients involved
Bass 2007	Not a randomised trial
Bengmark 2009a	Not a randomised trial
Bengmark 2011	Not a randomised trial
Bengmark 2013	Not a randomised trial
Bismuth 2011	Not a randomised trial
Boca 2004	Not a randomised trial
Bongaerts 2005	Not a randomised trial
Cabre 2005	Not a randomised trial
Cash 2010	Not a randomised trial
Chadalavada 2010	Not a randomised trial
Chauhan 2012	Not a randomised trial

Study	Reason for exclusion
Cheung 2012	Not a randomised trial
Chikhacheva 2014	Not a randomised trial
Ciorba 2012	Not a randomised trial
Colle 1989	Hepatic encephalopathy not confirmed
Conn 1970	Not a randomised trial
Crittenden 2013	Not a randomised trial
Dai 2014	No probiotic used
Dasarathy 2003	No probiotic used
Dbouk 2006	Not a randomised trial
De Micco 2012	Not a randomised trial
Demeter 2006	Not a randomised trial
Dhiman 2004	Not a randomised trial
Dhiman 2007	Not a randomised trial
Dhiman 2009	Not a randomised trial
Dhiman 2010	Not a randomised trial
Dhiman 2012	Hepatic encephalopathy not used as participant selection criteria
Dhiman 2013	Not a randomised trial
Dhiman 2014	Hepatic encephalopathy not used as participant selection criteria
Dhiman 2015	Not a randomised trial
Ding 2014	Not a randomised trial
Ding 2014a	Not a randomised trial
Doron 2005	Not a randomised trial
Druart 2014	Not a randomised trial
Dylag 2014	Not a randomised trial
EASL 2012	Not a randomised trial
Eguchi 2011	Not probiotic
El-Nezami 2006	No hepatic encephalopathy patients involved
Eslamparast 2014	No hepatic encephalopathy patients involved

Study	Reason for exclusion
Fan 2009	No hepatic encephalopathy patients involved
Fan 2013	Not a randomised trial
Fehervari 2012	Not a randomised trial
Ferenci 2001	Not a randomised trial
Ferenci 2007	Not a randomised trial
Feret 2010	Not probiotic
Ferreira 2010	Not a randomised trial
Festi 2014	Not a randomised trial
Finney 2007	No probiotics used
Floch 2015	Not a randomised trial
Fontana 2013	Not a randomised trial
Fooladi 2013	Not a randomised trial
Foster 2010	Not a randomised trial
Fujita 2008	No hepatic encephalopathy patients involved
Fuster 2007	Not a randomised trial
Galhenage 2006	Not a randomised trial
Ganguli 2013	No hepatic encephalopathy patients involved
Garcia 2012	Not a randomised trial
Garcovich 2012	Not a randomised trial
Gareau 2014	Not a randomised trial
Gluud 2013	Not a randomised trial
Gomez-Hurtado 2014	Not a randomised trial
Grat 2014	Not a randomised trial
Gratz 2010	Not a randomised trial
Greco 2007	Groups non-comparable
Gu 2014	No hepatic encephalopathy patients involved
Guarner 2009	Not a randomised trial
Guarner 2012	Not a randomised trial

Study	Reason for exclusion
Guerrero 2008	Not a randomised trial
Gupta 2010	No hepatic encephalopathy patients involved
Gupta 2010a	No hepatic encephalopathy patients involved
Gupta 2013	No hepatic encephalopathy patients involved
Hellinger 2002	No probiotic used
Higashikawa 2010	No hepatic encephalopathy patients involved
Holte 2012	Not a randomised trial
Hotten 2003	No hepatic encephalopathy patients involved
Hutt 2011	Not a randomised trial
Ianiro 2014	Not a randomised trial
Iannitti 2010	Not a randomised trial
Imler 1971	Not a randomised trial
Ivanovic 2015	Not a randomised trial
Janczyk 2012	Not a randomised trial
Jayakumar 2012	No hepatic encephalopathy patients involved
Jayakumar 2013	No hepatic encephalopathy patients involved
Jeejeebhoy 2004	Not a randomised trial
Jiang 2008	No probiotics used
Jones 2013	No hepatic encephalopathy patients involved
Jonkers 2007	Not a randomised trial
Jover-Cobos 2014	Not a randomised trial
Jun 2013	No hepatic encephalopathy patients involved
Jurado 2012	Not a randomised trial
Kachaamy 2011	Not a randomised trial
Kadayifci 2007	Not a randomised trial
Karczewski 2010	No hepatic encephalopathy patients involved
Keeffe 2007	Not a randomised trial
Khungar 2012	Not a randomised trial

Study	Reason for exclusion
Kirpich 2008	No hepatic encephalopathy patients involved
Kitagawa 2015	Not a randomised trial
Koga 2013	No hepatic encephalopathy patients involved
Kremer 1974	Not a randomised trial
Kumashiro 2008	Not a randomised trial
Kwak 2014	No hepatic encephalopathy patients involved
Lata 2006	No hepatic encephalopathy patients involved
Lata 2007	No hepatic encephalopathy patients involved
Lata 2007a	No hepatic encephalopathy patients involved
Lata 2009	No hepatic encephalopathy patients involved
Lata 2011	Not a randomised trial
Leber 2012	Not a randomised trial
Liboredo 2015	Not a randomised trial
Lien 2015	No hepatic encephalopathy patients involved
Lighthouse 2004	No hepatic encephalopathy patients involved
Liu 2006	Not available
Liu 2009	Not available
Liu 2010	Not a randomised trial
Liu 2012	Not a randomised trial
Llorente 2015	Not a randomised trial
Loguercio 2002	No hepatic encephalopathy patients involved
Loguercio 2005	No hepatic encephalopathy patients involved
Louvet 2015	Not a randomised trial
Lu 2011	Not a randomised trial
Luna 2010	Hepatic encephalopathy not used as patient selection criteria
Lunia 2012	Hepatic encephalopathy not used as patient selection criteria
Lunia 2014a	Hepatic encephalopathy not used as patient selection criteria
Luo 2011	Not a randomised trial

Study	Reason for exclusion
Ma 2013	Not a randomised trial
Machado 2012	Not a randomised trial
Madsen 2008	No hepatic encephalopathy patients involved
Malaguarnera 2007	Not a probiotic alone
Malaguarnera 2012	No hepatic encephalopathy patients involved
Marteau 2001	Not a randomised trial
Marteau 2002	Not a randomised trial
Marteu 2001	Not a randomised trial
Michelfelder 2010	Not a randomised trial
Minemura 2015	Not a randomised trial
Mishra 2012	Not a randomised trial
Mohammad 2012	Not a randomised trial
Montagnese 2012	Not a randomised trial
Montgomery 2011	Not a randomised trial
Montrose 2005	Not a randomised trial
Moreno-Luna 2011	Not a randomised trial
Morgan 2007	Not a randomised trial
Mullen 2007	Not a randomised trial
Nabavi 2014	No hepatic encephalopathy patients involved
Nazir 2010	Prophylaxis, not treatment
NCT01135628	Not a randomised trial
Olveira 2007	Not a randomised trial
Oshea 2010	Not a randomised trial
Pande 2009	No hepatic encephalopathy patients involved
Pande 2012	No hepatic encephalopathy patients involved
Paolella 2014	Not a randomised trial
Park 2007	Not a randomised trial
Patel 2015	Not a randomised trial

Study	Reason for exclusion
Pawar 2012	Hepatic encephalopathy not used as participant selection criteria
Phongsamran 2010	Not a randomised trial
Plaza-Diaz 2014	No hepatic encephalopathy patients involved
Poh 2012	Not a randomised trial
Poustchi 2013	No hepatic encephalopathy patients involved
Prakash 2013	Not a randomised trial
Quigley 2006	Not a randomised trial
Quigley 2013	Not a randomised trial
Quigley 2014	Not a randomised trial
Quigley 2014a	Not a randomised trial
Rahimi 2012	Not a randomised trial
Rahimi 2013	Not a randomised trial
Rayes 2001	No hepatic encephalopathy patients involved
Rayes 2002	No hepatic encephalopathy patients involved
Rayes 2005	No hepatic encephalopathy patients involved
Rayes 2012	No hepatic encephalopathy patients involved
Read 1966	Not a randomised trial
Reddy 2013	Not a randomised trial
Rifatbegovic 2010	No hepatic encephalopathy patients involved
Riggio 2009	Not a randomised trial
Rincon 2014	Not a randomised trial
Riordan 2007	No hepatic encephalopathy patients involved
Riordan 2010	No probiotic used
Rivkin 2011	Not a randomised trial
Romero-Gomez 2010	Not a randomised trial
Sanchez 2015	No hepatic encephalopathy patients involved
Scevola 1989	No probiotics used
Schiano 2010	Not a randomised trial

