Nonabsorbable disaccharides for hepatic encephalopathy (Review)

Als-Nielsen B, Gluud LL, Gluud C

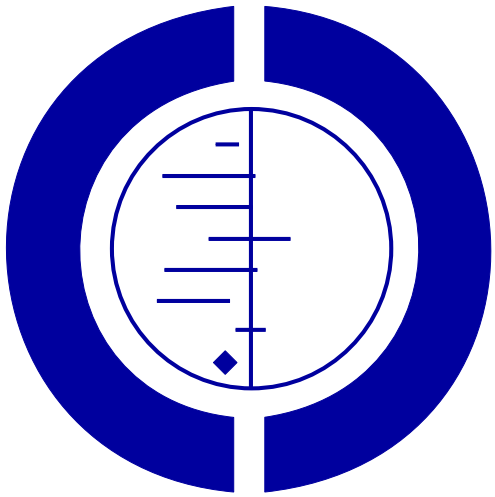

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TABLE OF CONTENTS

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ABSTRACT

Background
Nonabsorbable disaccharides (lactulose or lactitol) are considered the treatment of choice for hepatic encephalopathy.

Objectives
To assess the beneficial and harmful effects of nonabsorbable disaccharides for patients with hepatic encephalopathy.

Search strategy
Trials were identified through *The Cochrane Hepato-Biliary Group Controlled Trials Register* (March 2003), *The Cochrane Central Register of Controlled Trials* (Issue 1, 2003), *MEDLINE* (1966 to 2003/03), *EMBASE* (1980 to 2003/03), manual searches of bibliographies and journals, authors of trials, and pharmaceutical companies.

Selection criteria
Randomised trials comparing lactulose or lactitol versus no intervention, placebo, or antibiotics and trials comparing lactulose versus lactitol for hepatic encephalopathy.

Data collection and analysis
The primary outcome measures included no improvement of hepatic encephalopathy and all-cause mortality. Binary outcomes are reported as relative risks (RR) based on a random effects model. Subgroup analyses were performed with regard to methodological quality and form of hepatic encephalopathy.

Main results
Thirty trials assessed nonabsorbable disaccharides versus placebo, no intervention, or antibiotics or assessed lactulose versus lactitol. We could not extract data from all trials. Compared with placebo or no intervention, nonabsorbable disaccharides had no statistically significant effect on mortality (RR 0.41, 95% CI 0.02 to 8.68, four trials), but appeared to reduce the risk of no improvement of hepatic encephalopathy (RR 0.62, 95% CI 0.46 to 0.84, six trials). However, this result may reflect bias due to low methodological quality of the majority of included trials. Trials of high methodological quality found no significant effect of nonabsorbable disaccharides on the risk of no improvement (RR 0.92, 95% CI 0.42 to 2.04, two trials). We found no statistically significant difference between lactulose and lactitol on mortality (two trials) or risk of no improvement (four trials). However, our meta-analyses were underpowered to establish whether these treatments have comparable effect. Nonabsorbable disaccharides appeared to be inferior to antibiotics on reducing the risk of no improvement (RR 1.24, 95% CI 1.02 to 1.50, 10 trials).

Authors' conclusions
This systematic review questions the beneficial effects of nonabsorbable disaccharides and highlights that there is insufficient high-quality evidence to support this treatment. We found that antibiotics appeared to be superior to nonabsorbable disaccharides in improving hepatic encephalopathy, but it is unclear whether this difference in treatment effect is clinically important to patients. Nonabsorbable disaccharides should not serve as comparator in randomised trials on hepatic encephalopathy.

PLAIN LANGUAGE SUMMARY

There is insufficient evidence to confirm or exclude whether nonabsorbable disaccharides have an effect on patients with hepatic encephalopathy

Nonabsorbable disaccharides (lactulose or lactitol) are considered the treatment of choice for hepatic encephalopathy. When all the identified trials were combined, nonabsorbable disaccharides appeared to have a modest effect on improving encephalopathy. However, this effect was not seen when only trials of high quality were analysed. Antibiotics appeared to be superior to nonabsorbable disaccharides in improving hepatic encephalopathy, but it is unclear whether this difference in treatment effect is important to patients. Too few patients have been randomised to establish whether lactulose and lactitol have comparable effect.

BACKGROUND

Hepatic encephalopathy is a complex neuropsychiatric syndrome, which may complicate acute or chronic liver failure (Gitlin 1996). It is characterised by changes in mental state including a wide range of neuropsychiatric symptoms ranging from minor not readily discernible signs of altered brain function to deep coma (Conn 1979).

Treatment of hepatic encephalopathy aims at reducing the production and absorption of ammonia, which is involved in the pathogenesis (Bircher 1966; Weissenborn 1992). As colonic bacteria are the primary source of ammonia, treatment initially consisted of poorly absorbed antibiotics, especially neomycin (Conn 1977a - CHE; Atterbury 1978 - AHE) (in this review, we have suffixed the type of hepatic encephalopathy studied in each included trial, i.e., AHE for acute hepatic encephalopathy, CHE for chronic hepatic encephalopathy, SHE for subclinical hepatic encephalopathy, and '?' for trials not specifying the type of hepatic encephalopathy). However, neomycin was associated with several adverse events including nerve deafness, renal toxicity, malabsorption, and serious derangement of the intestinal flora (Conn 1977a - CHE). Lactulose was introduced in 1966 as a safer alternative (Bircher 1966). Lactulose (1-4 galactoside fructose) is a synthetic nonabsorbable disaccharide, which reduces the production and absorption of ammonia (Bircher 1966; Weissenborn 1992). Lactulose has been considered the treatment of choice for hepatic encephalopathy since the 1980s (Morgan 1999), although only a few, small randomised trials assessing lactulose against placebo (Elkington 1969 - CHE; Simmons 1970 - AHE; Germain 1973 - CHE) or neomycin (Conn 1977a - CHE; Atterbury 1978 - AHE) had been performed.

Lactulose has no serious adverse effects, but may be badly tolerated because of its overtly sweet taste and gastrointestinal reactions, which may be unresponsive to dose reductions. Lactitol (b-galactosido-sorbitol), another synthetic nonabsorbable disaccharide, was suggested as a more tolerable alternative in 1982 (Bircher 1982). Several randomised trials have compared lactulose versus lactitol (Uribe 1987a - AHE; Heredia 1987 - AHE; Morgan 1987a - AHE; Morgan 1987b - CHE; Morgan 1989 - SHE; Riggio 1989- CHE+SHE; Pai 1995 - AHE). However, the statistical power of the trials was weak and several employed a cross-over design, although this is not appropriate in hepatic encephalopathy given its spontaneously fluctuating nature (Freeman 1989; Basile 1991; Als-Nielsen 2001).

No systematic review has assessed the effect of lactulose or lactitol for hepatic encephalopathy or compared lactulose versus lactitol for acute or subclinical hepatic encephalopathy although several randomised trials have been published (Morgan 1987a - AHE; Heredia 1987 - AHE; Morgan 1989 - SHE; Blanc 1994; Watanabe 1997 - SHE; Dhiman 2000 - SHE). Two meta-analyses have compared lactulose versus lactitol for chronic hepatic encephalopathy and concluded they were equivalent (Blanc 1992; Camma 1993). We performed a systematic review to estimate and compare the efficacy and tolerance of lactulose or lactitol for acute and chronic (including subclinical) hepatic encephalopathy. Further, the disaccharide lactose is non-absorbable in populations with lactase deficiency and it is used as a less expensive alternative to lactulose in these populations. For the sake of completeness, we also present the results of the few trials on lactose for hepatic encephalopathy in additional analyses of the review.

OBJECTIVES

To assess the beneficial and harmful effects of nonabsorbable disaccharides (lactulose or lactitol) in patients with hepatic encephalopathy and to compare nonabsorbable disaccharides with antibiotics. Further, to examine whether the beneficial and harmful effects of lactulose and lactitol are equivalent. Finally, to assess the beneficial and harmful effect of lactose in lactase deficient patients with hepatic encephalopathy.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

We have included all randomised trials regardless of publication status or language. The trials could have been double blind, single blind, or unblinded. We excluded trials in which patients were

allocated by a quasi-random method, e.g., day of birth or date of admission.

Types of participants

Patients diagnosed as having hepatic encephalopathy in connection with acute or chronic liver disease or fulminant hepatic failure. Patients of either gender, any age, or any ethnic origin were included irrespective of the aetiology of the liver disease or the factors precipitating the hepatic encephalopathy.

Acute hepatic encephalopathy involves an abrupt onset of neuropsychiatric symptoms in patients with chronic liver disease. Acute hepatic encephalopathy may be idiopathic or precipitated by one or more causes including infections, gastrointestinal bleeding, electrolyte or acid-base disturbances, constipation, medications, hypo- or hyperglycaemia, renal dysfunction, large protein meals, alcohol withdrawal, or a superimposed acute liver disease.

Chronic hepatic encephalopathy involves persistent neuropsychiatric dysfunction in patients with chronic liver disease. The onset is usually insidious and the dysfunction may be clinically overt (i.e., chronic hepatic encephalopathy) or only demonstrable by psychometric testing (i.e., subclinical encephalopathy also known as latent or minimal hepatic encephalopathy).

Fulminant hepatic failure is a severe stage of hepatic functional deterioration in patients without pre-existing liver disease. The main clinical features are hepatic encephalopathy and direct symptoms of liver cell damage, mainly jaundice and coagulation disorders (Bernuau 1999).

Types of intervention

We examined four comparisons assessing any type or dose of:

- Lactulose or lactitol versus no intervention or placebo.

- Lactulose or lactitol versus antibiotics.

- Lactulose versus lactitol.

Additional analyses: lactose versus placebo, no intervention, antibiotics, lactulose or lactitol.

The randomised trials were included irrespective of the mode of administration, the dose, or the duration of administration. Only trials using comparable collateral interventions in the experimental and control groups were included.

Types of outcome measures

Primary outcome measures

The following primary outcomes were assessed at the end of treatment and at maximum follow-up according to the individual trial:

(1) Number of patients with no improvement of hepatic encephalopathy. Improvement was defined as a partial or complete resolution of clinical or subclinical symptoms of hepatic encephalopathy. Improvement could be assessed by clinical grading, electrophysiological testing, psychometrical testing or summary gradings including the Portal-systemic Encephalopathy Index (PSE Index) (Conn 1977a - CHE; Blei 1999).

(2) All-cause mortality.

Secondary outcome measures

The following secondary outcomes were assessed at end of treatment and at maximum follow-up according to the individual trial:

(3) Number and type of adverse events. Adverse events were graded as serious or non-serious according to the International Conference on Harmonisation Guidelines (ICH-GCP 1997).

(4) Number Connection Test and Digit Symbol Test (Conn 1977b; Groeneweg 2000).

(5) Quality of life.

(6) Cost-effectiveness.

(7) Plasma ammonia concentrations.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Hepato-Biliary Group methods used in reviews.

The Cochrane Hepato-Biliary Group Controlled Trials Register (March 2003), *The Cochrane Central Register of Controlled Trials* (*CENTRAL*) (Issue 1, 2003), *MEDLINE* on *PubMed* (March 2003), and *EMBASE* (1980-2003/03) were searched using the search strategies specified in Table 01.

The reference lists of relevant articles were checked for unidentified trials. We wrote to the principal authors of the identified trials and the pharmaceutical companies involved in the production of lactulose and lactitol and inquired about additional trials of which they might be aware.

METHODS OF THE REVIEW

Selection of trials for inclusion

Decisions on which trials to include were taken by BAN and validated by CG. We were unblinded with regard to the names of the authors, investigators, institutions, and results. Excluded trials were identified and listed with the reason for exclusion.

Data extraction

The data from the included randomised trials were extracted independently by BAN and LLK. We wrote to the authors of trials if the following data was not provided in the published report:

(1) Trial characteristics.
Methodological quality (see below). Whether the trial used a parallel or cross-over design.

(2) Patient characteristics.

Number of patients randomised to each intervention arm, proportion of men, mean (or median) age, type of underlying liver disease, form of hepatic encephalopathy, and aetiology of cirrhosis.

(3) Intervention characteristics.
Type and dose of intervention(s), duration of therapy, and mode of administration.

(4) All outcomes.

Methodological quality
Methodological quality is defined as the confidence that the design and report will restrict bias in the intervention comparison (Moher 1998). The methodological quality was assessed by the following three separate components supported by empirical evidence (Schulz 1995; Moher 1998; Kjaergard 2001; Jüni 2001).

Generation of the allocation sequence
Adequate: by table of random numbers, computer generated random numbers, coin tossing, shuffling or similar.
Unclear: if the trial was described as randomised, but the method used for the allocation sequence generation was not described.
Inadequate: if a system involving dates, names, or admittance numbers were used for the allocation of patients. Such trials were excluded from the review.

Allocation concealment
Adequate: if the allocation of patients involved a central independent unit, on-site locked computer, identically appearing numbered drug bottles or containers prepared by an independent pharmacist or investigator, or sealed envelopes.
Unclear: if the trial was described as randomised, but the method used to conceal the allocation was not described.
Inadequate: if the allocation sequence was known to the investigators who assigned participants or if the study was quasi-randomised.

Blinding
Adequate: if the trial was described as double blind and the method of blinding involved identical placebo or active drugs.
Unclear: if the trial was described as double blind, but the method of blinding was not described.
Not performed: if the trial was not double blind or the method of blinding was inappropriate.

We classified trials with adequate allocation concealment and adequate blinding as high quality. Considering the problems of equivalence trials (Pocock 1983; Piaggio 2001), we also extracted whether the trials reported sample size calculations. Additionally, we recorded follow-up and the use of intention-to-treat analyses as specified below.

Follow-up
Adequate: if the numbers and reasons for dropouts and withdrawals in all intervention groups were described or if it was specified that there were no dropouts or withdrawals.
Unclear: if the report gave the impression that there had been no dropouts or withdrawals, but this was not specifically stated.
Inadequate: if the number or reasons for dropouts and withdrawals were not described.

Intention-to-treat
Adequate: if all randomised participants were included in the analysis in the group to which they originally were assigned.
Unclear: if the report gave the impression that all participants were included in the analysis.
Inadequate: if randomised participants were excluded from the analysis.

Statistical methods
All analyses were performed according to the intention-to-treat method including all randomised patients irrespective of compliance or follow-up. If patients had missing outcome data, we used the last reported observed response ('carry forward') (Hollis 1999). The statistical package (RevMan Analyses) provided by the Cochrane Collaboration was used. Binary outcomes were expressed as relative risks (RR) with 95% confidence intervals (CI). Continuous outcomes were expressed as weighted mean difference (WMD) with 95% CI. We used a random effects model (DerSimonian 1986) due to anticipated variability between trials regarding patients and interventions. To assess the robustness of the results, analyses were also performed using a fixed effect model (DeMets 1987). In case of discrepancies, results from both models were reported. Otherwise only results from the random effects model were reported. The presence of statistical heterogeneity was explored by the chi-squared test with significance set at $P < 0.1$. Potential sources of heterogeneity were explored through subgroup analyses with regard to the methodological quality and the form of hepatic encephalopathy (acute, chronic, or subclinical). We used the test of interaction (Altman 2003) to compare the difference between the estimates of subgroup analyses.

We primarily included data from the first period of cross-over trials. This was not possible for all cross-over trials when assessing the outcomes 'adverse events', 'number connection test', 'ammonia concentration', and 'PSE index' in the comparison "lactulose versus lactitol". We then used the summary results from both treatment periods of the cross-over trials.

DESCRIPTION OF STUDIES

Search results
Figure 01 summarises the literature search. A total of 425 references were identified in *The Cochrane Hepato-Biliary Group Controlled Trials Register* (n = 70), *The Cochrane Controlled Trials Register* (n = 106), *MEDLINE* (n = 130), and *EMBASE* (n = 119). We excluded 202 duplicates and 134 clearly irrelevant references by reading abstracts. Nineteen additional references were identified through manual searches and correspondence with principal

authors. Accordingly, 108 references were retrieved for further assessment. Of these, we excluded 64 because they were reviews, meta-analyses, observational studies, or randomised trials that did not fulfil our inclusion criteria. Excluded studies are listed under 'Characteristics of excluded studies' with reasons for exclusion. The remaining 44 references referred to 30 randomised trials assessing lactulose or lactitol and four randomised trials assessing lactose for hepatic encephalopathy in populations where the majority of people are lactase deficient. One of the included papers is counted as three trials because it contains three comparisons: lactitol versus tap water, lactose versus tap water, and lactitol versus lactose (Uribe 1987a - AHE).

Lactulose or lactitol versus placebo or no intervention

Ten trials assessed lactulose or lactitol versus placebo or no intervention (Table 02). All trials were reported in full articles. Eight trials used a parallel group design and two a cross-over design. A total of 280 patients (75% males) were randomised. The median number of patients in each trial was 26 (range 3 to 86). The mean ages ranged from 45 to 67 years (median 53 years). All patients had cirrhosis and acute hepatic encephalopathy (one trial), chronic hepatic encephalopathy (four trials), either acute and chronic hepatic encephalopathy (one trial), or subclinical hepatic encephalopathy (four trials). The aetiology of cirrhosis was reported in four trials and was alcohol (53%), hepatitis (33%), postnecrotic (8%), or other reasons (3%). The experimental intervention was oral lactulose (eight trials), oral lactitol (one trial), or enemas of lactitol (one trial). The daily mean dosages of lactulose ranged from 30 to 84 gram (median 50 gram). The dose was adjusted to obtain 2-3 semisoft stools per day in six trials. The control intervention was placebo (one trial), glucose or saccharose (three trials), sorbitol (two trials), tap-water enemas (one trial), or no treatment (three trials). The median duration of treatment was 15 days (range five to 360 days).

Lactulose or lactitol versus antibiotics

Twelve trials assessed lactulose or lactitol versus antibiotics (Table 03). Two trials were reported as abstracts. The remaining trials were reported in full articles. Ten trials used a parallel group design and two a cross-over design. A total of 698 patients (72% males) were randomised. The median number of patients in each trial was 44 (range 15 to 190). The mean ages ranged from 54 to 62 years (median 57 years). All patients had cirrhosis and acute hepatic encephalopathy (three trials), chronic hepatic encephalopathy (five trials), either acute and chronic hepatic encephalopathy (one trial), or the type of encephalopathy was not defined but presumably was chronic (three trials). In three trials, lactulose was considered as the experimental intervention (Conn 1977a - CHE; Atterbury 1978 - AHE; Orlandi 1981-AHE+CHE), whereas antibiotics were considered as the experimental intervention in the remaining nine trials. In this review, we will consider nonabsorbable disaccharides as the experimental intervention and antibiotics as the control intervention. The nonabsorbable disaccharides were oral lactulose in nine trials and oral lactitol in three trials. The daily mean dosages of lactulose ranged from 30 to 120 gram (median 59 gram) and of lactitol from 30 gram (one trial) to 60 gram (two trials). The control intervention was neomycin (three trials), rifaximin (seven trials), vancomycin (one trial), or ribostamycin (one trial). The median duration of treatment was 15 days (range five to 90 days).

Lactulose versus lactitol

Eight trials assessed lactulose versus lactitol (Table 04). All trials were reported in full articles. Four trials used a parallel group design and four a cross-over design. A total of 237 patients (66% males) were randomised. The median number of patients in each trial was 29 (range 9 to 45). The mean ages ranged from 48 to 67 years (median 56 years). All patients had cirrhosis and acute hepatic encephalopathy (three trials), chronic hepatic encephalopathy (three trials), either chronic or subclinical hepatic encephalopathy (one trial), and subclinical hepatic encephalopathy (one trial). The daily mean dosages of lactulose ranged from 17 to 100 gram (median 35 gram) and of lactitol from 26 to 66 gram (median 31 gram). The dose was adjusted to obtain 2 to 3 semisoft stools per day in all trials. The median duration of treatment was 60 days (range five to 180 days).

Additional analyses: lactose versus tap water, neomycin, or lactitol

Four trials assessed lactose versus tap water, neomycin, or lactitol in populations where the majority of people are lactase deficient (Table 05). One trial contained two comparisons: lactose versus tap water and lactose versus lactitol (Uribe 1987a - AHE). A total of 85 patients were randomised. The median number of patients in each trial was 22 (range 10 to 40). All patients had cirrhosis and acute hepatic encephalopathy (three trials) or chronic hepatic encephalopathy (one trial). Lactose was either administered as enemas one litre three times a day (three trials) or orally with a mean dose of 65 gram. The control intervention was tap water enemas (one trial), neomycin + starch enemas (one trial), lactitol enemas (one trial), or oral lactitol (mean dose 39 gram). The median duration of treatment was four days (range four to 28 days).

METHODOLOGICAL QUALITY

Lactulose or lactitol versus placebo or no intervention

All trials were described as randomised, but an adequate method of generating the allocation sequence was only described in one trial (Rodgers 1973 - CHE). Treatment allocation was adequately concealed in five trials (Elkington 1969 - CHE; Simmons 1970 - AHE; Rodgers 1973 - CHE; Germain 1973 - CHE; Watanabe 1997 - SHE). Double blinding was reported for seven trials (Elkington 1969 - CHE; Simmons 1970 - AHE; Rodgers 1973 - CHE; Germain 1973 - CHE; Corazza 1982 - CHE; Uribe 1987a - AHE; Shi 1997 - SHE). A sample size calculation was reported in one trial (Uribe 1987a - AHE). This trial assessed three interventions: lactitol enemas versus lactose enemas versus tap water enemas. In the sample size calculations, the authors assumed a 0.90 response

rate in each of the three groups (including the tap water group). This is a very positive estimate of the response rate. Further, the authors considered a difference of 0.40 as clinically significant, which is far too large a margin of equivalence. Dropouts and withdrawals were adequately described in three trials (Simmons 1970 - AHE; Germain 1973 - CHE; Dhiman 2000 - SHE) and included in the analyses (intention to treat) in one trial (Germain 1973 - CHE). In five trials, dropouts and withdrawals were not mentioned, giving the impression that there had been no dropouts and that all randomised patients were included in the analyses (Elkington 1969 - CHE; Corazza 1982 - CHE; Uribe 1987a - AHE; Shi 1997 - SHE; Li 1999 - SHE). We classified four trials as having high methodological quality (Elkington 1969 - CHE; Simmons 1970 - AHE; Germain 1973 - CHE; Rodgers 1973 - CHE). However, only one trial (Rodgers 1973 - CHE) had adequate descriptions of all three methodological components (generation of the allocation sequence, allocation concealment and blinding).

Lactulose or lactitol versus antibiotics

All trials were described as randomised, but an adequate method of generating the allocation sequence was described in only three trials (Orlandi 1981-AHE+CHE; Russo 1989 - CHE; Mas 2003 - AHE). Treatment allocation was adequately concealed in five trials (Conn 1977a - CHE; Atterbury 1978 - AHE; Orlandi 1981-AHE+CHE; Massa 1993 - CHE; Mas 2003 - AHE). Double blinding was reported for eight trials (Conn 1977a - CHE; Atterbury 1978 - AHE; Bucci 1993 - ?; Fera 1993 - ?; Blanc 1993 - AHE; Massa 1993 - CHE; Loguercio 2003 - CHE; Mas 2003 - AHE) and one trial had blinded outcome assessment (Orlandi 1981-AHE+CHE). A sample size calculation was reported but not obtained in one trial (Mas 2003 - AHE). Dropouts and withdrawals were adequately described in five trials (Atterbury 1978 - AHE; Blanc 1993 - AHE; Song 2000 - ?; Loguercio 2003 - CHE; Mas 2003 - AHE) and included in the analyses (intention to treat) in one trial (Blanc 1993 - AHE). In five trials, dropouts and withdrawals were not mentioned, giving the impression that there had been no dropouts (Russo 1989 - CHE; Bucci 1993 - ?; Festi 1993 - CHE; Fera 1993 - ?; Massa 1993 - CHE). In six trials, the impression was given that the analyses included all randomised patients (Russo 1989 - CHE; Festi 1993 - CHE; Fera 1993 - ?; Massa 1993 - CHE; Song 2000 - ?; Mas 2003 - AHE). We classified five trials as having high methodological quality (Conn 1977a - CHE; Atterbury 1978 - AHE; Orlandi 1981-AHE+CHE; Massa 1993 - CHE; Mas 2003 - AHE). Two trials (Orlandi 1981-AHE+CHE; Mas 2003 - AHE) had adequate descriptions of the generation of the allocation sequence, allocation concealment and blinding.

Lactulose versus lactitol

All trials were described as randomised, but an adequate method of generating the allocation sequence was described in only three trials (Heredia 1987 - AHE; Heredia 1988 - CHE; Pai 1995 - AHE). Treatment allocation was adequately concealed in five trials (Heredia 1987 - AHE; Morgan 1987a - AHE; Morgan 1987b - CHE; Heredia 1988 - CHE; Morgan 1989 - SHE). Double blinding was reported for two trials (Morgan 1987a - AHE; Morgan 1987b - CHE). None of the trials reported a sample size calculation or had statements implying an equivalence hypothesis or stated a margin of equivalence. Dropouts and withdrawals were adequately described in five trials (Morgan 1987a - AHE; Heredia 1987 - AHE; Riggio 1989-CHE+SHE; Morgan 1989 - SHE; Pai 1995 - AHE) and one trial gave the impression of no drop-outs (Grandi 1991 - CHE). One trial included all randomised patients in the analyses (Heredia 1987 - AHE) and one gave the impression of including all randomised patients (Grandi 1991 - CHE). Two trials were considered of high methodological quality (Morgan 1987a - AHE; Morgan 1987b - CHE). However, none of the eight included trials had adequate descriptions of both the generation of the allocation sequence, allocation concealment, and blinding.

Additional analyses: lactose versus tap water, neomycin, or lactitol

All trials were described as randomised and double blind, but it was not reported how the allocation sequence was generated or concealed in any of the trials. A sample size calculation was reported in one trial, but the assumptions were inadequate (Uribe 1987a - AHE) (see above). Dropouts and withdrawals were adequately described in one trial but were not included in the analyses (Uribe 1987b - CHE). In the two other trials, dropouts and withdrawals were not mentioned, giving the impression that there had been no dropouts and that all randomised patients were included in the analyses (Uribe 1987a - AHE; Uribe 1981 - AHE). None of the trials were considered of high methodological quality.

RESULTS

Lactulose or lactitol versus placebo or no intervention

Compared with placebo or no intervention, lactulose or lactitol appeared to reduce the risk of no improvement (RR 0.62, 95% CI 0.46 to 0.84, six trials). High-quality trials found no significant effect of lactulose or lactitol on the risk of no improvement (RR 0.92, 95% CI 0.42 to 2.04, two trials), whereas low-quality trials found a significant beneficial effect of lactulose or lactitol (RR 0.57, 95% CI 0.40 to 0.83, four trials). Although this difference in treatment response was not statistically significant (P = 0.3 by test of interaction) it is noteworthy, that the control event rate of risk of no improvement was significantly associated with methodological quality (high quality trials: 38% (8/21), low quality trials: 78% (54/69); P = 0.0005 by chi square). The event rate on risk of no improvement in the experimental group was not significantly different in trials with high (35%; 8/23) and low (43%; 40/94) methodological quality (P=0.5 by chi square). The treatment responses in acute, chronic, and subclinical hepatic encephalopathy did not differ significantly (P = 0.47 by chi square) (Deeks 2001). However, there was no statistically significant effect of lactulose or lactitol on acute hepatic encephalopathy (RR 0.27, 95% CI 0.02 to 3.28, two trials) or chronic hepatic encephalopathy (RR 1.33,

95% CI 0.41 to 4.33, one trial). Trials on subclinical hepatic encephalopathy found that lactulose or lactitol significantly reduced the risk of no improvement assessed by various psychometric tests (RR 0.61, 95% CI 0.47 to 0.79, three trials), but these trials were all of low methodological quality.