Study	Reason for exclusion
Schuster-Wolff-Bühring 2010a	Not a randomised trial
Schuster-Wolff-Bühring 2010b	Not a randomised trial
Segura-Ortega 2010	No hepatic encephalopathy patients involved
Shang 2013	No hepatic encephalopathy patients involved
Sharma 2010	Not a randomised trial
Sharma 2012	No probiotic used
Sharma 2013	Not a randomised trial
Sharma 2014a	Hepatic encephalopathy not used as participant selection criteria
Sharma 2014b	Not a randomised trial
Sharma 2015	Not a randomised trial
Shawcross 2005	Not a randomised trial
Shen 2013	Not available
Shen 2014	Not available
Sheth 2008	Not a randomised trial
Shu 2008	Not available
Shukla 2009	Not a randomised trial
Shukla 2010	Not a randomised trial
Shukla 2010a	Not a randomised trial
Shukla 2011	Not a randomised trial
Solga 2003	Not a randomised trial
Soriano 2013	Not a randomised trial
Soriano 2013a	Not a randomised trial
Stadlbauer 2008	No hepatic encephalopathy patients involved
Stewart 2007	Not a randomised trial
Strasser 2011	Not a randomised trial
Suk 2012	No hepatic encephalopathy patients involved
Sundaram 2009	Not a randomised trial
Tang 2011	Not a randomised trial

Study	Reason for exclusion
Tapper 2015	Not a randomised trial
Tarantino 2015	Not a randomised trial
Tarao 1995	No probiotics used
Tojo 2014	Not a randomised trial
Toris 2011	Not a randomised trial
Tsochatzis 2012	Not a randomised trial
Tsochatzis 2014	Not a randomised trial
Upadhyay 2012	Not a randomised trial
Usami 2011	No hepatic encephalopathy patients involved
Valentini 2015	No hepatic encephalopathy patients involved
Videhult 2015	No hepatic encephalopathy patients involved
Vilstrup 2014	Not a randomised trial
Vilstrup 2014a	Not a randomised trial
Vyas 2012	Not a randomised trial
Waghray 2014	Not a randomised trial
Waghray 2015	Not a randomised trial
Wang 2012	Not available
Wang 2015	Not available
Welliver 2012	Not a randomised trial
Wong 2013a	No hepatic encephalopathy patients involved
Woo 2012	Not a randomised trial
Wright 2007	Not a randomised trial
Wu 2008	Not a randomised trial
Xu 2012	Not a randomised trial
Xu 2014	Not a randomised trial
Xu 2014a	Not a randomised trial
Yakabe 2009	No hepatic encephalopathy patients involved
Yao 2014	Not a randomised trial

Study	Reason for exclusion
Yasutake 2012	Not a randomised trial
Zafirova 2010	Not a randomised trial
Zamberlin 2012	Not a randomised trial
Zhang 2014	Not a randomised trial
Zhao 2004	No hepatic encephalopathy patients involved
Zucker 2014	Not a randomised trial

Characteristics of studies awaiting assessment *[ordered by study ID]*

ACTRN12610001021066

Methods	Design: randomised controlled trial Trial duration: 2 months Treatment duration: 2 months
Participants	Country: Australia Age range (years): Total numbers randomised: 80 target sample size Inclusions: Child's B or C cirrhosis on lactulose aged between 18 and 70 years who are abstinent from alcohol and illegal drugs for at least 6 months. If on methadone, must be dose stable for > 6 months. Exclusions: • Pregnancy. • < 18 years. • > 70 years. • Current alcohol use. • Current intravenous drug use. • Sepsis. • Grade 4 encephalopathy.
Interventions	1. Synbiotics + branched-chain amino acids (BCAAs). 2. BCAAs + placebo for synbiotics. 3. Placebo for BCAAs + placebo for synbiotics. Synbiotic 2000 Forte is packaged in 10-gram single-dose sachets containing the following: Natural and digestible fibres: * 2.5 g oat bran; * 2.5 g pectin; * 2.5 g resistant starch; * 2.5 g inulin. Probiotic bacteria: * *Lactobacillus paracasei* ssp *paracasei* 10 x 10^{11}; * *Lactobacillus plantarum* 10 x 10^{11}; * *Leuconostoc mesenteroides* 10 x 10^{11}; * *Pediococcus pentosaceus* 10 x 10^{11} (Medipharm). Dose is 1 sachet/day mixed with juice, jam, or honey according to participant's tolerance. Duration of supplementation is 56 days. Branched-chain amino acid preparation is HepatAmine (Nutricia), which is a mixture of branched-chain amino acids + sugars. Dose is 1 sachet at night mixed with 200 mL lemonade or fruit juice. Duration of supplementation is 56 days.

ACTRN12610001021066 *(Continued)*

	Placebo for synbiotics is 10 g crystalline starch packaged similarly to Synbiotic 2000 Forte. Dose is 1 sachet/day mixed with juice, jam, or honey according to participant's tolerance. Duration of supplementation is 56 days. Placebo for BCAAs is 29 g glucose + 15 g Vitafresh. Dose is 1 sachet at night mixed with 200 mL lemonade or fruit juice. Duration of supplementation is 56 days.
Outcomes	Primary outcome: 1. Effects of supplementation with synbiotics and/or BCAAs on levels of hepatic encephalopathy (Trail Making Tests A and B and the Inhibitory Control Test). Secondary outcomes: 1. Effects of synbiotics or BCAAs or both on quality of life outcomes measured by liver disease short form quality of life (SFLDQOL) questionnaire and depression and anxiety score (DASS). 2. Effects of supplementation with synbiotics or BCAAs or both on frequency of hospitalisation. 3. Effects of supplementation with synbiotics or BCAAs or both on severity of the participant's chronic liver disease using the Child-Pugh Score and Model for End-Stage Liver Disease (MELD). 4. Effects of supplementation with synbiotics or BCAAs or both on body composition and hand grip strength. (Body composition is assessed by anthropometry, measurements of midarm circumference and triceps skinfold and calculated midarm muscle circumference. Hand grip strength is measured using a dynamometer.) 5. Effects of supplementation with synbiotics or BCAAs or both on appetite and oral intake. (Appetite is a subjective assessment by the participant using a visual analogue scale. Oral intake is assessed using a 3-day food history recorded by the participant at each time point).
Notes	Data obtained from trial registry www.anzctr.org.au/, trial ID: ACTRN12610001021066.

IRCT201211012417N9

Methods	Design: randomised controlled trial Trial duration: 14 days Treatment duration: 14 days
Participants	Country: Iran Age range: between 18 to 65 years Total number randomised: target sample size 40 Inclusion criteria: • Age between 18 to 65 years. • Diagnosis of hepatic encephalopathy. • Filling consent form. Exclusion criteria: • Refusal to fill consent form. • Active gastrointestinal bleeding. • Alcohol usage. • Active infection. • Lactolos or antibiotic therapy within the previous 2 weeks. • Space-occupying lesion in central nervous system.
Interventions	Intervention 1: probiotic capsule (Protexin).

IRCT201211012417N9 *(Continued)*

	Intervention 2: placebo capsule.
Outcomes	Consiousness level. (Time point: beginning and 14 days postintervention. Method of measurement: questionnaire.)
Notes	Data obtained from apps.who.int/trialsearch/Trial2.aspx?TrialID=IRCT201211012417N9.

NCT01798329

Methods	Design: randomised controlled trial Trial duration: 15 weeks Treatment duration: 15 weeks
Participants	Country: Italy Age range (years): 4 to 20 Total numbers randomised: target sample size 50 Inclusion criteria: • Extra-hepatic portal vein thrombosis. • Age between 4 and 20 years. • Knowledge of Italian language. • Absence of perceptive or communicative deficit. • Absence of psychiatric disease or mental retardation. Exclusion criteria: • Medical contraindications for required evaluations. • Infective pathologies. • Parenchymal hepatic pathologies.
Interventions	Dietary supplement: probiotic VSL#3
Outcomes	Primary outcome 1. Neuropsychological and electrophysiological aspects [Time Frame: after 15 weeks of probiotic or placebo treatment]. Secondary outcomes 1. Abdomen scan with colour Doppler technique [Time Frame: after 15 weeks of probiotic or placebo treatment]. 2. Biochemical blood test [Time Frame: after 15 weeks of probiotic or placebo treatment]. 3. Bowel frequency and characteristics [Time Frame: after 15 weeks of probiotic or placebo treatment]. 4. Dietary anamnesis (last 3 days) [Time Frame: after 15 weeks of probiotic or placebo treatment]. 5. Neurological evaluation [Time Frame: after 15 weeks of probiotic or placebo treatment]. 6. Urine and faeces analysis [Time Frame: after 15 weeks of probiotic or placebo treatment].
Notes	Data obtained from apps.who.int/trialsearch/Trial2.aspx?TrialID=NCT01798329.