Compared with placebo or no intervention, lactulose or lactitol had no statistically significant effect on mortality (RR 0.41, 95% CI 0.02 to 8.68, four trials) or the number connection test (WMD -9 seconds, 95% CI -20 to 2, one trial), but tended to lower blood ammonia with an average of 13.9 µg/dl (95% CI -28.0 to 0.3, four trials). Data regarding adverse events were incompletely reported. Three trials did not mention this aspect, whereas the majority mentioned only the adverse events associated with nonabsorbable disaccharides. We were therefore unable to perform a reliable meta-analysis of this outcome. All reported adverse events were non-serious and gastrointestinal (diarrhoea, flatulence, abdominal pain, or nausea). All results were reported at the end of treatment. None of the trials followed the patients after end of treatment.

Lactulose or lactitol versus antibiotics

We found that lactulose or lactitol had significantly less favourable treatment responses than antibiotics on several outcomes. Compared with antibiotics, lactulose or lactitol had a significantly higher risk of no improvement (RR 1.24, 95% CI 1.02 to 1.50, 10 trials). Compared with antibiotics, patients in the group of lactulose or lactitol used on average six more seconds to complete the number connection test (WMD 6.4 seconds, 95% CI 1.4 to 11.3, six trials) and had a higher blood ammonia concentration af the end of treatment (WMD 4.0 µg/dl, 95 % CI 0.1 to 7.9, 10 trials). We found no statistically significant difference between lactulose or lactitol versus antibiotics on mortality (RR 0.90, 95% CI 0.48 to 1.67, five trials) or adverse events (RR 1.62, 95% CI 0.57 to 4.58, eight trials). All reported adverse events were non-serious and gastrointestinal (diarrhoea, flatulence, abdominal pain, or nausea).

We found no statistically significant difference in treatment response on the risk of no improvement between aminoglycosides and rifaximin (P = 0.2 by test of interaction) or when trials were stratified according to methodological quality or form of hepatic encephalopathy. One trial assessed all outcomes 15 days after end of treatment (Loguercio 2003 - CHE) and another trial reported mortality data 28 days after end of treatment (Mas 2003 - AHE). All other trials followed the patients to end of treatment.

Lactulose versus lactitol

We found no statistically significant difference between lactulose and lactitol (considered the 'control' in all analyses) on risk of no improvement (RR 1.13, 95% CI 0.71 to 1.82, four trials), mortality (RR 1.33, 95% CI 0.34 to 5.21, two trials), the number connection test (WMD -0.5 seconds, 95% CI -10.5 to 9.6, five trials), venous blood ammonia (WMD 0.72 µg/dl, 95% CI -9.76 to 11.20, six trials), or PSE Index (WMD 0.00, 95% CI -0.04 to 0.04, five trials). The analysis regarding adverse events revealed heterogeneity (P = 0.06, I^2 = 53,4%). There was a non-significant trend towards more adverse events in the lactulose group when a random effects model was applied (RR (random) 1.24, 95% 0.85 to 1.80, seven trials) and this trend became significant when a fixed effect model was applied (RR (fixed) 1.36, 95% CI 1.03 to 1.79, seven trials). This heterogeneity could be due to differences in trial design. Although there was no significant difference in treatment response between parallel and cross-over trials (P = 0.16 by test of interaction), there was a trend towards more adverse events in the lactulose group in the parallel group trials compared with the cross-over trials. This could be due to a carry-over effect in the cross-over trials. There were no statistically significant differences in treatment response when trials were stratified according to methodological quality or the form of hepatic encephalopathy. One trial reported mortality data 13 days after end of treatment (Morgan 1987a - AHE). None of the other trials followed the patients after end of treatment.

Additional analyses: lactose versus tap water, neomycin, or lactitol

In patients where the majority had lactose deficiency, we found no statistically significant difference on the risk of no improvement between lactose enemas and tap water enemas (RR 0.50, 95% CI 0.16 to 1.59, one trial), between lactose enemas and neomycin (RR 0.42, 95% CI 0.05 to 3.28, one trial), or between lactose and lactitol (RR 1.27, 95% CI 0.27 to 6.03, 2 trials). The occurrence of adverse events was reported in one trial (Uribe 1987b - CHE) with no statistical significant difference between oral lactose and lactitol (RR 0.86, 95% 0.36 to 2.05).

We were unable to extract data on quality of life, cost-effectiveness, or the Digit Symbol Test from any of the included trials.

DISCUSSION

We did not find sufficient evidence to confirm or exclude that lactulose and lactitol (nonabsorbable disaccharides) have a significant beneficial effect on patients with hepatic encephalopathy. The nonabsorbable disaccharides appeared to improve encephalopathy in our overall analysis, but this effect was not seen when only trials of high quality were included.

The beneficial effect in trials of low methodological quality was not due to a higher improvement rate in the nonabsorbable disaccharides group but to a significantly worse improvement rate in the control group. This finding concurs with empirical evidence showing that low quality trials find significantly larger beneficial treatment effects than high quality trials (Schulz 1995; Moher 1998; Kjaergard 2001; Jüni 2001). Accordingly, the overall result may reflect bias due to low methodological quality of the majority of the included trials.

The review is also limited by the small number of trials comparing nonabsorbable disaccharides with placebo and the low number

of patients randomised in each trial. Nonabsorbable disaccharides did not significantly improve patients with either acute or chronic hepatic encephalopathy, but far too few patients have been randomised to reliably exclude a potential beneficial effect. Low-quality trials on minimal hepatic encephalopathy found that lactulose had a beneficial effect assessed by various non-validated psychometric tests of which the clinical relevance is uncertain and controversial (Weissenborn 2002). We were not able to identify any randomised clinical trials assessing the effects of nonabsorbable disaccharides for fulminant hepatic failure.

The choice of comparator in trials assessing nonabsorbable disaccharides is complex. In order to assess the efficacy of nonabsorbable disaccharides, the comparator should be inert. In order to maintain the blindness of patients, caregivers, and outcome assessors, the two interventions should be indistinguishable from each other. Due to the cathartic effect of nonabsorbable disaccharides these two premises cannot be fulfilled concurrently. Methodological studies have shown that trials with inadequate or no double blinding overestimate the benefit of the experimental treatment (Schulz 1995; Moher 1998; Kjaergard 2001; Jüni 2001). In accordance with these studies, we found that the unblinded trials using no treatment as comparator reported a significant beneficial effect of nonabsorbable disaccharides. However, the trials attempting to obtain double blinding through the use of control interventions with the taste and appearance of nonabsorbable disaccharides but without the cathartic effect found no significant effect of nonabsorbable disaccharides (Germain 1973 - CHE; Simmons 1970 - AHE). Two trials (Atterbury 1978 - AHE; Rodgers 1973 - CHE) compared nonabsorbable disaccharides with sorbitol, which was known to have a cathartic effect, but nevertheless thought to have no therapeutic effects, due to its inability to acidify the colon. We could not extract data from these two small trials, but they found no significant difference in treatment response between nonabsorbable disaccharides and sorbitol. The inability of sorbitol to acidify the colon has later been questioned (McClain 1981). If nonabsorbable disaccharides has an effect on hepatic encephalopathy this could be due to the cathartic effects of nonabsorbable disaccharides. However, it is uncertain whether nonabsorbable disaccharides are better than other laxatives.

Lactulose has been considered the treatment of choice for hepatic encephalopathy and its efficacy has been considered to be beyond doubt (Conn 1979; Corazza 1982 - CHE; Uribe 1987a - AHE; Pai 1995 - AHE; Conn 1997). When it was introduced, the few trials that compared lactulose against placebo (Germain 1973 - CHE; Simmons 1970 - AHE) found no beneficial effect of lactulose. Still, it was implemented in clinical practice because two trials found it "equally effective" to neomycin (Conn 1977a - CHE; Atterbury 1978 - AHE), which had been the standard treatment for hepatic encephalopathy since 1957 (Dawson 1957). However, there are two major pitfalls in this reasoning. First, the efficacy of neomycin on hepatic encephalopathy has never been shown. We have only identified one randomised trial comparing neomycin with placebo (Strauss 1992) and another trial comparing neomycin plus lactulose with placebo (Blanc 1994), both for acute hepatic encephalopathy. Both trials failed to find statistically significant beneficial effect of neomycin. Secondly, lactulose was considered equally effective to neomycin due to lack of statistical significant difference of event rates in the two intervention groups. However, lack of statistical significance does not imply that the treatments have equal effects (Pocock 1983). Both trials (Conn 1977a - CHE; Atterbury 1978 - AHE) were small, and none of them reported sample size calculations with statements implying an equivalence hypothesis or stated a margin of equivalence (Pocock 1983; Piaggio 2001). It would require a far larger sample size than these two trials combined (a total of 78 patients) (Conn 1977a - CHE; Atterbury 1978 - AHE) to establish with confidence that lactulose and neomycin have comparable efficacy.

Later on, new trials compared other antibiotics to nonabsorbable disaccharides in the treatment of hepatic encephalopathy. All trials were underpowered to demonstrate equivalence. Sample size calculations with statements implying an equivalence hypothesis or a margin of equivalence were not reported in any of the trials, but equivalence from lack of statistical significance was concluded in all trials. It appears that the research was continuously built on both insufficient evidence and insufficient methodology. Our analyses show that antibiotics appear to be statistically superior to nonabsorbable disaccharides in improving hepatic encephalopathy and lowering blood ammonia. However, it is unclear whether the effects are clinically important. Given the evidence from placebo controlled trials (Strauss 1992; Blanc 1994), the risk of multiresistance (Hunter 2001), and the potential risk of more severe adverse events of antibiotics (Conn 1977a - CHE), we would conclude that there is insufficient evidence to recommend antibiotics for hepatic encephalopathy.

We found no statistically significant difference in treatment efficacy between lactulose and lactitol, but again there was insufficient evidence to confirm or exclude comparable efficacy. The eight included trials were all underpowered to demonstrate equivalence, but nevertheless all concluded equivalence from lack of statistical significance. Our meta-analyses were at best based on 187 patients. This number is far to small to establish with any confidence whether lactulose and lactitol have comparable efficacy (Pocock 1983; Piaggio 2001). Lactitol appeared to cause fewer adverse events than lactulose, but there was insufficient evidence to confirm an important difference. This was mainly due to the inconsistent results of parallel and cross-over trials. The parallel trials found significantly fewer adverse events in the lactitol group, whereas the cross-over trials found no difference between the two groups. The most plausible explanation for this discrepancy is that the results of cross-over trials are biased due to a carry-over effect. Only one (Morgan 1989 - SHE) of the five cross-over trials comparing lactulose with lactitol included a wash-out period between the two treatments. In addition, conditions with spontaneously evolving symptoms are not suitable for cross-over trials

(Freeman 1989; Als-Nielsen 2001). Hepatic encephalopathy has a spontaneously fluctuating nature (Basile 1991) and the patients' underlying condition and ability to respond to treatment might not remain stable from the first to the second treatment period.

Recent reviews (Ferenci 1999; Kircheis 2002) have pointed out that there is uncertain efficacy of nonabsorbable disaccharides given orally, but highlighted that there is evidence for proven efficacy of lactulose and lactitol enemas. However, this statement is based on interim analyses of a single small three-arm trial comparing lactitol enemas, lactose enemas, and tap water enemas (Uribe 1987a - AHE). All other trials have assessed orally administrated nonabsorbable disaccharides. The small three-arm trial was stopped prematurely after an interim analysis based on 20 patients, which indicated a significant benefit of lactitol enemas (ten patients) compared to tap water enemas (five patients) (P = 0.004 by chi squared). However, the interim analyses also showed that lactitol enemas (ten patients) were superior to lactose enemas (five patients) (P = 0.01 by chi squared) and that there was no significant difference between lactose enemas (five patients) compared to tap water enemas (five patients) (P = 0.3 by chi squared). Due to statistical and ethical considerations, the tap water group was discontinued, but the trial continued as a two-arm trial comparing lactitol enemas (22 patients) with lactose enemas (18 patients). The authors found no statistical significant difference between these two groups and concluded that lactose and lactitol enemas are equally effective and superior to tap water enemas in the treatment of acute hepatic encephalopathy. We do not believe that there is evidence for proven efficacy of lactitol or lactose enemas based on this single trial. Interim analyses have a considerable risk of generating false positive results and require very small significance levels before a trial is stopped (Peto 1976; O'Brien 1979; Pocock 1983). One generally accepted method for assessing interim analyses (Peto 1976) specifies that the significance level should be less than P = 0.001. The decision to terminate the trial by Uribe and colleagues is therefore debatable.

It was not our intention to include randomised trials on lactose in lactase deficient patients. However, for the sake of completeness, we have included the few trials in a separate meta-analysis and in Table 05. Lactose has not been compared to placebo or no intervention, otherwise than described above in the interim analysis showing no significant difference between lactose enemas and tap water enemas. Overall, there was no statistical significant difference between lactose and neomycin, or oral lactose and oral lactitol, or lactose enemas and lactitol enemas, but again the trials were vastly underpowered to demonstrate equivalence. Accordingly, there was insufficient evidence to confirm or exclude equivalence between lactose and neomycin or lactose and lactitol.

When assessing intervention effects for hepatic encephalopathy, it is important to consider the fluctuating course as well as the impact of treating precipitating factors in acute hepatic encephalopathy. Well-conducted placebo-controlled trials on ornithine aspartate to patients with subclinical or chronic hepatic encephalopathy (Kircheis 1997; Stauch 1998) and lactulose plus neomycin (Blanc 1994) in acute hepatic encephalopathy found improvement rates in the placebo group ranging from 40% to 70%. Many clinicians feel they have witnessed beneficial effects of nonabsorbable disaccharides on patients with hepatic encephalopathy. This effect may represent a high rate of spontaneous improvement and successful treatment of precipitating factors.

It appears that nonabsorbable disaccharides have been introduced into clinical practice without appropriate documentation. This leads to at least three major problems. First, patients are given a treatment of uncertain efficacy. It may be either beneficial, harmful or have no influence on hepatic encephalopathy. Second, there is reluctance towards performing randomised trials assessing lactulose or lactitol versus placebo, because it is considered unethical. Third, most randomised trials on new treatments for hepatic encephalopathy use lactulose as comparator (Table 06). New treatments (Table 06) are considered effective if improvement rates do not differ significantly from the group treated with lactulose, although trials are vastly underpowered to show equivalence. This approach is most undesirable. Nonabsorbable disaccharides should not serve as comparator in randomised trials on hepatic encephalopathy until randomised trials have shown that lactulose or lactitol have beneficial effect on hepatic encephalopathy.

AUTHORS' CONCLUSIONS

Implications for practice

This systematic review questions the efficacy of nonabsorbable disaccharides and highlights that there is insufficient high-quality evidence either to support or refute this treatment. In contrast, we found that antibiotics appeared to be superior to nonabsorbable disaccharides in improving hepatic encephalopathy, but it is unclear whether this difference is clinically important.

Implications for research

The absence of evidence for an effect of nonabsorbable disaccharides does not mean that there is evidence of no effect. However, nonabsorbable disaccharides should not serve as comparator in randomised trials on hepatic encephalopathy until randomised trials have proved without reasonable doubt that lactulose or lactitol have beneficial effect on hepatic encephalopathy.

Large, randomised double-blinded trials using sound research design and methodology are warranted. All trials should use a parallel group design, due to the spontaneously fluctuating nature of hepatic encephalopathy. Such trials could randomise patients stratified with regard to the various forms of hepatic encephalopathy (acute, chronic overt, or subclinical hepatic encephalopathy) to lactulose or lactitol versus placebo. The choice of placebo is complex. It would be interesting to perform a large, multicentre

three-arm trial comparing nonabsorbable disaccharides, another laxative (e.g., magnesium or sorbitol) prepared to appear and taste as nonabsorbable disaccharides, and a placebo of similar taste and appearance, but without a cathartic effect (e.g., glucose).

More research is needed on the effects of antibiotics for hepatic encephalopathy, including placebo-controlled trials assessing patients relevant outcomes like clinical improvement, recovery, and mortality as well as the occurrence of resistant bacterial strains. Future trials should report their data according to the recommendations of the CONSORT Group (www.consort-statement.org)

POTENTIAL CONFLICT OF INTEREST

None known.

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* *Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	**Atterbury 1978 - AHE**
Methods	Parallel group trial. Generation of the allocation sequence: not reported. Allocation concealment: adequate using sealed envelopes. Double blinding: adequate using placebo with similar taste and appearance. Follow-up: adequately reported. Sample size estimation: no. Intention to treat analyses: no.
Participants	37 patients with cirrhosis and 47 episodes of acute hepatic encephalopathy (grade 2-4) were randomised. Mean age: 55 years. Aetiology of cirrhosis: alcohol 89%, not reported 11%. Proportion of men: 93%.
Interventions	Experimental: lactulose 30 ml + placebo tablets four times daily. Control: Neomycin 1.5 gram + 30 ml sorbitol four times daily. The dosages of lactulose and sorbitol were adjusted to obtain two or three soft stools daily. Treatment duration: Patients were treated according to the regimen to which they were randomised until maximum clinical response had been achieved.
Outcomes	Clinical grading of mental state according to Conn 1977. PSE Index.
Notes	Number of patients with missing data: two patients were excluded after randomisation (one in each group). The trial report did not include these patients in the analyses. 20 of the randomised episodes occurred in 10 patients during the wash-out period in a cross-over trial (Conn 1977a). However, the results of this trial is included in our meta-analyses, although we are aware of the potential problems with re-randomisation of the 20 patients. Exclusion of this trial would not change the overall results significantly.
Allocation concealment	A – Adequate

Study	**Blanc 1993 - AHE**
Methods	Parallel group trial. Generation of the allocation sequence: not reported. Allocation concealment: not reported. Double blinding: the trial was described as double blind, but the method of blinding was not described. Follow-up: adequately reported. Sample size estimation: no. Intention to treat analyses: yes.
Participants	60 patients with cirrhosis and acute hepatic encephalopathy (grade not reported) were randomised. Mean age: 57 years. Aetiology of cirrhosis: not reported. Proportion of men: 67%.
Interventions	Experimental: vancomycin 2 gram/day Control: lactitol, 30 gram/day. Treatment duration: 5 days.

Characteristics of included studies (*Continued*)

Outcomes	Mortality. Clinical grading of mental state according to Conn 1977. PSE Index.
Notes	Abstract. Number of patients with missing data: Four patients were lost to the study (2 in each intervention group).
Allocation concealment	B – Unclear

Study	**Bucci 1993 - ?**
Methods	Parallel group trial. Generation of the allocation sequence: not reported. Allocation concealment: not reported. Double blinding: adequate using placebo. Follow-up: gave the impression of no drop-outs, but not stated. Sample size estimation: no. Intention to treat analyses: no.
Participants	58 patients with cirrhosis and mild (9 patients), moderate (38 patients) or severe (11 patients) hepatic encephalopathy were randomised. The encephalopathy was not defined as acute or chronic. Mean age: 57 years. Aetiology of cirrhosis: alcohol 64%, hepatitis 31, other 5%. Proportion of men: 52%.
Interventions	Experimental: rifaximin, 2 x 200 mg + 10 g placebo (sorbitol) three times daily. Control: Lactulose 10 gram + 2 tablets of rifaximin placebo three times. Treatment duration: 15 days.
Outcomes	Clinical grading of mental state according to Conn 1977. Asterixis. Cancellation test. Reitan test. Electroencephalogram. Fasting serum ammonia concentration. Adverse events.
Notes	Number of patients with missing data: uncertain. The trial only reported continuous outcomes and did not report the number of patients that are included in the analyses. However, the confidence interval regarding all outcomes are much more narrow at the end of treatment (15 days) than at the beginning, indicating that fewer patients contribute to the analyses at the end of treatment. Lactulose and rifaximin were reported to be about equally effective, but numerical data were not available.
Allocation concealment	B – Unclear

Study	**Conn 1977a - CHE**
Methods	Cross-over trial. Generation of the allocation sequence: not reported. Allocation concealment: adequate using sealed envelopes. Double blinding: adequate using placebo. Follow-up: inadequately reported. Sample size estimation: no. Intention to treat analyses: no.
Participants	33 patients with cirrhosis and chronic hepatic encephalopathy (grade not reported) were randomised. Mean age: 55 years. Aetiology of cirrhosis: alcohol 88%, postnecrotic 11%.

Characteristics of included studies (*Continued*)

	Proportion of men: 94%.
Interventions	Experimental: lactulose 30 ml + placebo tablets four times daily. Control: Neomycin 1.5 gram + 30 ml sorbitol four times daily. Dosages of lactulose and sorbitol were adjusted to obtain two or three soft stools daily. Treatment duration: 10 days in each period with at least 10 days washout period.
Outcomes	Clinical grading of mental state according to Conn 1977. PSE Index. Adverse events.
Notes	Number of patients with missing data: all patients completed the first treatment period. four patients did not complete the second treatment period (three died, one left the hospital). Only data from the first treatment period are used in this review.
Allocation concealment	A – Adequate

Study	**Corazza 1982 - CHE**
Methods	Parallel group trial with three intervention arms. Generation of the allocation sequence: not reported. Allocation concealment: not reported. Double blinding: adequate using placebo. Follow-up: gave the impression of no drop-outs, but not stated. Sample size estimation: no. Intention to treat analyses: uncertain.
Participants	52 patients with cirrhosis and chronic hepatic encephalopathy (grade 1) were randomised. Of these, 32 patients were randomised to either lactulose or placebo. The characteristics for these patients were: Mean age: 54 years. Aetiology of cirrhosis: alcohol 88%, hepatitis 12%. Proportion of men: 56%.
Interventions	Experimental 1: pyridoxine-alpha-ketoglutarate (PAK) 2300 mg/day in 250 ml of saline + placebo resembling lactulose. Experimental 2: lactulose, 10-35 ml three times daily + placebo resembling PAK. Control: placebo resembling lactulose + PAK placebo. Treatment duration: 10 days.
Outcomes	Encephalopathy intensity score. Plasma ammonia.
Notes	Number of patients with missing data: uncertain. Lactulose was reported to be superior to placebo, but no numerical data were available.
Allocation concealment	B – Unclear

Study	**Dhiman 2000 - SHE**
Methods	Parallel group trial. Generation of the allocation sequence: not reported. Allocation concealment: not reported. Double blinding: unblinded trial. Follow-up: adequately reported. Sample size estimation: no. Intention to treat analyses: no.
Participants	26 patients with cirrhosis and subclinical hepatic encephalopathy were randomised. Mean age: 46 years. Aetiology of cirrhosis: alcohol 31%, hepatitis 31%, other 38%.

	Proportion of men: 77%.
Interventions	Experimental: lactulose, 30-60 ml in two divided doses. Control: no treatment. The dosages of lactulose was adjusted to obtain two to three semisoft stools daily. Treatment duration: three months.
Outcomes	Number connection tests. Figure connection tests. Two performance subtests of Wechsler adult intelligence scale. Number of abnormal tests. Number of patients improving.
Notes	Number of patients with missing data: Eight patients did not complete the study (four in each group). The trial report did not include these patients in the analyses. Subclinical HE was defined as diagnosed if two or more psychometric tests were abnormal (out of a series of six tests). The authors report the numbers of patients improving, but they do not define what they consider an improvement. Further, they do not report post-treatment results of the psychometric tests.
Allocation concealment	B – Unclear

Study	**Elkington 1969 - CHE**
Methods	Cross-over trial. Generation of the allocation sequence: not reported. Allocation concealment: adequate, the randomisation procedure was administered by a pharmacist . Double blinding: adequate using placebo with identical taste and appearance. Follow-up: gave the impression of no drop-outs, but not stated. Sample size estimation: no. Intention to treat analyses: uncertain.
Participants	7 patients with cirrhosis and chronic hepatic encephalopathy (grade 0-1) were randomised. However, only one patient had overt signs of hepatic encephalopathy. Mean age: not reported. Aetiology of cirrhosis: not reported. Proportion of men: not reported.
Interventions	Experimental: lactulose 100 ml daily in two divided doses. Control: sorbitol, dosages not reported. The dosages of lactulose was adjusted to obtain two to three semisoft stools daily. The dosages of sorbitol was adjusted to produce “the bowel activity as lactulose”. Treatment duration: 15 days in each period with 18 days washout period.
Outcomes	Clinical grading of mental state according to Parson-Smith. EEG. Arterial ammonia. Stool pH.
Notes	Number of patients with missing data: uncertain. Lactulose and sorbitol were reported to be about equally effective in most of the patients, but numerical data were not available.
Allocation concealment	A – Adequate

Study	**Fera 1993 - CHE**
Methods	Parallel group trial. Generation of the allocation sequence: not reported.

Characteristics of included studies (*Continued*)

	Allocation concealment: not reported. Double blinding: adequate using identical placebo. Follow-up: gave the impression of no drop-outs, but not stated. Sample size estimation: no. Intention to treat analyses: uncertain.
Participants	40 patients with cirrhosis and hepatic encephalopathy (grade 1, type not specified) were randomised. Mean age: 59 years. Aetiology of cirrhosis: not reported. Proportion of men: 73%.
Interventions	Experimental: rifaximin 400 mg + 40 gram lactulose placebo three times daily. Control: Lactulose 40 gram + rifaximin placebo tablets three times daily. Treatment duration: the interventions were given the first two weeks of 3 months.
Outcomes	Clinical grading of mental state according to Conn 1977 Psychometric tests. EEG. Venous blood ammonia. Asterixis. Adverse events.
Notes	Number of patients with missing data: uncertain.
Allocation concealment	B – Unclear

Study	**Festi 1993 - CHE**
Methods	Parallel group trial. Generation of the allocation sequence: not reported. Allocation concealment: not reported. Double blinding: unblinded study. Follow-up: gave the impression of no drop-outs, but not stated. Sample size estimation: no. Intention to treat analyses: uncertain.
Participants	21 patients with cirrhosis and chronic hepatic encephalopathy (grade 1) were randomised. Mean age: 60 years. Aetiology of cirrhosis: not reported. Proportion of men: 81%.
Interventions	Experimental: rifaximin 1200 mg/day. Control: lactulose 40 gram/day. Treatment duration: 21 days.
Outcomes	EEG. Asterixis. Venous ammonia.
Notes	Number of patients with missing data: uncertain. Lactulose and rifaximin were reported to be about equally effective, but numerical data were not available.
Allocation concealment	B – Unclear

Study	**Germain 1973 - CHE**
Methods	Parallel group trial. Generation of the allocation sequence: not reported. Allocation concealment: adequate using coded identical-looking bottles. Double blinding: adequate using similar placebo.