DATA AND ANALYSES

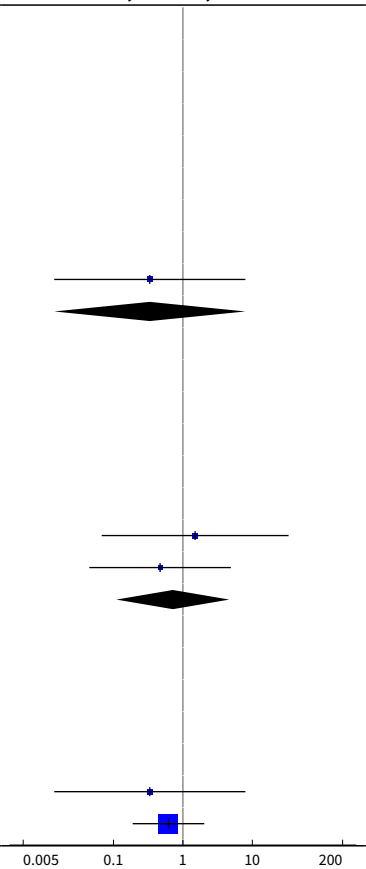
Comparison 1. Probiotic versus placebo or no intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	7	404	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.23, 1.44]
1.1 2 weeks	1	46	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 1 month	1	80	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 7.95]
1.3 2 months	3	117	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.11, 4.66]
1.4 3 months	2	161	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.19, 1.74]
2 No recovery (incomplete resolution of clinical symptoms)	10	574	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.56, 0.79]
2.1 1 month	4	228	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.58, 0.96]
2.2 2 months	3	117	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.38, 1.10]
2.3 3 months	3	229	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.43, 0.78]
3 Adverse events	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Overt hepatic encephalopathy	10	585	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.16, 0.51]
3.2 Infection	1	37	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 Hospitalisation	3	163	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.11, 4.00]
3.4 Intolerance leading to discontinuation	1	37	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.5 Change of/or withdrawal from treatment	9	551	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.46, 1.07]
4 Quality of life	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 SF-36 Physical	1	20	Mean Difference (IV, Random, 95% CI)	0.0 [-5.47, 5.47]
4.2 SF-36 Mental	1	20	Mean Difference (IV, Random, 95% CI)	-4.0 [-9.82, 1.82]
4.3 Change in Total SIP Score	2	95	Mean Difference (IV, Random, 95% CI)	-3.66 [-7.75, 0.44]
4.4 Change in SIP Psychological Score	2	95	Mean Difference (IV, Random, 95% CI)	-3.54 [-4.95, -2.12]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
4.5 Change in SIP Physical Score	2	95	Mean Difference (IV, Random, 95% CI)	-2.94 [-4.44, -1.44]
5 Plasma ammonia concentration (final and change scores) (µmol/L)	10	705	Mean Difference (IV, Random, 95% CI)	-8.29 [-13.17, -3.41]
5.1 1 month	5	357	Mean Difference (IV, Random, 95% CI)	-5.55 [-10.67, -0.42]
5.2 2 months	4	211	Mean Difference (IV, Random, 95% CI)	-5.11 [-14.56, 4.34]
5.3 3 months	1	73	Mean Difference (IV, Random, 95% CI)	-6.79 [-10.39, -3.19]
5.4 6 months	1	64	Mean Difference (IV, Random, 95% CI)	-31.08 [-40.50, -21.66]

Analysis 1.1. Comparison 1 Probiotic versus placebo or no intervention, Outcome 1 All-cause mortality.

Study or subgroup	Probiotic n/N	No intervention n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 2 weeks					
Shavakhi 2014	0/23	0/23			Not estimable
Subtotal (95% CI)	**23**	**23**			**Not estimable**
Total events: 0 (Probiotic), 0 (No intervention)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.1.2 1 month					
Zhao 2013	0/40	1/40		8.33%	0.33[0.01,7.95]
Subtotal (95% CI)	**40**	**40**		**8.33%**	**0.33[0.01,7.95]**
Total events: 0 (Probiotic), 1 (No intervention)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.68(P=0.5)					
1.1.3 2 months					
Bajaj 2014a	0/14	0/16			Not estimable
Bajaj 2008	1/17	0/8		8.73%	1.5[0.07,33.26]
Sharma 2014	1/32	2/30		15.2%	0.47[0.04,4.91]
Subtotal (95% CI)	**63**	**54**		**23.92%**	**0.72[0.11,4.66]**
Total events: 2 (Probiotic), 2 (No intervention)					
Heterogeneity: Tau^2=0; Chi^2=0.34, df=1(P=0.56); I^2=0%					
Test for overall effect: Z=0.35(P=0.73)					
1.1.4 3 months					
Mittal 2009	0/40	1/40		8.33%	0.33[0.01,7.95]
Lunia 2014	4/42	6/39		59.41%	0.62[0.19,2.03]



Study or subgroup	Probiotic n/N	No intervention n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Subtotal (95% CI)	**82**	**79**		**67.74%**	**0.57[0.19,1.74]**
Total events: 4 (Probiotic), 7 (No intervention)					
Heterogeneity: Tau^2=0; Chi^2=0.13, df=1(P=0.72); I^2=0%					
Test for overall effect: Z=0.98(P=0.33)					
Total (95% CI)	**208**	**196**		**100%**	**0.58[0.23,1.44]**
Total events: 6 (Probiotic), 10 (No intervention)					
Heterogeneity: Tau^2=0; Chi^2=0.64, df=4(P=0.96); I^2=0%					
Test for overall effect: Z=1.17(P=0.24)					
Test for subgroup differences: Chi^2=0.17, df=1 (P=0.92), I^2=0%					

Favours probiotic 0.005 0.1 1 10 200 Favours control

Analysis 1.2. Comparison 1 Probiotic versus placebo or no intervention, Outcome 2 No recovery (incomplete resolution of clinical symptoms).

Study or subgroup	Probiotic n/N	No intervention n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 1 month					
Liu 2004	10/20	10/20		6%	1[0.54,1.86]
Sharma 2008	13/30	14/31		6.86%	0.96[0.55,1.69]
Ziada 2013	13/27	27/30		10.2%	0.53[0.36,0.81]
Zhao 2013	24/36	30/34		15%	0.76[0.58,0.98]
Subtotal (95% CI)	**113**	**115**		**38.06%**	**0.75[0.58,0.96]**
Total events: 60 (Probiotic), 81 (No intervention)					
Heterogeneity: Tau^2=0.02; Chi^2=4.19, df=3(P=0.24); I^2=28.32%					
Test for overall effect: Z=2.3(P=0.02)					
1.2.2 2 months					
Bajaj 2008	5/17	8/8		4.84%	0.32[0.16,0.66]
Bajaj 2014a	10/14	12/16		9.51%	0.95[0.62,1.47]
Sharma 2014	16/32	21/30		9.96%	0.71[0.47,1.09]
Subtotal (95% CI)	**63**	**54**		**24.31%**	**0.65[0.38,1.1]**
Total events: 31 (Probiotic), 41 (No intervention)					
Heterogeneity: Tau^2=0.15; Chi^2=6.55, df=2(P=0.04); I^2=69.45%					
Test for overall effect: Z=1.62(P=0.11)					
1.2.3 3 months					
Vlachogiannakos 2014	14/35	30/33		9.92%	0.44[0.29,0.67]
Lunia 2014	20/42	34/39		12.28%	0.55[0.39,0.77]
Mittal 2009	26/40	36/40		15.44%	0.72[0.56,0.93]
Subtotal (95% CI)	**117**	**112**		**37.63%**	**0.58[0.43,0.78]**
Total events: 60 (Probiotic), 100 (No intervention)					
Heterogeneity: Tau^2=0.04; Chi^2=4.82, df=2(P=0.09); I^2=58.54%					
Test for overall effect: Z=3.63(P=0)					
Total (95% CI)	**293**	**281**		**100%**	**0.67[0.56,0.79]**
Total events: 151 (Probiotic), 222 (No intervention)					
Heterogeneity: Tau^2=0.04; Chi^2=17.48, df=9(P=0.04); I^2=48.5%					
Test for overall effect: Z=4.49(P<0.0001)					

Favours probiotic 0.1 0.2 0.5 1 2 5 10 Favours control

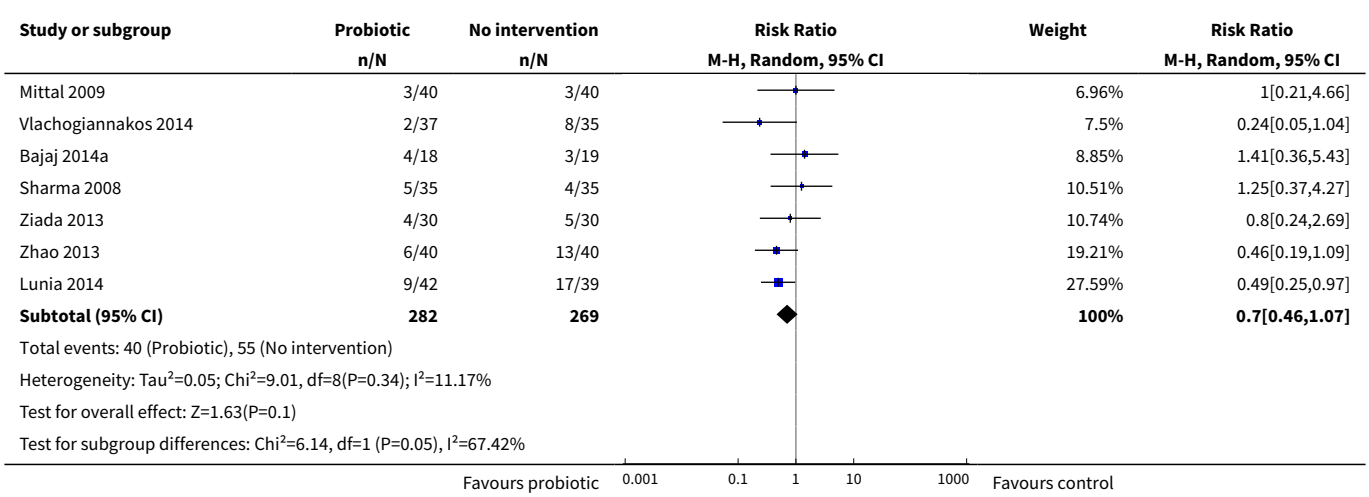
Study or subgroup	Probiotic n/N	No intervention n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for subgroup differences: Chi²=1.68, df=1 (P=0.43), I²=0%					