	Follow-up: adequately reported. Sample size estimation: no. Intention to treat analyses: yes.
Participants	18 patients with cirrhosis and chronic hepatic encephalopathy (grade 1-4) after portacaval anastomosis were randomised. Mean age: 47 years. Aetiology of cirrhosis: not reported. Proportion of men: 72%.
Interventions	Experimental: lactulose 50 gram daily. Control: placebo formula containing saccharose. The dose of lactulose was fixed regardless of the number or character of stools. Treatment duration: 15 days.
Outcomes	Clinical grading of mental state according to the authors own grading system. Psychometric tests. EEG grading according to Parsons-Smith. Venous blood ammonia.
Notes	Number of patients with missing data: none, all randomised patients are accounted for.
Allocation concealment	A – Adequate

Study	**Grandi 1991 - CHE**
Methods	Cross-over trial. Generation of the allocation sequence: not reported. Allocation concealment: not reported. Double blinding: unblinded study. Follow-up: gave the impression of no drop-outs, but not stated. Sample size estimation: no. Intention to treat analyses: uncertain.
Participants	40 patients with cirrhosis and chronic hepatic encephalopathy (grade 1-3) were randomised. Mean age: 59 years. Aetiology of cirrhosis: not reported. Proportion of men: 63%.
Interventions	Experimental: Crystalline pure lactulose, 20 gram three times daily. Control: lactitol, 10 gram three times daily. Treatments were adjusted to induce one to two bowel movements daily. Treatment duration: 60 days in each period (cross-over trial). No washout period.
Outcomes	PSE Index. Adverse events.
Notes	Number of patients with missing data: uncertain. The summary results from both treatment periods were used in the analysis regarding adverse events whereas the results from the first period were used in the analysis regarding mental grade.
Allocation concealment	B – Unclear

Study	**Heredia 1987 - AHE**
Methods	Parallel group trial. Generation of the allocation sequence: adequate using a random number table. Allocation concealment: adequate using sealed envelopes. Double blinding: unblinded study. Follow-up: adequately reported.

Characteristics of included studies (*Continued*)

	Sample size estimation: no. Intention to treat analyses: yes.
Participants	40 patients with cirrhosis and acute hepatic encephalopathy (grade 1-3) were randomised. Mean age: 59 years. Aetiology of cirrhosis: alcohol 48%. Proportion of men: 50%.
Interventions	Experimental: Lactitol 12 gram four times daily, orally (mean [SD] 26 [5] gram/day). Control: Lactulose 30 ml four times daily, orally (mean [SD] 150 [53] ml/day). Dosages of both drugs were adjusted to obtain two soft stools daily. Treatment duration: 5 days.
Outcomes	Clinical grading of mental state. PSE grade.
Notes	Number of patients with missing data: none.
Allocation concealment	A – Adequate

Study	**Heredia 1988 - CHE**
Methods	Cross-over trial. Generation of the allocation sequence: adequate using a random number table. Allocation concealment: adequate using sealed envelopes. Double blinding: unblinded study. Follow-up: inadequately reported. Sample size estimation: no. Intention to treat analyses: no.
Participants	25 patients with cirrhosis and chronic recurrent hepatic encephalopathy (grade not reported) were randomised. Mean age: 55 years. Aetiology of cirrhosis: alcohol 60%, hepatitis 24%, other 16%. Proportion of men: 70%.
Interventions	Experimental: Lactitol 10 gram four times daily, orally (mean [SD] 36 [18] gram). Control: Lactulose 15 ml four times daily, orally (mean [SD] 60 [29] ml). Dosages of both drugs were adjusted to obtain two soft stools daily. Treatment duration: 3 months in each period with no washout period.
Outcomes	PSE Index. Adverse events.
Notes	Number of patients with missing data: Five patients were excluded from the trial (two died and three dropped out). However, the number of patients are not reported separately for each intervention arm. Only the summary results from both treatment periods were reported and accordingly, only these data could be used in the analyses of the review.
Allocation concealment	A – Adequate

Study	**Li 1999 - SHE**
Methods	Parallel group trial. Generation of the allocation sequence: not reported. Allocation concealment: not reported. Double blinding: unblinded study. Follow-up: gave the impression of no drop-outs, but not stated. Sample size estimation: no.

Characteristics of included studies (*Continued*)

	Intention to treat analyses: uncertain.
Participants	86 patients with cirrhosis and subclinical hepatic encephalopathy were randomised. Mean age: 45 years. Aetiology of cirrhosis: not reported. Proportion of men: 83%.
Interventions	Experimental: lactulose 45-60 ml/day, orally + 'common treatment for SHE' (bedrest, low protein diet). Control: Common treatment for SHE. Treatment duration: 30 days.
Outcomes	Improvement defined as normalization of either the number-connection-test or the digit-symbol-test. Liver functional grade (Child-Pugh grading).
Notes	Number of patients with missing data: uncertain. SHE was defined if one of two psychometric test was abnormal.
Allocation concealment	B – Unclear

Study	**Loguercio 2003 - CHE**
Methods	Parallel group trial with three intervention arms. Generation of the allocation sequence: not reported. Allocation concealment: not reported. Double blinding: adequate using identical placebo. Follow-up: adequately reported. Sample size estimation: no. Intention to treat analyses: no.
Participants	47 patients with cirrhosis and chronic hepatic encephalopathy (grade 1-2) were randomised. Of these, 27 patients were randomised to either lactitol or rifaximin . The characteristics for these patients were: Mean age: 59 years. Aetiology of cirrhosis: hepatitis 100%. Proportion of men: 82%.
Interventions	Experimental 1: rifaximin 400 mg + sorbitol 20 gram three times daily. Experimental 2: rifaximin 400 mg + lactitol 20 mg three times daily. Control: lactitol 20 mg + rifaximin placebo tablets three times daily. Treatment duration: 3 cycles of 15 days each with 15 days washout period.
Outcomes	Clinical grading of mental state according to Conn 1977. Asterixis. Number connection test. Arterial ammonia. Grading of hepatic encephalopathy according to the authors own grading system. Adverse events.
Notes	Number of patients with missing data: 7 patients did not complete the trial and was also excluded from the analyses: 2 patients in the rifaximin group (1 died, one did not attend controls), 3 patients in the lactitol group (1 due to ascites, 2 did not attend controls), and 2 patients in the rifaximin + lactulose group (1 due to ascites, 1 did not attend controls).
Allocation concealment	B – Unclear

Study	**Mas 2003 - AHE**
Methods	Parallel group trial. Generation of the allocation sequence: adequate using computer generated random list. Allocation concealment: adequate, using serially numbered, sealed, opaque envelopes. Double blinding:adequate using identical placebo.

	Follow-up: adequately reported. Sample size estimation: yes, but the full sample size (120 patients) was not reached. Intention to treat analyses: uncertain.
Participants	103 patients with cirrhosis and acute hepatic encephalopathy (grade 1-3) were randomised. Mean age: 62 years. Aetiology of cirrhosis: alcohol 48%, hepatitis 36%, other 16%. Proportion of men: 70%.
Interventions	Experimental: rifaximin 400 mg + 20 gram lactitol placebo three times daily. Control: Lactitol 20 gram + rifaximin placebo tablets three times daily. Dosages of lactitol were adjusted to obtain two soft stools daily. Treatment duration: 5-10 days.
Outcomes	PSE Index. Adverse events.
Notes	Number of patients with missing data: 15 patients were withdrawn: 11 due to inefficacy (rifaximin:6, lactitol: 5) and 4 due to intolerance (2 in each group). Follow-up: patients were followed for at least 28 days.
Allocation concealment	A – Adequate

Study	**Massa 1993 - CHE**
Methods	Parallel group trial. Generation of the allocation sequence: not reported. Allocation concealment: adequate using coded identical-looking containers. Double blinding: adequate using placebo with identical taste and appearance. Follow-up: gave the impression of no drop-outs, but not stated. Sample size estimation: no. Intention to treat analyses: uncertain.
Participants	40 patients with cirrhosis and chronic hepatic encephalopathy (grade 1-3) were randomised. Mean age: 55 years. Aetiology of cirrhosis: alcohol 48%, hepatitis 52%. Proportion of men: 68%.
Interventions	Experimental: rifaximin 400 mg + 20 gram sorbitol three times daily. Control: Lactulose 20 gram + rifaximin placebo tablets three times daily. Treatment duration: 15 days.
Outcomes	Clinical grading of mental state according to Conn 1977. Asterixis. Psychometric tests Venous Ammonia. EEG. Adverse events.
Notes	Number of patients with missing data: uncertain.
Allocation concealment	A – Adequate

Study	**Morgan 1987a - AHE**
Methods	Parallel group trial. Generation of the allocation sequence: not reported. Allocation concealment: adequate using sealed envelopes. Double blinding: adequate with identical appearance and taste of both interventions. Follow-up: adequately reported.

	Sample size estimation: no. Intention to treat analyses: no.
Participants	27 patients experiencing 30 episodes of acute hepatic encephalopathy (grade 1-4) were randomised. Two patients were excluded because they had acute fulminant hepatic failure. The remaining patients had cirrhosis. Mean age: 48 years. Aetiology of cirrhosis: alcohol 54%, hepatitis 18%, other 28%. Proportion of men: 54%.
Interventions	Experimental: Lactitol 0.5 gram/kg divided in four doses (mean [SD] 26 [5] gram). Control: Lactulose 0.5 ml/kg divided in four doses (mean [SD] 31 [7] ml). Dosages of both drugs were adjusted to obtain two soft stools daily. Treatment duration: 5 days.
Outcomes	Clinical grading of mental state according to Conn 1977. PSE Index.
Notes	Number of patients with missing data: 5 patients did not complete the trial: 2 patients had acute fulminant hepatic failure and were excluded from the analyses. 3 patients (in the lactitol group) discontinued treatment, but are included in the analyses.
Allocation concealment	A – Adequate

Study	**Morgan 1987b - CHE**
Methods	Cross-over trial. Generation of the allocation sequence: not reported. Allocation concealment: adequate using sealed envelopes. Double blinding: adequate with identical appearance and taste of both interventions. Follow-up: inadequate reported. Sample size estimation: no. Intention to treat analyses: no
Participants	12 patients with cirrhosis and chronic hepatic encephalopathy (grade 0-2) were randomised. Mean age: 57 years. Aetiology of cirrhosis: alcohol 56%, other 44%. Proportion of men: 56%.
Interventions	Experimental: Lactitol 0.5 gram/kg divided in four doses (mean [SD] 32 [11] gram). Control: Lactulose 0.5 gram/kg divided in four doses (mean [SD] 33 [17] ml). Dosages of both drugs were adjusted to obtain two soft stools daily. Treatment duration: 3 months in each period with no washout period.
Outcomes	PSE Index. Adverse events. Psychometric tests.
Notes	Number patients with missing data: 3 patients were excluded after randomisation. Reasons were given, but it was not reported which intervention arm they had been randomised to. The results from the first period were used in the analyses regarding ammonia concentration and PSE Index. The summary results from both treatment periods were used in the analysis of adverse events.
Allocation concealment	A – Adequate

Study	**Morgan 1989 - SHE**
Methods	Cross-over trial. Generation of the allocation sequence: not reported. Allocation concealment: adequate using sealed envelopes. Double blinding: unblinded study.

Characteristics of included studies (*Continued*)

	Follow-up: adequately reported. Sample size estimation: no. Intention to treat analyses: no
Participants	20 patients with cirrhosis and subclinical hepatic encephalopathy were randomised. Mean age: 52 years. Aetiology of cirrhosis: alcohol 100%. Proportion of men: 79%.
Interventions	Experimental: Lactitol 0.5 gram/kg daily (mean [SD] 26 [9] gram). Control: lactulose 20 ml/day in divided doses (not specified) (mean [SD] 25 [13] ml). Dosages of both drugs were adjusted to obtain two soft stools daily. Treatment duration: 2 months in each period with a 4-6 weeks washout period.
Outcomes	Clinical grading of mental state according to Conn 1977. Psychometric tests. EEG. Adverse events.
Notes	Number patients with missing data: 6 patients were excluded from the analyses (lactulose: 2, lactitol: 4). 5 patients dropped out, 1 patient discontinued treatment (lactitol) due to severe flatulence. Subclinical hepatic encephalopathy was defined as the presence of at least two abnormal psychometric tests out of 13 applied. Lactitol and lactulose were reported to be equally effective, but data were not available for analyses.
Allocation concealment	A – Adequate

Study	**Orlandi 1981-AHE+CHE**
Methods	Parallel group trial. Generation of the allocation sequence: adequate using a random sequence provided by a statistical unit. Allocation concealment: adequate using sealed envelopes. Double blinding: not double blinded, but outcome assessors and investigators performing the statistical analyses were blinded. Follow-up: inadequately reported. Sample size estimation: no. Intention to treat analyses: no.
Participants	A total of 190 patients with cirrhosis and chronic or acute (grade 1-3) hepatic encephalopathy were randomised. Characteristics were only given for the 173 patients included in the analyses. Mean age: 54 years. Aetiology of cirrhosis: alcohol 64%, hepatitis 14%, other 22%. Proportion of men: 79%.
Interventions	Experimental: Neomycin 1 g four times daily + magnesium sulfate 30-60 gram given to patients with grade 1 hepatic encephalopathy. Patients with grade 2 or 3 received 2 gram neomycin four times daily + same dose magnesium sulfate. Control: 10-35 ml 50% lactulose syrup given three times daily (mean [SD] 28 [8] ml). The aim of both therapies was to induce at least two soft stools daily. Treatment duration: at least 19 days.
Outcomes	Mortality. Clinical grading of hepatic encephalopathy according to authors' own definition. Psychometric tests. EEG. Venous ammonia concentration. Adverse events.

Characteristics of included studies (*Continued*)

Notes	Number of patients with missing data: 17 patients were excluded from the analyses due to gastrointestinal haemorrhage, death, intolerance to the drugs, or unsatisfactory compliance. The complete number of drop-outs in each intervention group is not reported.
Allocation concealment	A – Adequate

Study	**Pai 1995 - AHE**
Methods	Parallel group trial. Generation of the allocation sequence: adequate using a random number table. Allocation concealment: not reported. Double blinding: not double blinded, but blinded outcome assessor. Follow-up: adequately reported. Sample size estimation: no. Intention to treat analyses: no.
Participants	45 patients with cirrhosis and acute hepatic encephalopathy (grade 2 or more) were randomised. Mean age: 67 years. Aetiology of cirrhosis: alcohol 18%, hepatitis 69%, other 14%. Proportion of men: 83%.
Interventions	Experimental: lactitol 10 gram four times daily (mean [SD] 66 [36] gram). Control: Lactulose 10 ml four times daily (mean [SD] 57 [32] ml. The dosages of both treatments were adjusted to induce two to three bowel movement daily. Treatment duration: 5 days.
Outcomes	PSE Index. Adverse events.
Notes	Number of patients with missing data: 4 patients (2 in each group).
Allocation concealment	B – Unclear

Study	**Riggio 1989-CHE+SHE**
Methods	Parallel group trial. Generation of the allocation sequence: not reported. Allocation concealment: not reported. Double blinding: not double blinded, but blinded outcome assessor. Follow-up: adequately reported. Sample size estimation: no. Intention to treat analyses: no.
Participants	31 patients with cirrhosis, surgical portal-systemic anastomosis and chronic (40%) or subclinical (60%) hepatic encephalopathy (grade 0-2). Mean age: 54 years. Aetiology of cirrhosis: alcohol %, hepatitis %, other %. Proportion of men: 71%.
Interventions	Experimental: lactitol 0.5 gram/kg daily (mean [SD] 36 [7] gram). Control: lactulose, 30 ml daily (mean [SD] 48 [25] ml). The dosages of both treatments were adjusted to induce 2 bowel movements daily. Treatment duration: 6 months.
Outcomes	PSE Index. Number of patients with new episodes of hepatic encephalopathy. Adverse events.
Notes	Number of patients with missing data: Two patients in the lactitol group dropped out due to adverse events and inefficacy of the intervention.

Allocation concealment	B – Unclear

Study	**Rodgers 1973 - CHE**
Methods	Cross-over trial. Generation of the allocation sequence: adequate using flip of coin. Allocation concealment: adequate, using identical coded bottles. Double blinding: adequate using placebo with similar appearance. Follow-up: inadequately reported. Sample size estimation: no. Intention to treat analyses: no.
Participants	6 patients with cirrhosis and chronic hepatic encephalopathy (grade not reported) were randomised. Characteristics were only given for the 3 patients included in the analyses. Mean age: 67 years. Aetiology of cirrhosis: not reported. Proportion of men: 66%.
Interventions	Experimental: lactulose 20-30 ml three times daily. Control: sorbitol dosages not reported. The dosages of lactulose was adjusted to obtain two or more soft stools per day. Treatment duration: 2 years. During the first year, patients were on one medication for two months and then switched to the other for a similar length of time without any washout period. During the second year, a washout period of two to four weeks separated treatment periods.
Outcomes	Clinical grading. EEG. Blood ammonia.
Notes	Number of patients with missing data: three patients were excluded from the study (two patients died shortly after entering the study and one patient was found not to require therapy for his encephalopathy). Lactulose and sorbitol were reported to be about equally effective in most of the patients, but numerical data were not available.
Allocation concealment	A – Adequate

Study	**Russo 1989 - CHE**
Methods	Cross-over trial. Generation of the allocation sequence: adequate using a random number table. Allocation concealment: not reported. Double blinding: unblinded study. Follow-up: gave the impression of no drop-outs, but not stated. Sample size estimation: no. Intention to treat analyses: uncertain.
Participants	15 patients with cirrhosis and chronic hepatic encephalopathy (grade 1-2) were included. Mean age: 56 years. Aetiology of cirrhosis: alcohol 20%, hepatitis 13%, other 67%. Proportion of men: 53%.
Interventions	Experimental: ribostamycin 1.5 gram daily. Control: lactulose 60-90 ml daily (mean 57 gram). Treatment duration: 7-11 days in each period (cross-over) with a 4 days washout period.
Outcomes	Mean score of 15 parameters (behaviour, attention, sleep disorders etc.) Venous ammonia. Adverse events.
Notes	Number of patients with missing data: uncertain.

	Only data from the first treatment period are used in this review.
Allocation concealment	B – Unclear

Study	**Shi 1997 - SHE**
Methods	Parallel group trial. Generation of the allocation sequence: not reported. Allocation concealment: not reported. Double blinding: adequate using placebo with similar taste and appearance. Follow-up: gave the impression of no drop-outs, but not stated. Sample size estimation: no. Intention to treat analyses: uncertain.
Participants	31 patients with cirrhosis and subclinical hepatic encephalopathy were randomised. Mean age: 54 years. Aetiology of cirrhosis: non-alcoholic, otherwise not reported. Proportion of men: 87%.
Interventions	Experimental: lactitol 0.55-1.75 ml/kg daily in three daily doses (mean 1.05 ml/kg). Control: 10 ml 5% glucose three times daily. The dosages of lactitol were adjusted to obtain one to two soft stools daily. Treatment duration: 2 weeks.
Outcomes	Number connection test. Digit symbol. Somatosensory evoked potentials. Blood ammonia. Adverse events.
Notes	Number of patients with missing data: uncertain. Lactitol was reported to be superior to placebo, but no numerical data were available. Subclinical hepatic encephalopathy was not defined.
Allocation concealment	B – Unclear

Study	**Simmons 1970 - AHE**
Methods	Parallel group trial. Generation of the allocation sequence: not reported. Allocation concealment: adequate, the randomisation code was unknown. Double blinding: adequate using placebo with similar taste and appearance. Follow-up: adequately reported. Sample size estimation: no. Intention to treat analyses: no.
Participants	26 patients with cirrhosis and chronic or acute hepatic encephalopathy (grade not reported) were randomised. Mean age: 51 years. Aetiology of cirrhosis: alcohol 100%. Proportion of men: 100%.
Interventions	Experimental: lactulose 20 gram four times daily (mean 80 gram). Control: glucose 15 gram four times daily. The dosages of lactulose were adjusted to obtain two or more soft stools per day. Treatment duration: 10 days.
Outcomes	Clinical grading of mental state according to Sherlock. Stool production. Venous blood ammonia.

Notes	Number of patients with missing data: 5 patients (3 given lactulose and 2 given glucose) were excluded from the study and the analyses due to complications of their hepatic disease.
Allocation concealment	A – Adequate

Study	**Song 2000 - ?**
Methods	Parallel group trial. Generation of the allocation sequence: not reported. Allocation concealment: not reported. Double blinding: not reported. Follow-up: adequately reported. Sample size estimation: no. Intention to treat analyses: uncertain.
Participants	64 patients with cirrhosis and hepatic encephalopathy (grade 1-3, type not specified) were randomised. Mean age: not reported Aetiology of cirrhosis: not reported Proportion of men: not reported.
Interventions	Experimental: rifaximin 1200 mg daily. Control: lactulose 90 ml daily. Treatment duration: 7 days.
Outcomes	PSE index.
Notes	Abstract. Number of patients with missing data: 2 patients (one in each group) dropped out due to abdominal pain (rifaximin) and severe diarrhoea (lactulose).
Allocation concealment	B – Unclear

Study	**Uribe 1981 - AHE**
Methods	Parallel group trial. Generation of the allocation sequence: not reported. Allocation concealment: not reported. Double blinding: adequate. Follow-up: gave the impression of no drop-outs, but not stated. Sample size estimation: no. Intention to treat analyses: uncertain.
Participants	18 patients with cirrhosis and acute hepatic encephalopathy (grade 2-4) were randomised. Mean age: 53 years. Aetiology of cirrhosis: alcohol 61%, other 39%. Proportion of men: 33%.
Interventions	Experimental: 1 liter 20% lactose enemas + 2 tbl. neomycin placebo three times daily. Control: neomycin 0.5 gram 2 tbl. + 1 liter starch enemas three times daily. Treatment duration: 3-4 days.
Outcomes	Clinical grading of mental state according to Conn 1977. Number connection test. Asterixis. EEG. Arterial blood ammonia. PSE Index. Faecal pH. Adverse events.

Characteristics of included studies (*Continued*)

Notes	Number of patients with missing data: uncertain.
Allocation concealment	B – Unclear

Study	**Uribe 1987a - AHE**
Methods	Parallel group trial with three intervention arms. Generation of the allocation sequence: not reported. Allocation concealment: not reported. Double blinding: adequate using identical containers. Follow-up: gave the impression of no drop-outs, but not stated. Sample size estimation: yes, but the assumptions were inadequate. Intention to treat analyses: uncertain.
Participants	37 patients with cirrhosis and 45 episodes of acute hepatic encephalopathy (grade 2 or more) were randomised. Mean age: not reported. Aetiology of cirrhosis: not reported. Proportion of men: not reported.
Interventions	Experimental 1: 20% lactose enemas. Experimental 2: 20% lactitol enemas. Control: Tap-water enemas. All enemas was given at a dose of 1 liter t.i.d. Duration of the enema administration varied and was response-dependent. The mean duration of therapy +/- SD was for the tap-water group: 2.6 +/- 0.9, lactose group: 3.5 +/- 1.2, lactitol group 3.7 +/- 1.2.
Outcomes	Mortality. Clinical grading of mental state according to Conn 1977. Number connection test. Asterixis. Electroencephalograms. Arterial blood ammonia. PSE Index. Faecal pH.
Notes	Number of patients with missing data: uncertain. An interim analysis revealed a significant higher number of patients failures in the control group (tap water). The control group was therefore suspended and the study continued after re-randomisation for lactose and lactitol groups.
Allocation concealment	B – Unclear

Study	**Uribe 1987b - CHE**
Methods	Cross-over trial. Generation of the allocation sequence: not reported. Allocation concealment: not reported. Double blinding: adequate using identical containers and both interventions were of similar appearance. Follow-up: adequately reported. Sample size estimation: no. Intention to treat analyses: no
Participants	20 patients with cirrhosis, chronic hepatic encephalopathy and lactose insufficiency were randomised. Mean age: 54 years. Aetiology of cirrhosis: alcohol 44%, hepatitis 56%. Proportion of men: 45%.
Interventions	Experimental: lactose 0.25 gram/kg daily (mean [SD] 65 [12] gram). Control: lactitol 0.25 gram/kg (mean [SD] 39 [14] gram).

Characteristics of included studies (*Continued*)

	Treatment was adjusted to induce two to four bowel movements per day. Treatment duration: 4 weeks in each period with a 2 weeks washout period.
Outcomes	PSE Index. Mental state. Adverse events.
Notes	Number of patients with missing data: two patients, both randomised to receive lactitol during the first treatment period. The results from the first period were used in the analysis regarding 'no improvement of hepatic encephalopathy. The summary results from both treatment periods were used in the analysis regarding adverse events.
Allocation concealment	B – Unclear

Study	**Watanabe 1997 - SHE**
Methods	Parallel group trial. Generation of the allocation sequence: not reported. Allocation concealment: adequate using serial numbered, sealed envelopes. Double blinding: unblinded study. Follow-up: inadequately reported (see notes). Sample size estimation: no. Intention to treat analyses: no.
Participants	75 patients with cirrhosis with and without subclinical hepatic encephalopathy were randomised. Of these, 36 had subclinical hepatic encephalopathy (22 given lactulose and 14 receiving no treatment). Mean age: 64 years. Aetiology of cirrhosis: alcohol 11%, hepatitis 78%, other 11%. Proportion of men: 47%.
Interventions	Experimental: Lactulose 45 ml daily divided in two to three doses. Control: no treatment. The dosages of lactulose was adjusted to induce two to three bowel movements daily. Treatment duration: 8 weeks.
Outcomes	Number connection test. Two performance subtests of Wechsler adult intelligence scale. Number of patients with subclinical hepatic encephalopathy.
Notes	Number of patients with missing data: from the full paper article it appears that data regarding three patients were missing at 8 weeks follow-up. However, comparing the numbers reported in the full paper article with the abstract presented at the AASLD meeting in 1996, the full paper article have excluded 16 of the original randomised patients. Although the mean number of abnormal test result was not significantly different between the lactulose and control group, the authors reported that the prevalence of SHE diminished. SHE was defined if all of the three psychometric tests used were abnormal.
Allocation concealment	A – Adequate

EEG: Electroencephalogram
PSE Index: Portal systemic encephalopathy index (includes five parameters: mental state, number connection test, asterixis, EEG, and arterial ammonia concentration).
In the column 'Interventions', we classify the experimental and control interventions according to the individual trials.

Characteristics of excluded studies

Anokhina 2001	Observational study of 15 patients with hepatic encephalopathy given lactulose.
Anonymous 1971	Short article summarising the results of the trial performed by Simmons 1970.