Favours probiotic 0.1 0.2 0.5 1 2 5 10 Favours control

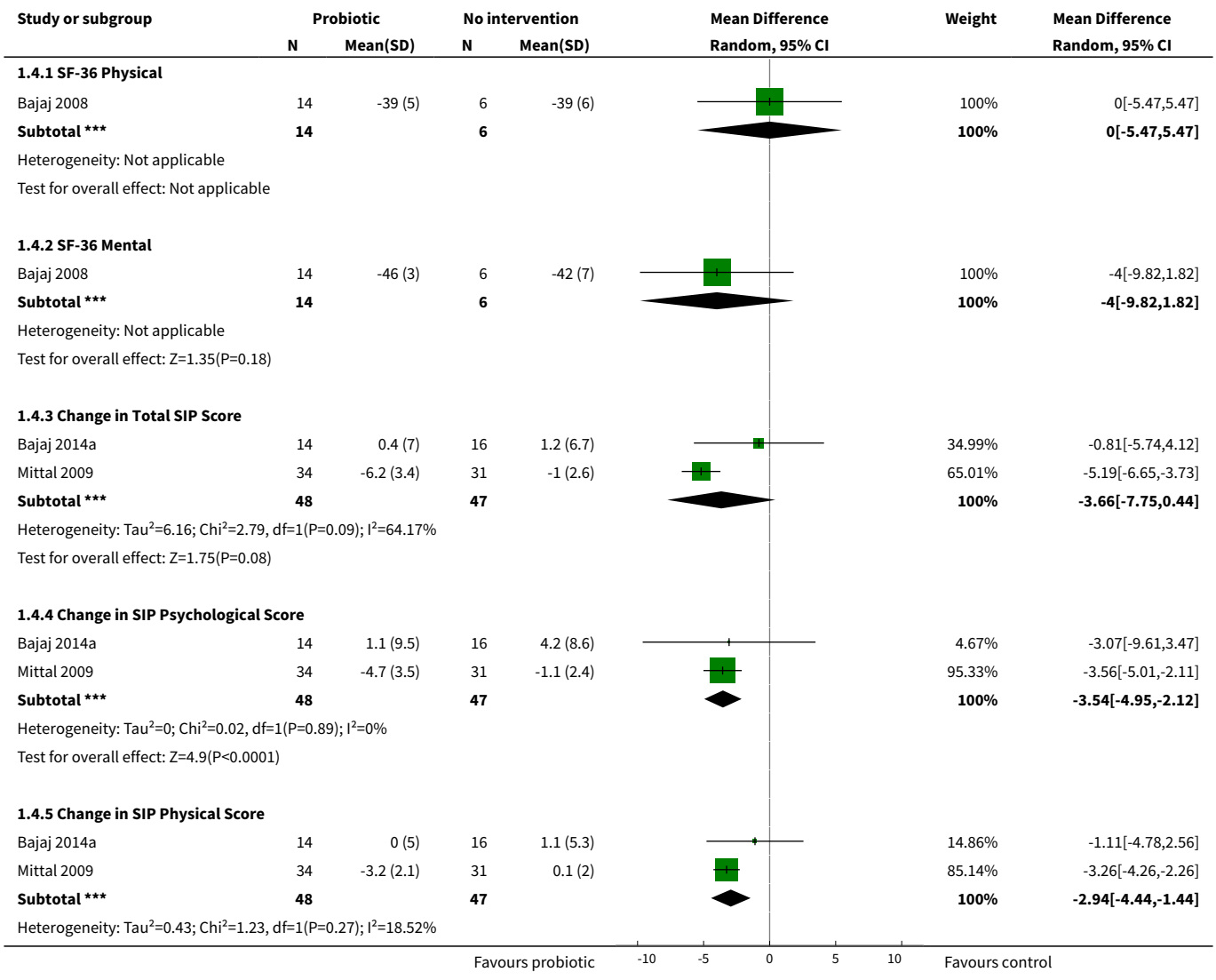
Analysis 1.3. Comparison 1 Probiotic versus placebo or no intervention, Outcome 3 Adverse events.

Study or subgroup	Probiotic n/N	No intervention n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 Overt hepatic encephalopathy					
Liu 2004	0/20	0/20			Not estimable
Bajaj 2014a	0/18	0/19			Not estimable
Shavakhi 2014	0/23	1/23		3.4%	0.33[0.01,7.78]
Bajaj 2008	0/17	2/8		3.94%	0.1[0.01,1.87]
Vlachogiannakos 2014	0/37	6/35		4.19%	0.07[0,1.25]
Ziada 2013	1/30	5/30		7.76%	0.2[0.02,1.61]
Mittal 2009	2/40	4/40		12.56%	0.5[0.1,2.58]
Zhao 2013	2/40	7/40		14.83%	0.29[0.06,1.29]
Qiao 2010	2/32	12/32		16.89%	0.17[0.04,0.69]
Lunia 2014	5/42	11/39		36.42%	0.42[0.16,1.11]
Subtotal (95% CI)	**299**	**286**		**100%**	**0.29[0.16,0.51]**
Total events: 12 (Probiotic), 48 (No intervention)					
Heterogeneity: Tau²=0; Chi²=3.26, df=7(P=0.86); I²=0%					
Test for overall effect: Z=4.22(P<0.0001)					
1.3.2 Infection					
Bajaj 2014a	0/18	0/19			Not estimable
Subtotal (95% CI)	**18**	**19**			**Not estimable**
Total events: 0 (Probiotic), 0 (No intervention)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.3.3 Hospitalisation					
Bajaj 2014a	0/18	0/19			Not estimable
Shavakhi 2014	1/23	1/23		43.12%	1[0.07,15.04]
Mittal 2009	1/40	2/40		56.88%	0.5[0.05,5.3]
Subtotal (95% CI)	**81**	**82**		**100%**	**0.67[0.11,4]**
Total events: 2 (Probiotic), 3 (No intervention)					
Heterogeneity: Tau²=0; Chi²=0.14, df=1(P=0.71); I²=0%					
Test for overall effect: Z=0.43(P=0.66)					
1.3.4 Intolerance leading to discontinuation					
Bajaj 2014a	0/18	0/19			Not estimable
Subtotal (95% CI)	**18**	**19**			**Not estimable**
Total events: 0 (Probiotic), 0 (No intervention)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.3.5 Change of/or withdrawal from treatment					
Bajaj 2008	3/17	0/8		2.13%	3.5[0.2,60.7]
Shavakhi 2014	4/23	2/23		6.51%	2[0.41,9.87]

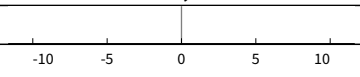
Favours probiotic 0.001 0.1 1 10 1000 Favours control



Analysis 1.4. Comparison 1 Probiotic versus placebo or no intervention, Outcome 4 Quality of life.

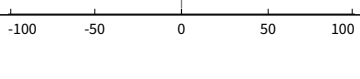


Study or subgroup	Probiotic N	Probiotic Mean(SD)	No intervention N	No intervention Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Test for overall effect: Z=3.85(P=0)							



Analysis 1.5. Comparison 1 Probiotic versus placebo or no intervention, Outcome 5 Plasma ammonia concentration (final and change scores) (µmol/L).

Study or subgroup	Probiotic N	Probiotic Mean(SD)	No intervention N	No intervention Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.5.1 1 month							
Sharma 2008	30	68.7 (28.4)	31	69.3 (33.3)		5.81%	-0.6[-16.11,14.91]
Ziada 2013	26	52.5 (21.7)	25	74.5 (23.3)		7.38%	-22.07[-34.45,-9.69]
Malaguarnera 2010	63	66.2 (28.8)	62	71.5 (29.8)		8.67%	-5.25[-15.53,5.03]
Zhao 2013	40	72.9 (15.8)	40	76.4 (10.2)		11.72%	-3.48[-9.32,2.36]
Liu 2004	20	38.6 (3.9)	20	41.5 (5.2)		13.44%	-2.9[-5.75,-0.05]
Subtotal ***	**179**		**178**			**47.02%**	**-5.55[-10.67,-0.42]**
Heterogeneity: Tau^2=16.49; Chi^2=9, df=4(P=0.06); I^2=55.54%							
Test for overall effect: Z=2.12(P=0.03)							
1.5.2 2 months							
Pereg 2011	18	42.1 (26.9)	18	45.2 (23.6)		5.38%	-3.1[-19.63,13.43]
Bajaj 2008	14	50 (26)	6	40 (3)		6.61%	10[-3.83,23.83]
Bajaj 2014a	14	29.3 (13.7)	16	43.4 (19.7)		7.59%	-14.1[-26.13,-2.07]
Malaguarnera 2010	63	55.9 (15.5)	62	65.3 (22.3)		11.1%	-9.35[-16.09,-2.61]
Subtotal ***	**109**		**102**			**30.67%**	**-5.11[-14.56,4.34]**
Heterogeneity: Tau^2=55.43; Chi^2=7.82, df=3(P=0.05); I^2=61.65%							
Test for overall effect: Z=1.06(P=0.29)							
1.5.3 3 months							
Mittal 2009	37	-7.3 (7.9)	36	-0.5 (7.8)		13.08%	-6.79[-10.39,-3.19]
Subtotal ***	**37**		**36**			**13.08%**	**-6.79[-10.39,-3.19]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.7(P=0)							
1.5.4 6 months							
Qiao 2010	32	43.8 (17.6)	32	74.8 (20.8)		9.23%	-31.08[-40.5,-21.66]
Subtotal ***	**32**		**32**			**9.23%**	**-31.08[-40.5,-21.66]**
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%							
Test for overall effect: Z=6.46(P<0.0001)							
Total ***	**357**		**348**			**100%**	**-8.29[-13.17,-3.41]**
Heterogeneity: Tau^2=43.98; Chi^2=47.57, df=10(P<0.0001); I^2=78.98%							
Test for overall effect: Z=3.33(P=0)							
Test for subgroup differences: Chi^2=24.67, df=1 (P<0.0001), I^2=87.84%							



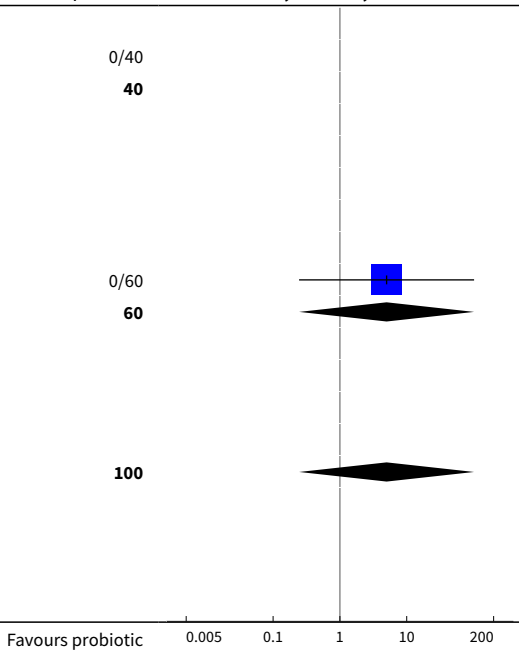
Comparison 2. Probiotic versus lactulose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	2	200	Risk Ratio (M-H, Random, 95% CI)	5.00 [0.25, 102.00]
1.1 1 month	1	80	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 2 months	1	120	Risk Ratio (M-H, Random, 95% CI)	5.00 [0.25, 102.00]
2 No recovery (incomplete resolution of clinical symptoms)	7	430	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.85, 1.21]
2.1 1 month or less	5	255	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.75, 1.20]
2.2 2 months	1	95	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.65, 1.47]
2.3 3 months	1	80	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.85, 1.80]
3 Adverse events	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Overt hepatic encephalopathy	6	420	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.63, 2.17]
3.2 Infection	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 Hospitalisation	1	80	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.04, 3.07]
3.4 Intolerance leading to discontinuation	3	220	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.08, 1.43]
3.5 Change of/or withdrawal from treatment	7	490	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.88, 1.82]
4 Health-related quality of life	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 Change in Total SIP Score	1	69	Mean Difference (IV, Random, 95% CI)	0.65 [-1.13, 2.43]
4.2 Change in SIP Psychological Score	1	69	Mean Difference (IV, Random, 95% CI)	0.48 [-1.04, 2.00]
4.3 Change in SIP Physical Score	1	69	Mean Difference (IV, Random, 95% CI)	0.38 [-0.61, 1.37]
5 Plasma ammonia concentration (final and change scores) (µmol/L)	6	325	Mean Difference (IV, Random, 95% CI)	-2.93 [-9.36, 3.50]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
5.1 1 month or less	5	248	Mean Difference (IV, Random, 95% CI)	-4.30 [-13.17, 4.56]
5.2 3 months	1	77	Mean Difference (IV, Random, 95% CI)	1.16 [-1.96, 4.28]

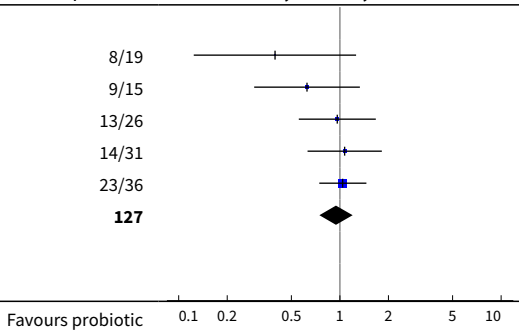
Analysis 2.1. Comparison 2 Probiotic versus lactulose, Outcome 1 All-cause mortality.

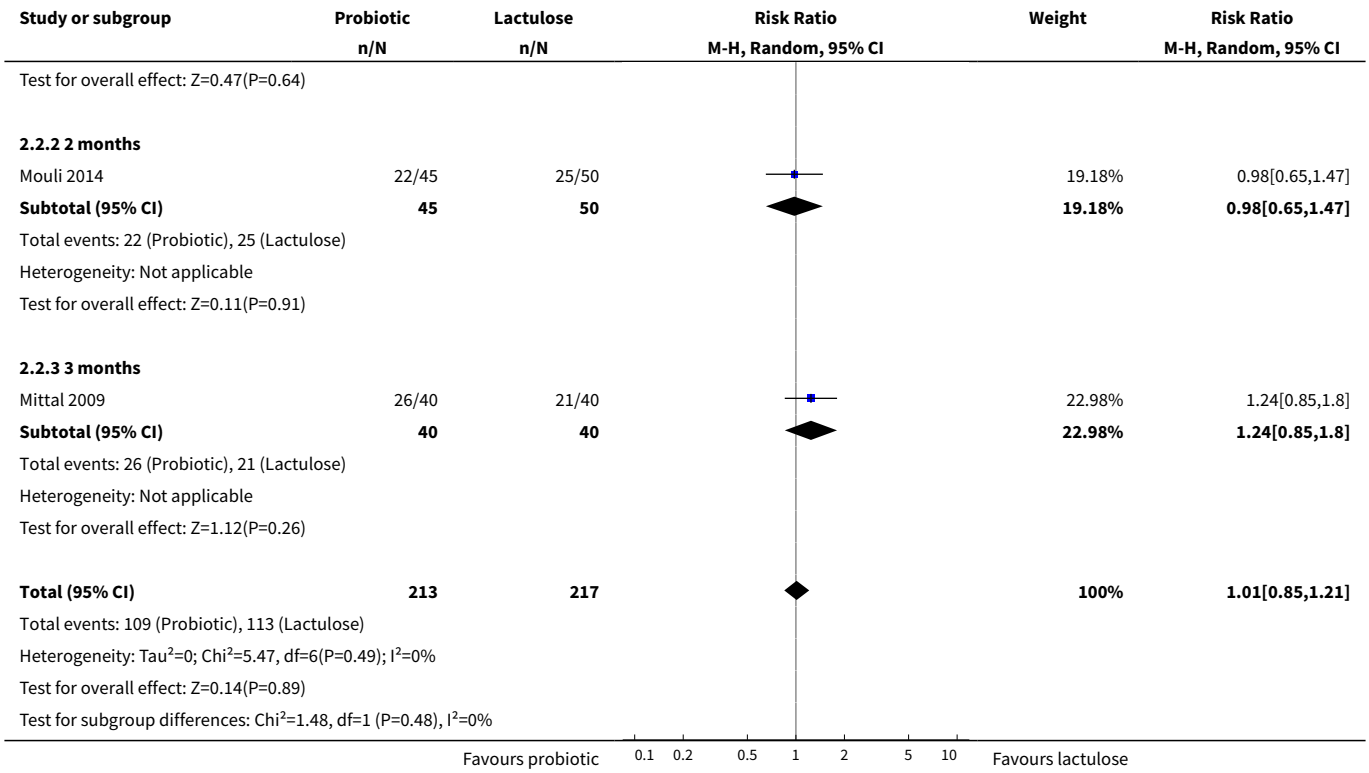
Study or subgroup	Probiotic n/N	Lactulose n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 1 month					
Zhao 2013	0/40	0/40			Not estimable
Subtotal (95% CI)	**40**	**40**			**Not estimable**
Total events: 0 (Probiotic), 0 (Lactulose)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
2.1.2 2 months					
Mouli 2014	2/60	0/60		100%	5[0.25,102]
Subtotal (95% CI)	**60**	**60**		**100%**	**5[0.25,102]**
Total events: 2 (Probiotic), 0 (Lactulose)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.05(P=0.3)					
Total (95% CI)	**100**	**100**		**100%**	**5[0.25,102]**
Total events: 2 (Probiotic), 0 (Lactulose)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.05(P=0.3)					
Test for subgroup differences: Not applicable					