Characteristics of excluded studies (*Continued*)

Anonymous 1976	Summary of two trials on lactulose for hepatic encephalopathy (Bircher 1971 and Conn 1974).
Anonymous 1981	Narrative review.
Barreto-Zuniga 2001	Randomised trial comparing a probiotic preparation versus lactulose on plasma endotoxin-inactivating capacity and blood chemistry in patients with liver cirrhosis. The patients did not have hepatic encephalopathy at entry and this was not assessed as an outcome.
Berenguer 1971	A quasi-randomised study (allocation by day of inclusion) comparing lactulose versus neomycin or paromomycin in 29 patients with portosystemic encephalopathy .
Bircher 1966	A controlled study of two patients observed during several periods of different treatment regimens (neomycin, lactulose, sorbitol).
Bircher 1970	A report of a symposium on unpublished and published experiences with lactulose.
Bircher 1971	A controlled study of six patients observed through different treatment periods (lactulose, neomycin, magnesium sulfate, or sorbitol). The results in two of the patients were published in the first report by Bircher (Bircher 1966).
Bircher 1982	Case report of lactitol for one patient with hepatic encephalopathy.
Blanc 1994	Randomised trial comparing lactulose + neomycin with placebo in 80 patients with cirrhosis and acute hepatic encephalopathy. According to our inclusion criteria, trials were only included if collateral interventions were given to both intervention and control group.
Bresci 1993	Randomised trial comparing zinc plus lactulose plus protein restriction with lactulose plus protein in patients with chronic hepatic encephalopathy.
Brown 1971	A report of five cases from a randomised double blind trial comparing lactulose with sorbitol. The authors report that 20 patients were studied (randomised?), but do not report outcomes for the two intervention groups separately. The authors conclude that the five patients summarised in this report responded equally well to lactulose and sorbitol.
Chervak 1998	Controlled study comparing lactulose with no treatment in 112 patients with hepatic encephalopathy.
Chesta 1994	Randomised trial comparing neomycin versus placebo on intestinal digestion, absorption, and fermentation of carbohydrates in patients with liver cirrhosis. Included patients did not have hepatic encephalopathy.
Conn 1981	Editorial.
Cook 1970	Observational study.
Córdoba 1996	The article reports the results from a cross-sectional study and a quasi-randomised study assessing the effect of lactulose on five patients with subclinical hepatic encephalopathy.
Dmitriev 1995	A randomised trial comparing the effect of lactulose versus no treatment on premature infants with hyperammonaemia. The presence of hepatic encephalopathy was not reported as a baseline characteristic or assessed as an outcome.
Dubrisay 1968	An observational study comparing 72 patients with hepatic encephalopathy with 33 control subjects with other liver diseases.
Fiaccadori 1980	A three-arm randomised trial comparing branched-chain amino acids with lactulose and with branched-chain amino acids plus lactulose (see table 6).
Fung 1971	Case series evaluating the effect of lactulose on acute and chronic hepatic encephalopathy in 11 patients.
Garcia-Compean 1995	Review.
Gonzalez 1994	Randomised trial comparing sodium benzoate plus lactose enemas with lactose enemas plus placebo in 18 cirrhotic patients with acute hepatic encephalopathy.
Horsmans 1997	Randomised trial comparing lactulose with placebo in patients with liver cirrhosis. The patients had normal venous ammonia and normal EEG at entry and the presence of subclinical hepatic encephalopathy was not an inclusion criteria.
Imler 1971	A controlled study including seven patients comparing the effect of lactulose with antibiotics (six were given neomycin and one patient aurémycine) during several periods of different treatment regimens.

Characteristics of excluded studies (*Continued*)

Lanthier 1985	A controlled study including five patients with chronic hepatic encephalopathy comparing the effect of lactitol with lactulose during periods of different treatment regimens.
Loguercio 1987	Randomised trial comparing lactobacillus SF68 with lactulose in 40 patients with chronic hepatic encephalopathy (see table 6).
Loguercio 1995	Randomised trial comparing lactobacillus SF68 with lactulose in 40 patients with chronic hepatic encephalopathy (see table 6).
Ma 1969	Case series evaluating the effect of lactulose on chronic hepatic encephalopathy in 10 patients.
McClain 1984	Randomised trial comparing lactulose with placebo in patients with alcoholic cirrhosis. The presence of subclinical hepatic encephalopathy was not an inclusion criteria. Accordingly, the number of patients who might have had subclinical hepatic encephalopathy is uncertain.
Mendenhall 1986	Randomised cross-over trial including eight patients with chronic hepatic encephalopathy comparing sodium benzoate with sodium phenylacetate.
Merli 1992	A randomised metabolic trial evaluating the effect of lactulose and lactitol on fecal fat excretion in patients with cirrhosis. The patients did not have hepatic encephalopathy at entry.
Messner 1982	A randomised cross-over trial comprising 11 patients with chronic hepatic encephalopathy comparing lactulose with bromocriptine (see table 6).
Mutchnick 1974	A randomised trial comparing portacaval anastomosis with no operation on the occurrence of hepatic encephalopathy.
Patil 1987	A randomised cross-over trial of six healthy volunteers evaluating the effect of lactitol and lactulose on terminal ileal and colonic pH.
Piotraschke 1996	Observational study comparing lactulose with no treatment in 119 patients who had an increased risk of hepatic encephalopathy due to transjugular intrahepatic portosystemic shunt placement.
Quero 1997	Randomised trial comparing lactulose with placebo in patients with liver cirrhosis and elevated arterial ammonia concentration. Subclinical hepatic encephalopathy was not an inclusion criteria and the patients were not included on the basis of abnormal psychometric tests or EEG. Accordingly, the number of patients who might have had subclinical hepatic encephalopathy is uncertain.
Quinton 1982	Randomised trial comparing mannitol lavage with lactulose plus kanamycin in the prevention (48 episodes) and treatment (10 episodes) of post-haemorrhagic hepatic encephalopathy (48 episodes) (see table 6).
Reding 1984	Randomised trial comparing zinc plus lactulose with lactulose plus placebo.
Riggio 1990	Observational metabolic study comparing the effect of lactitol with lactulose on fecal flora in 21 cirrhotic patients without hepatic encephalopathy.
Riggio 1991	Randomised trial comparing zinc with placebo in 15 patients with chronic hepatic encephalopathy.
Riggio 2001	A three-arm randomised trial comparing rifaximin versus lactitol versus no treatment for the prevention of hepatic encephalopathy in 33 patients with post transjugular intrahepatic portosystemic shunt placement.
Rorsman 1970	Case series evaluating the effect of lactulose on hepatic encephalopathy in three patients.
Rossi-Fanelli 1982	Randomised trial comparing branched-chain amino acids with lactulose in 40 patients with acute hepatic encephalopathy (see table 6).
Sala Felis 1974	Observational study comparing lactulose with neomycin in 12 patients with hepatic encephalopathy.
Salerno 1994	Randomised trial comparing two different doses of lactitol in patients with subclinical hepatic encephalopathy.
Sherlock 1954	Case series evaluating neurological complications in 18 patients with liver disease.
Shibasaki 2001	Observational study comparing the efficacy of lactitol with lactulose in 31 patients with chronic hepatic encephalopathy.
Siebner 1970	Case series evaluating the effect of lactulose on hepatic encephalopathy in 12 patients.
Sushma 1992	Randomised trial comparing sodium benzoate with lactulose in 74 patients with acute hepatic encephalopathy (see table 6).

Characteristics of excluded studies (*Continued*)

Tarao 1990	Randomised cross-over trial comparing vancomycin with lactulose in patients with lactulose resistant chronic hepatic encephalopathy. However, before the patients were randomised they were given vancomycin for eight weeks. During this period, the encephalopathy resolved completely in 10 of the 12 included patients. Accordingly, the patients did not have hepatic encephalopathy at entry and the trial is therefore excluded.
Trey 1970	Observational metabolic study with 10 patients who had responded to lactulose therapy in a randomised trial (Brown 1971). No clinical outcomes were reported.
Tromm 2000	Randomised trial comparing mannite lavage with lactulose plus paromomycin in the prophylaxis of hepatic encephalopathy in patients with cirrhosis and upper gastrointestinal bleeding. Accordingly, the patients did not have hepatic encephalopathy at entry.
Trovato 1982	Randomised cross-over trial comparing amantadine versus levodopa-benserazide versus both drugs versus lactulose in 10 patients with chronic hepatic encephalopathy (see table 6).
Trovato 1995	This study was in its origin a randomised cross-over trial comprising ten patients and comparing lactitol versus no treatment. However, when the authors analysed the data, they found that in one of the groups there was no significant difference between the treatment effect seen in the placebo and lactitol group. They interpreted this as due to a possible carry-over phenomenon and then they skipped the comparison between the two randomised groups. Instead they combined the data of the two groups when receiving lactitol and compared these data with the baseline values (before entering the trial). Accordingly, the reported results do not come from a randomised study, but from a 'before-after' study.
Uribe 1980	Controlled cross-over study comparing lactose with neomycin plus magnesia in 10 patients with cirrhosis and chronic hepatic encephalopathy. The study is not described as randomised.
Uribe 1990	Randomised trial comparing bromocriptine with placebo in seven patients with chronic hepatic encephalopathy.
Uribe 1998	Randomised trial comparing AO-128 (a disaccharidase inhibitor) with placebo in 35 patients with chronic hepatic encephalopathy.
Vendemiale 1992	Randomised trial comparing lactulose with no treatment in 20 patients with cirrhosis. It is uncertain whether patients had subclinical hepatic encephalopathy at entry. The number connection test was unchanged in both groups after treatment.
Vogelsang 1986	Observational study evaluating the effect of lactulose and neomycin alone or in combination on bacterial hydrogen production in 16 patients with cirrhosis.
Weber 1979	Observational study evaluating the effect of lactulose on urea metabolism and nitrogen excretion in six cirrhotic patients.
Weber 1981	Editorial.
Zeegen 1970	Observational study comparing the effect of lactulose with magnesium in seven patients.

ADDITIONAL TABLES

Table 01. Search strategies

MEDLINE	EMBASE	CHBG-CTR	CENTRAL
#1 hepatic encephalopathy [Mesh] #2 liver cirrhosis [Mesh] #3 hepatic encephalopathy #4 cirrhosis #5 (#1 or #2 or #3 or #4)	#1 lactulose #2 lactitol #3 disaccharide #4 (#1 or #2 or #3) #5 encephalopathy #6 cirrhosis	lactulose or lactitol or disaccharide	#1 (lactulose or lactitol or disaccharide) #2 (encephalopathy or cirrhosis) #3 (#1 and #2)

Table 01. Search strategies (*Continued*)

MEDLINE	EMBASE	CHBG-CTR	CENTRAL
#6 lactulose [Mesh] #7 disaccharide [Mesh] #8 lactulose #9 lactitol #10 (#6 or #7 or #8 or #9) #11 trial #12 placebo* #13 blind* #14 random* #15 clinical #16 Clinical trials [Mesh] #17 (#11 or #12 or #13 or #14 or #15 or #16) #18 (#5 and #10 and #17)	#7 (#5 or #6) #8 trial #9 blind* #10 placebo #11 random* #12 explode "clinical-trial"/ all subheadings #13 (#8 or #9 or #10 or #11 or #12) #14 (#4 and #7 and #13)		

Table 02. Randomised trials on lactulose or lactitol versus placebo/no intervention

Study	Study design	Adequate quality	No. of patients	Type of HE	Experimental/control	Outcome measure	Lactulose (n/N)	Control (n/N)
		allocation sequence generation / allocation concealment / blinding					Number of patients with no improvement / number of patients	Number of patients with no improvement / number of patients
Elkington 1969	Cross-over	No / Yes / Yes	7	CHE	Lactulose / sorbitol	EEG, ammonia, stool pH	No data available. Interventions about equally effective	
Simmons 1970	Parallel	No / Yes / Yes	26	AHE + CHE	Lactulose / glucose	Clinical grading, ammonia, stool production	4/14	5/12
Rodgers 1973	Cross-over	Yes / Yes / Yes	3	CHE	Lactulose / sorbitol	Clinical grading, EEG, ammonia	No data available. Interventions about equally effective	
Germain 1973	Parallel	No / Yes / Yes	18	CHE	Lactulose / saccharose	Clinical grading, EEG, psy-	4/9	3/9

Table 02. Randomised trials on lactulose or lactitol versus placebo/no intervention (*Continued*)

Study	Study design	Adequate quality	No. of patients	Type of HE	Experimental/control	Outcome measure	Lactulose (n/N)	Control (n/N)
						chometric tests		
Corazza 1982	Parallel, 3-arm trial	No / No / Yes	52	CHE	Pyridoxine-alpha-ketoglutarate / lactulose / placebo	Encephalopathy intensity score, ammonia	No data available. Lactulose reported to be superior	
Uribe 1987a	Parallel	No / No / Yes	15	AHE	Lactitol enemas / tap water enemas	Mortality, clinical grading	0/10	4/5
Watanabe 1997	Parallel	No / Yes / No	36	SHE	Lactulose / no treatment	Three psychometric tests, ammonia	12/22	11/14
Shi 1997	Parallel	No / No / Yes	31	SHE	Lactitol / glucose	Two psychometric tests	No data available. Lactulose reported to be superior	
Li 1999	Parallel	No / No / No	86	SHE	Lactulose / no treatment	Two psychometric tests	22/48	27/38
Dhiman 2000	Parallel	No / No / No	26	SHE	Lactulose / no treatment	Six psychometric tests	6/14	12/12

Table 03. Randomised trials on lactulose or lactitol versus antibiotics

Study	Study design	Adequate quality	No. of patients	Type of HE	Experimental/control	Outcome measure	Lactulose (n/N)	Antibiotics (n/N)
		allocation sequence generation / allocation concealment / blinding					Number of patients with no improvement / number of patients	Number of patients with no improvement / number of patients
Conn 1977	Cross-over	No / Yes / Yes	33	CHE	Lactulose + placebo / neomycin + sorbitol	Clinical grading, PSE Index	3/18	2/15
Atterbury	Parallel	No / Yes /	47	AHE	Lactulose +	Clinical	4/23	4/24