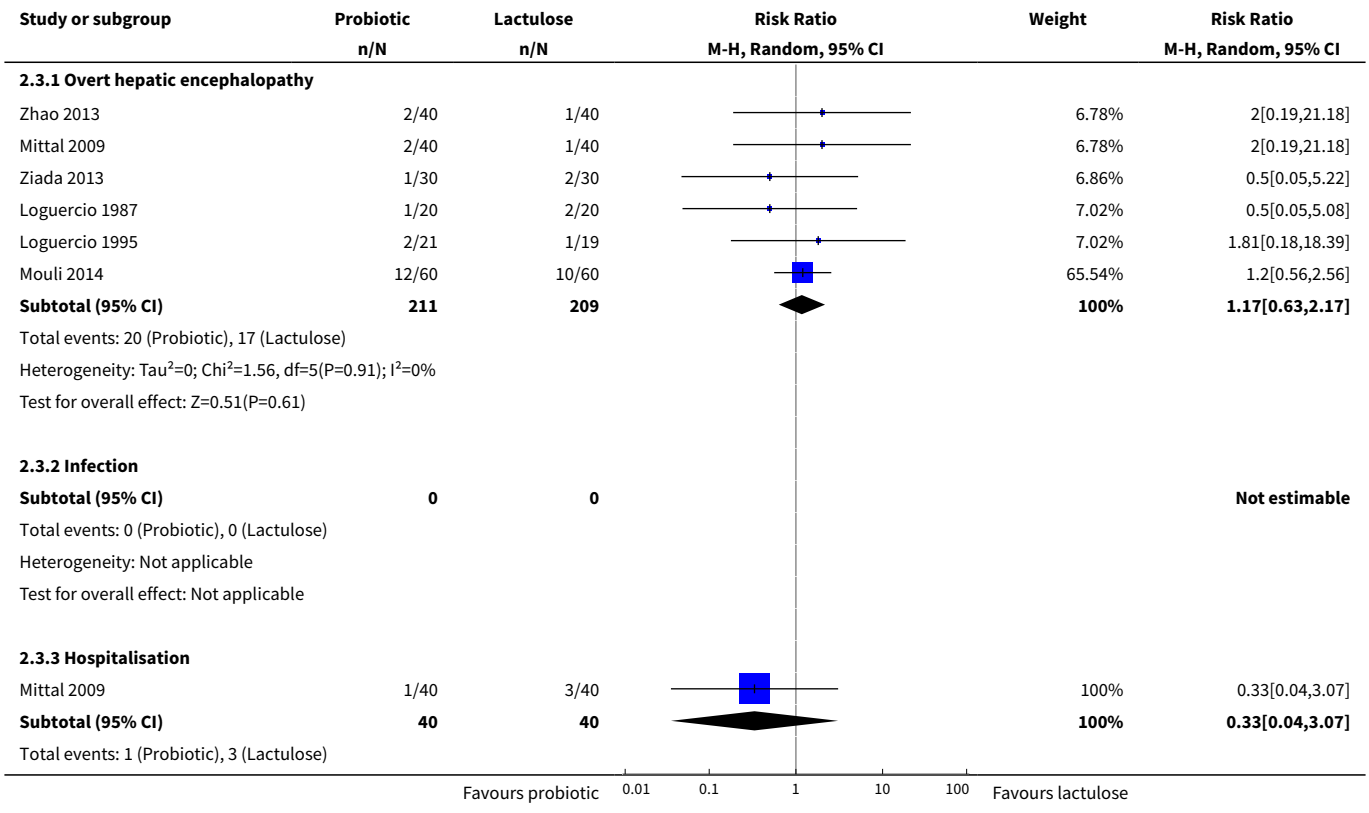
Analysis 2.2. Comparison 2 Probiotic versus lactulose, Outcome 2 No recovery (incomplete resolution of clinical symptoms).

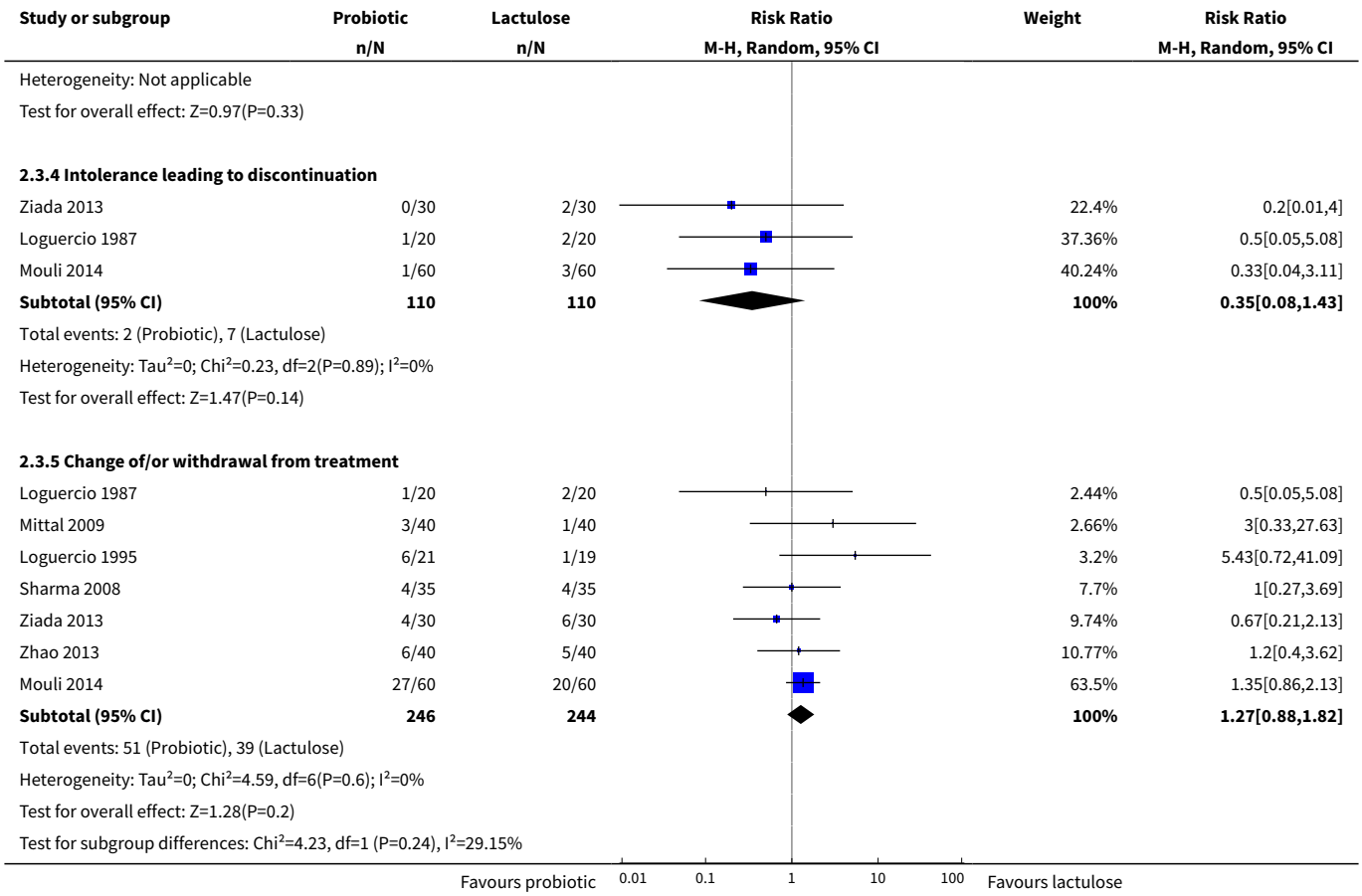
Study or subgroup	Probiotic n/N	Lactulose n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 1 month or less					
Loguercio 1995	3/18	8/19		2.37%	0.4[0.12,1.26]
Loguercio 1987	6/16	9/15		5.58%	0.63[0.29,1.33]
Ziada 2013	13/27	13/26		10.59%	0.96[0.56,1.67]
Sharma 2008	15/31	14/31		11.27%	1.07[0.63,1.82]
Zhao 2013	24/36	23/36		28.03%	1.04[0.74,1.46]
Subtotal (95% CI)	**128**	**127**		**57.83%**	**0.94[0.75,1.2]**
Total events: 61 (Probiotic), 67 (Lactulose)					
Heterogeneity: Tau²=0; Chi²=4.03, df=4(P=0.4); I²=0.66%					



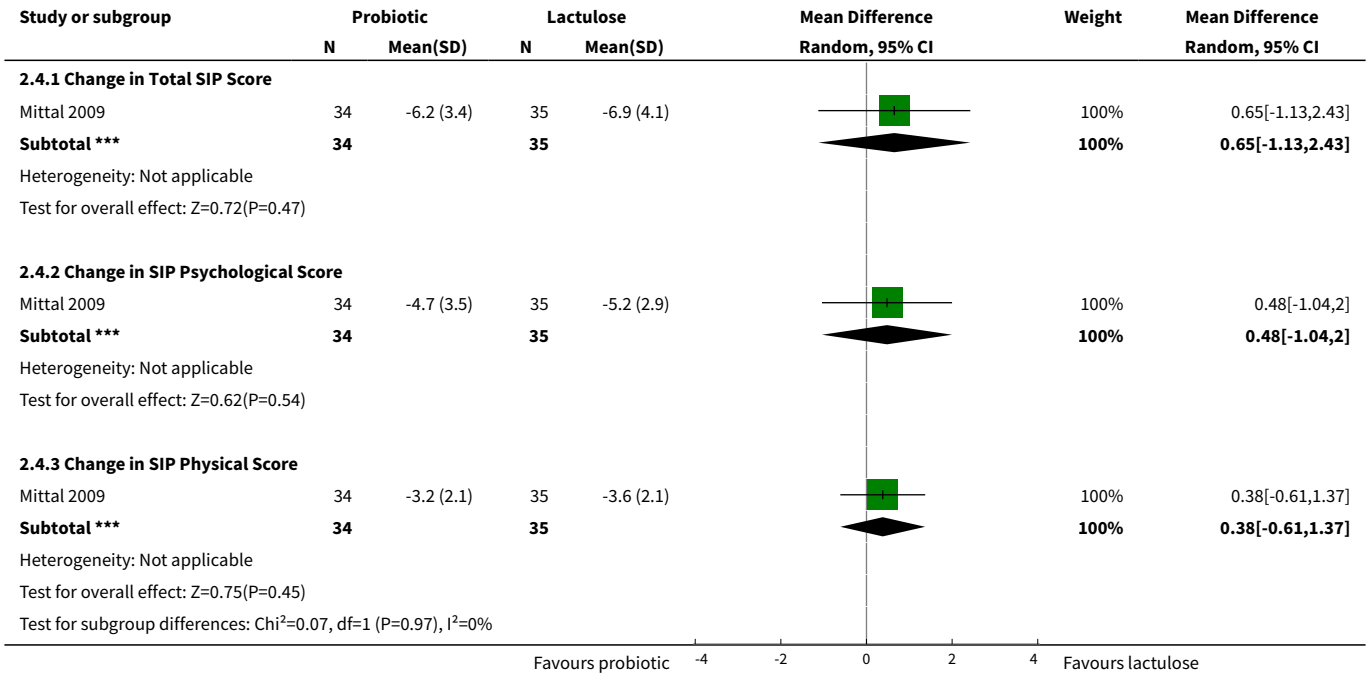


Analysis 2.3. Comparison 2 Probiotic versus lactulose, Outcome 3 Adverse events.

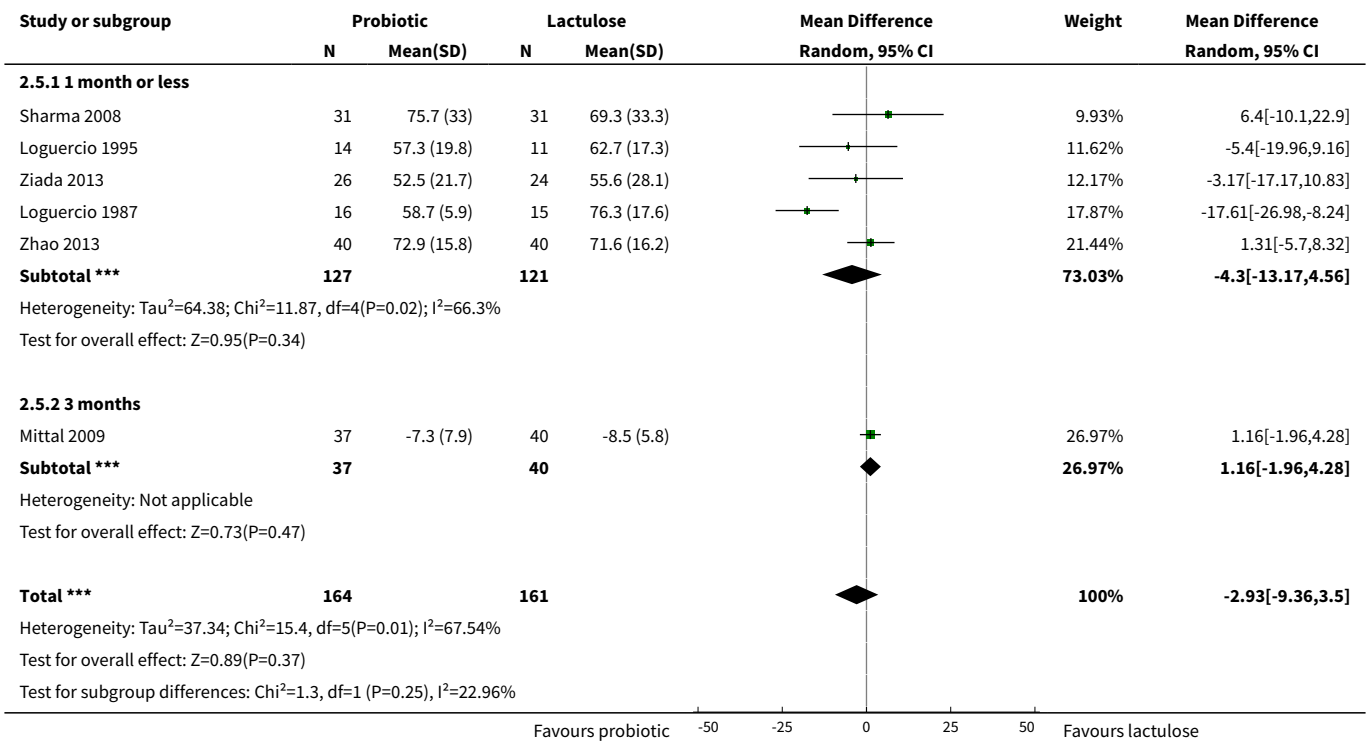




Analysis 2.4. Comparison 2 Probiotic versus lactulose, Outcome 4 Health-related quality of life.



Analysis 2.5. Comparison 2 Probiotic versus lactulose, Outcome 5 Plasma ammonia concentration (final and change scores) (µmol/L).



ADDITIONAL TABLES

Table 1. Types of probiotics used across studies

Study	Probiotics used
Bajaj 2008	*Streptococcus thermophilus*,*Lactobacillus bulgaricus*,*Lactobacillus acidophilus*,*Lactobacillus casei*,*Bifidobacteria*
Bajaj 2014a	*Lactobacillus* GG AT strain 53103
Dhiman 2013a	VSL#3 (containing *Bifidobacterium breve*,*Bifidobacterium longum*,*Bifidobacterium infantis*,*Lactobacillus acidophilus*,*Lactobacillus plantarum*,*Lactobacillus paracasei*,*Lactobacillus bulgaricus*, *Streptococcus thermophilus*)
Liu 2004	*Pediacoccus pentosaceus*,*Leuconostoc mesenteroides*,*Lactobacillus paracasei*,*Lactobacillus plantarum*
Loguercio 1987	*Enterococcus* lactic acid bacteria strain SF68
Loguercio 1995	*Enterococcus faecium* strain SF68
Lunia 2014	VSL#3 (containing *Streptococcus thermophilus*,*Bifidobacterium breve*,*Bifidobacterium longum*,*Bifidobacterium infantis*,*Lactobacillus acidophilus*,*Lactobacillus plantarum*,*Lactobacillus paracasei*,*Lactobacillus bulgaricus*)

Table 1. Types of probiotics used across studies *(Continued)*

Malaguarnera 2010	*Bifidobacterium* (subtype not available)
Mittal 2009	VSL#3 (containing *Streptococcus thermophilus*,*Bifidobacterium breve*,*Bifidobacterium longum*,*Bifidobacterium infantis*,*Lactobacillus acidophilus*,*Lactobacillus plantarum*,*Lactobacillus paracasei*,*Lactobacillus bulgaricus*)
Mouli 2014	VSL#3 (4 strains of *Lactobacillus* (*L acidophilus* DSM 24735, *L plantarum* DSM 24730, *L paracasei* DSM 24733, *L delbrueckii* subsp. *bulgaricus* DSM 24734), 3 strains of *Bifidobacterium* (*B longum* DSM 24736, *B breve* DSM 24732, *B infantis* DSM 24737), and 1 strain of *Streptococcus* (*S thermophilus* DSM 24731))
Nair 2008	*Lactobacillus acidophilus*,*Lactobacillus rhamnosus*,*Bifidobacterium longum*,*Saccharomyces boulardii*
Pereg 2011	*Lactobacillus acidophilus, Lactobacillus bulgaricus, Bifidobacterium bifidum*, *Streptococcus thermophilus* (Bio Plus, Supherb, Israel)
Qiao 2010	Bifid triple viable (not further specified)
Saji 2011	*Lactobacillus acidophilus*,*Lactobacillus rhamnosus*,*Bifidobacterium longum*,*Saccharomyces boulardii*
Sharma 2008	*Enterococcus faecalis*,*Clostridium butyricum*,*Bacillus mesentricus*, lactic acid *Bacillus*
Sharma 2014	Velgut ERIS Pharmaceuticals, Ahmadabad, India (*Lactobacillus acidophilus*,*Lactobacillus rhamnosus*,*Lactobacillus plantarum*,*Lactobacillus casei*,*Bifidobacterium longum*,*Bifidobacterium infantis*,*Bifidobacterium breve*,*Saccharomyces boulardii*,*Streptococcus thermophilus*)
Shavakhi 2014	Balance (Protexin Co., Somerset, UK) *Lactobacillus* strains (*L casei*,*L rhamnosus*,*L acidophilus*,*L bulgaricus*),*Bifidobacterium* strains (*B breve*, *B longum)*, and*Streptococcus thermophilus*
Vlachogiannakos 2014	*Lactobacillus plantarum* 299v
Zhao 2013	Unclear
Zhitai 2013	Live *Bacillus cereus* capsules
Ziada 2013	*Lactobacillus acidophilus*

Table 2. Heterogeneity subgroup analysis

Probiotic versus placebo or no intervention				
No-recovery	**Studies**	**Participants**	**Effect estimate** **Risk ratio [95% CI]**	**Difference P**
Type of probiotic	10	574	—	0.69
Lactobacillus	4	195	0.67 [0.45, 1.00]	—
Mixed	5	309	0.65 [0.50, 0.83]	—
Unclear	1	70	0.76 [0.58, 0.98]	—

Table 2. Heterogeneity subgroup analysis *(Continued)*

Grade of hepatic encephalopathy	10	574	—	0.06
Minimal	8	473	0.63 [0.52, 0.76]	—
Overt	2	101	0.98 [0.64, 1.48]	—
Duration of therapy	10	574	—	0.43
<= 1 month	4	228	0.75 [0.58, 0.96]	—
1 > 2 months	3	117	0.65 [0.38, 1.10]	—
2 + months	3	229	0.58 [0.43, 0.78]	—
Co-interventions	10	574	—	0.17
No treatment	8	473	0.63 [0.52, 0.76]	—
Bioactive fermentable fibre	1	40	1.00 [0.54, 1.86]	—
Lactulose	1	61	0.96 [0.55, 1.69]	—
Plasma ammonia concentration	**Studies**	**Partici-pants**	**Effect estimate** **Mean difference [95% CI]**	**Differ-ence P**
Type of probiotic	10	580	—	0.35
Bifidobacterium	1	125	-9.35 [-16.09, -2.61]	—
Lactobacillus	3	121	-11.90 [-24.41, 0.60]	—
Mixed	4	190	-1.80 [-9.65, 6.06]	—
Unclear	2	144	-17.02 [-44.07, 10.02]	—
Grade of hepatic encephalopathy	10	580	—	0.85
Minimal	9	455	-8.50 [-14.38, -2.62]	—
Overt	1	125	-9.35 [-16.09, -2.61]	—
Duration of therapy	10	580	—	0.58
<=1 month	4	232	-5.93 [-12.25, 0.39]	—
1 > 2 months	4	211	-5.11 [-14.56, 4.34]	—
2 + months	2	137	-18.53 [-42.32, 5.26]	—
Co-interventions used	10	580	—	0.11
No treatment	7	354	-10.42 [-18.68, -2.17]	—
Bioactive fermentable fibre	1	40	-2.90 [-5.51, -0.29]	—

Table 2. Heterogeneity subgroup analysis *(Continued)*

Lactulose	2	186	-7.88 [-14.29, -1.47]	—
Probiotic versus lactulose				
Plasma ammonia concentration	**Studies**	**Partici-pants**	**Effect estimate** **Mean difference [95% CI]**	**Differ-ence P**
Type of probiotic	6	325	—	0.13
Enterococcus SF68	2	56	-12.83 [-24.51, -1.15]	—
Mixed	2	139	1.34 [-1.72, 4.40]	—
Lactobacillus	1	50	-3.17 [-17.17, 10.83]	—
Unclear	1	80	1.31 [-5.70, 8.32]	—
Grade of hepatic encephalopathy	6	325	—	0.02
Minimal	4	269	1.16 [-1.59, 3.91]	—
Overt	2	56	-12.83 [-24.51, -1.15]	—

CI: confidence interval

APPENDICES

Appendix 1. Search strategies

Database	Span of search	Search strategy
The Cochrane Hepato-Biliary Group Controlled Trials Register	August 2015	(probiot* OR lactobacil* OR bifidobacter*) AND ('hepatic encephalopath*' OR (liver AND (diseas* OR cirrhosis*)))
Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library	2016, Issue 5.	#1 LIVER CIRRHOSIS explode all trees (MeSH) #2 (liver cirrhosis):ti,ab,kw #3 HEPATIC ENCEPHALOPATHY explode all trees (MeSH) #4 (hepatic encephalopathy):ti,ab,kw #5 (liver next cirrhosis) #6 (hepatic next encephalopathy) #7 (#1 or #2 or #3 or #4 or #5 or #6) #8 probiotics explode all trees (MeSH) #9 (probiotics):ti,ab,kw #10 lactobacillus explode all trees (MeSH) #11 (lactobacillus):ti,kw,ab #12 bifidobacterium explode all trees (MeSH) #13 (bifidobacterium):ti,kw,ab #14 (#8 or #9 or #10 or #11 or #12 or #13) #15 (#7 and #14)
MEDLINE Ovid	1946 to June 2016.	#1 randomised controlled trial.pt. [#1 randomized controlled trial.pt. in 2015 update]

(Continued)

		#2 controlled clinical trial.pt. #3 randomized.ab. #4 placebo.ab. #5 drug therapy.fs. #6 randomly.ab. #7 trial.ab. #8 groups.ab. #9 or/1-8 #10 animals.sh. #11 9 not 10 #12 exp hepatic encephalopathy/ #13 hepatic encephalopathy.tw #14 exp liver cirrhosis/ #15 liver cirrhosis.tw #16 12 or 13 or 14 or 15 #17 exp probiotics/ #18 probiotic.tw #19 exp lactobacillus/ #20 lactobacillus.tw #21 exp bifidobacterium/ #22 bifidobacterium.tw #23 17 or 18 or 19 or 20 or 21 or 22 #24 11 and 16 and 23
Embase Ovid	1974 to June 2016.	#1 random:.tw. #2 clinical trial:.mp. #3 exp health care quality/ #4 1 or 2 or 3 #5 exp hepatic encephalopathy/ #6 hepatic encephalopathy.tw #7 exp liver cirrhosis/ #8 liver cirrhosis.tw #9 5 or 6 or 7 or 8 #10 exp probiotics/ #11 probiotic.tw #12 exp lactobacillus/ #13 lactobacillus.tw #14 exp bifidobacterium/ #15 bifidobacterium.tw #16 10 or 11 or 12 or 13 or 14 or 15 #17 4 and 9 and 16
Science Citation Index Expanded (Web of Science)	1900 to June 2016.	# 1 TS=(probiotic OR probiot* OR lactobacil* OR bifidobacter*) # 2 TS=(hepatic encephalopath* OR liver diseas*) # 3 #1 AND #2 # 4 TS=(random* OR blind* OR placebo*) # 5 #3 AND #4

FEEDBACK

Comment on an intervention in the 'Probiotics for people with hepatic encephalopathy' review, published 23 February 2017. Comment submitted, 16 July 2019

Summary

The randomised clinical trials included in the systematic review assessed a probiotic formulation know at the time of the conduct of the trials as VSL#3. This probiotic formulation has been renamed the 'De Simione Formulation' (DSF) after me, as I invented it. The De Simone Formulation is available under the brand names Visbiome® and Vivomixx®. To the best of my knowledge, current products known as VSL#3 have not been assessed in people with inflammatory bowel disease, irritable bowel disease, or liver diseases. The current products known as VSL#3 are not the same formulation as the original product I invented.

I hereby ask you to bring this notice as well as to update your review accordingly.

Yours sincerely,

Professor Claudio De Simone, Switzerland
claudio.desimone@bluewin.ch

Conflicts of interest: I am the inventor of 'De Simione Formulation' (DSF).

Comment submitted 16.07.2019

Reply

Dear Professor Claudio De Simone,

In this review, 'VSL#3' refers only to the product used in the cited literature, independent from present product labelling. Since the time our literature searches were performed, this product is now known by the generic name 'De Simone Formulation" (See Reference*).

Yours sincerely,

Richard G McGee and co-authors

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*Reference: De Simone C. Letter: what gastroenterologists should know about VSL#3. Alimentary Pharmacology & Therapeutics. 2018 Mar;47(5):698-9 (onlinelibrary.wiley.com/doi/full/10.1111/apt.14515).

Reply submitted 20.07.2019

Contributors

Submitter of the comment: Claudio De Simone, Switzerland

Submitter of the reply: Richard G McGee, Australia, on behalf of the review authors

WHAT'S NEW

Date	Event	Description
24 July 2019	Amended	Feedback received and reply to comment provided

HISTORY

Protocol first published: Issue 9, 2010
Review first published: Issue 11, 2011

Date	Event	Description
14 June 2016	New search has been performed	June 2016 search update: Seven new trials added. The review is now based on 21 trials with a total of 1420 participants.
14 June 2016	New citation required and conclusions have changed	The conclusions changed from "While probiotics appear to reduce plasma ammonia concentration when compared with placebo or no intervention, we are unable to conclude that probiotics are efficacious in altering clinically relevant outcomes" (McGee 2011), to "Overall, probiotics appear to help symptom resolution, reduce plasma ammonia concentrations, and result in less overt hepatic encephalopathy compared with no treatment, although we consider the evidence to be of low quality".

CONTRIBUTIONS OF AUTHORS

RD: participated in all stages of the review.
RMG: conceived the review, designed the protocol, and participated in all stages of the review.
SMR: drafted the protocol, contributed to the search, provided content area advice, and reviewed the manuscript.
ACW: drafted the protocol, provided methodological advice, contributed to study design, and reviewed the manuscript.

DECLARATIONS OF INTEREST

RD: is a recipient of a scholarship from The University of Sydney. This scholarship had no influence on the conduct of this review.
RMG: none to declare.
SMR: is an author of a trial included in the review. SMR had no influence on its inclusion or data extraction and analysis.
ACW: none to declare.

SOURCES OF SUPPORT

Internal sources

- No financial support was received for the conduct of this review, Australia.

External sources

- No financial support was received for the conduct of this review, Australia.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The following changes have been made in the update.

- The search terms used have been updated to keep the search strategy up to date.
- The outcome adverse events, which previously reported "number of adverse events", has been expanded to include overt hepatic encephalopathy, infections, hospitalisations, intolerance leading to discontinuation, and change of/or withdrawal from treatment.
- The previous outcome "change of/or withdrawal from treatment" is now a subgroup of adverse events.
- Final and change scores have been combined into the same analysis for plasma ammonia concentration.

INDEX TERMS

Medical Subject Headings (MeSH)

Cause of Death; Gastrointestinal Agents [*therapeutic use]; Hepatic Encephalopathy [mortality] [*therapy]; Lactulose [*therapeutic use]; Probiotics [*therapeutic use]; Quality of Life; Randomized Controlled Trials as Topic

MeSH check words

Humans