Table 03. Randomised trials on lactulose or lactitol versus antibiotics (*Continued*)

Study	Study design	Adequate quality	No. of patients	Type of HE	Experimental/control	Outcome measure	Lactulose (n/N)	Antibiotics (n/N)
1978		Yes			placebo / neomycin + sorbitol	grading, PSE Index		
Orlandi 1981	Parallel	Yes / Yes / Yes	173	AHE + CHE	Lactulose / neomycin + magnesium sulfate	Mortality, clinical grading ammonia, adverse events	63/91	48/82
Bucci 1993	Parallel	No / No / Yes	58	?	Lactulose / rifaximin + sorbitol	Clinical grading, ammonia, EEG, psychometric tests	No data available. Interventions about equally effective	
Festi 1993	Parallel	No / No / No	21	CHE	Lactulose / rifaximin	EEG, asterixis, ammonia, adverse events	No data available. Interventions about equally effective	
Massa 1993	Parallel	No / Yes / Yes	40	CHE	Lactulose + placebo/ rifaximin + sorbitol	Clinical grading, ammonia, EEG, psychometric tests, adverse events	2/20	0/20
Blanc 1993	Parallel	No / No / Yes	60	AHE	Lactitol / vancomycin	Mortality, clinical grading, PSE Index, adverse events	9/29	10/31
Mas 2003	Parallel	Yes / Yes / Yes	103	AHE	Lactitol + placebo/ rifaximin + placebo	Clinical grading, PSE Index	12/53	10/50
Fera 1993	Parallel	No / No / Yes	40	?	Lactulose + placebo/ rifaximin + placebo	Clinical grading, score of PSE, EEG, ammonia	4/20	0/20

Table 03. Randomised trials on lactulose or lactitol versus antibiotics (*Continued*)

Study	Study design	Adequate quality	No. of patients	Type of HE	Experimental/control	Outcome measure	Lactulose (n/N)	Antibiotics (n/N)
Russo 1989	cross-over	Yes / No / No	15	CHE	Lactulose / rifaximin	Mean score of 15 parameters	1/8	2/7
Song 2000	Parallel	No / No / No	64	?	Lactulose / rifaximin	PSE index	7/25	8/39
Loguercio 2003	Parallel	No / No / Yes	27	CHE	Lactitol + placebo/ rifaximin + sorbitol	Clinical grading, asterixis, ammonia, adverse events	11/13	6/14

Table 04. Randomised trials on lactulose versus lactitol

Study	Study design	Adequate quality	No. of patients	Type of HE	Experimental/control	Outcome measure	Lactitol (n/N)	Lactulose (n/N)
		allocation sequence generation / allocation concealment / blinding					Number of patients with no improvement / number of patients	Number of patients with no improvement / number of patients
Morgan 1987a	Parallel	No / Yes / Yes	27	AHE	Lactitol / lactulose	Mortality, PSE Index	5/15	4/13
Morgan 1987b	Cross-over	No / Yes / Yes	9	CHE	Lactitol / lactulose	PSE Index, adverse events	No data available. Interventions about equally effective	
Heredia 1987	Parallel	Yes / Yes / No	40	AHE	Lactitol / lactulose	Mortality, clinical grading, PSE grade, adverse events	3/20	4/20
Heredia 1988	Cross-over	Yes / Yes / No	25	CHE	Lactitol / lactulose	PSE Index, adverse events	No data available. Interventions about equally effective	
Riggio 1989	Parallel	No / No /	31	CHE +	Lactitol /	PSE	8/16	9/15

Table 04. Randomised trials on lactulose versus lactitol (*Continued*)

Study	Study design	Adequate quality	No. of patients	Type of HE	Experimental/control	Outcome measure	Lactitol (n/N)	Lactulose (n/N)
		No		SHE	lactulose	Index, new episodes of HE, adverse events		
Morgan 1989	Cross-over	No / Yes / No	20	SHE	Lactitol / lactulose	Psychometric tests, EEG	No data available. Interventions about equally effective	
Grandi 1991	Cross-over	No / No / No	40	CHE	Lactitol / lactulose	PSE Index, adverse events	No data available. Interventions about equally effective	
Pai 1995	Parallel	Yes / No / No	45	AHE	Lactitol / lactulose	PSE Index, adverse events	4/23	4/22

Table 05. Randomised trials on lactose

Study	Study design	Adequate quality	No. of patients	Type of HE	Lactose/ control	Outcome measure	Lactose (n/N)	Control (n/N)
		allocation sequence generation / allocation concealment / blinding					Number of patients with no improvement / number of patients	Number of patients with no improvement / number of patients
Uribe 1981	Parallel	No / No / Yes	18	AHE	Lactose enemas / neomycin	Clinical grading, PSE Index	1/8	3/10
Uribe 1987a	Parallel	No / No / Yes	10	AHE	Lactose enemas / tapwater enemas	Clinical grading, PSE Index	2/5	4/5
Uribe 1987a	Parallel	No / No / Yes	40	AHE	Lactose enemas / lactitol enemas	Clinical grading, PSE Index	4/18	3/22
Uribe 1987b	Cross-over	No / No / Yes	20	CHE	Lactose / lactitol	Clinical grading,	9/10	10/10

Table 05. Randomised trials on lactose (*Continued*)

Study	Study design	Adequate quality	No. of patients	Type of HE	Lactose/ control	Outcome measure	Lactose (n/N)	Control (n/N)
						PSE Index		

Table 06. Randomised trials on other treatments versus lactulose for HE

Study	Study design	Adequate quality	No. of patients	Type of HE	Experimental/control	Outcome measure	Experimental (n/N)	Disaccharides (n/N)
		allocation sequence generation / allocation concealment / blinding					Number of patients with no improvement / number of patients	Number of patients with no improvement / number of patients
Uribe 1988 (abstract)	Parallel	No / No / Yes	10	CHE	Sodium benzoate / lactulose	PSE parameters, adverse events	No data available. Interventions about equally effective	
Trovato 1982	Cross-over	Uncertain Rct?	10	CHE	Amantadine/ leveodopa-benserazide / both drugs / lactulose	PSE Index, ammonia	Experimental therapies (amantadine and/or levodopa-benserazide) were significantly better than lactulose	
Quinton 1982 (abstract)	Parallel	No / No / No	10	AHE	Mannitol lavage / lactulose + kanamycin	Mortality, clinical grading	0/6	2/4
Uribe 1990 (abstract)	Parallel	No / No / Yes	35	CHE	Sodium benzoate / lactulose/ lactitol	PSE parameters, adverse events	6/18	8/17
Messner 1982 (abstract)	Cross-over†	No / No / Yes	11	CHE	Bromocriptine + sorbitol placebo / lactulose + placebo	Clinical grading, EEG, asterixis	9/11	4/11
Sushma	Parallel	No / Yes /	74	AHE	Sodium	Mortality,	9/38	7/36

Table 06. Randomised trials on other treatments versus lactulose for HE (*Continued*)

Study	Study design	Adequate quality	No. of patients	Type of HE	Experimental/control	Outcome measure	Experimental (n/N)	Disaccharides (n/N)
1992		Yes			benzoate / lactulose	PSE parameters		
Loguercio 1987	Parallel	No / No / No	40	CHE	Lactobacillus SF68 / lactulose	PSE parameters, adverse events	3/20	5/20
Loguercio 1995	Parallel	Yes / No / No	40	CHE	Lactobacillus SF68 / lactulose	PSE parameters, adverse events	7/21	7/19
Rossi-Fanelli 1982	Parallel	Yes / No / No	40	AHE	BCAA / lactulose	Clinical grading	8/20	12/20
Fiaccadori 1980	Parallel	No / No / No	23	AHE + CHE	BCAA/BCAA + lactulose / lactulose	Clinical grading	1/16	6/16

ANALYSES

Comparison 01. Lactulose or lactitol versus placebo or no intervention

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Number of patients without improvement of hepatic encephalopathy	6	207	Relative Risk (Random) 95% CI	0.62 [0.46, 0.84]
02 All-cause mortality	4	85	Relative Risk (Random) 95% CI	0.41 [0.02, 8.68]
03 Number connection test (seconds)	1	36	Weighted Mean Difference (Random) 95% CI	-9.00 [-20.10, 2.10]
04 Ammonia (µg/dl)	4	85	Weighted Mean Difference (Random) 95% CI	-13.89 [-28.02, 0.25]

Comparison 02. Sensitivity analyses - lactulose or lactitol versus placebo or no intervention

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Methodological quality - number of patients without improvement of hepatic encephalopathy	6	207	Relative Risk (Random) 95% CI	0.62 [0.46, 0.84]
02 Form of hepatic encephalopathy - number of patients without improvement of hepatic encephalopathy	6	207	Relative Risk (Random) 95% CI	0.62 [0.46, 0.84]

Comparison 03. Lactulose or lactitol versus antibiotics

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Number of patients without improvement of hepatic encephalopathy	10	600	Relative Risk (Random) 95% CI	1.24 [1.02, 1.50]
02 All-cause mortality	5	403	Relative Risk (Random) 95% CI	0.90 [0.48, 1.67]
03 Adverse events	8	527	Relative Risk (Random) 95% CI	1.62 [0.57, 4.58]
04 Number connection test (seconds)	6	370	Weighted Mean Difference (Random) 95% CI	6.35 [1.40, 11.30]
05 Ammonia (µg/dl)	8	407	Weighted Mean Difference (Random) 95% CI	4.00 [0.10, 7.90]

Comparison 04. Sensitivity analyses - lactulose or lactitol versus antibiotics

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Methodological quality - number of patients without improvement of hepatic encephalopathy	10	600	Relative Risk (Random) 95% CI	1.24 [1.02, 1.50]
02 Form of hepatic encephalopathy - number of patients without improvement of hepatic encephalopathy	10	600	Relative Risk (Random) 95% CI	1.24 [1.02, 1.50]

Comparison 05. Lactulose versus lactitol

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Number of patients without improvement of hepatic encephalopathy	4	144	Relative Risk (Random) 95% CI	1.13 [0.71, 1.82]
02 All-cause mortality	2	68	Relative Risk (Random) 95% CI	1.33 [0.34, 5.21]
03 Adverse events	7	282	Relative Risk (Random) 95% CI	1.24 [0.85, 1.80]
04 Number connection test (seconds)	5	145	Weighted Mean Difference (Random) 95% CI	-0.47 [-10.52, 9.57]
05 Ammonia (µg/dl)	6	187	Weighted Mean Difference (Random) 95% CI	0.72 [-9.76, 11.20]
06 PSE Index after treament	5	149	Weighted Mean Difference (Random) 95% CI	0.00 [-0.04, 0.04]

Comparison 06. Sensitivity analyses - lactulose versus lactitol

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Methodological quality - number of patients without improvement of hepatic encephalopathy			Relative Risk (Random) 95% CI	Subtotals only

02 Form of hepatic encephalopathy - number of patients without improvement of hepatic encephalopathy	4	144	Relative Risk (Random) 95% CI	1.13 [0.71, 1.82]

Comparison 07. Additional analyses of lactose versus tapwater, neomycin, or lactitol

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Number of patients without improvement of hepatic encephalopathy			Relative Risk (Random) 95% CI	Subtotals only
02 Adverse events	1	36	Relative Risk (Random) 95% CI	0.86 [0.36, 2.05]

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Bacterial Agents [*therapeutic use]; Hepatic Encephalopathy [*drug therapy]; Lactulose [*therapeutic use]; Neomycin [therapeutic use]; Randomized Controlled Trials; Sugar Alcohols [*therapeutic use]

MeSH check words

Humans

COVER SHEET

Title Nonabsorbable disaccharides for hepatic encephalopathy

Authors Als-Nielsen B, Gluud LL, Gluud C

Contribution of author(s) Bodil Als-Nielsen redrafted the protocol, identified trials, extracted data, performed the statistical analyses, and drafted the review. Lise Lotte Gluud extracted data and Christian Gluud validated the decisions on which trials to include. All reviewers contributed to the writing of the protocol and review and all have approved of the final version.

Issue protocol first published 2001/2

Review first published 2004/2

Date of most recent amendment 26 May 2004

Date of most recent SUBSTANTIVE amendment 11 February 2004

What's New Changes to the original protocol:
In 'Types of interventions' we specified the comparisons to be 1) lactulose or lactitol versus no intervention or placebo, 2) lactulose or lactitol versus antibiotics, and 3) lactulose versus lactitol. Further, for the sake of completeness we also included 4) lactose versus placebo, no intervention, antibiotics, or nonabsorbable disaccharides.
In 'Types of outcome measures' we changed our primary outcome measure from a favourable (improvement of hepatic encephalopathy) to an unfavourable outcome (no improvement of hepatic encephalopathy). We did this to comply with the convention within The Cochrane Collaboration and to be consistent with the other outcomes (mortality, adverse events). Further, we had included too many secondary outcomes that actually were part of our primary outcome (risk of no improvement of hepatic encephalopathy). Accordingly, we have excluded the following secondary outcomes: 'Number of patients with recovery from hepatic encephalopathy', 'Number of patients with worsening of hepatic encephalopathy', and

	'Number of patients with new acute episodes of hepatic encephalopathy during treatment and follow-up'. Our primary outcomes have not been changed. In the comparison: 'Lactulose versus lactitol' we included the 'PSE Index', because this outcome was reported by the majority of trials. Due to lack of data we did not perform the following planned subgroup analyses: stage of hepatic encephalopathy at entry, daily protein intake (low versus high), study design (cross-over versus parallel trials), cross-over trials (data from the first period alone versus data from both treatment periods). We performed our analyses based on a random effects model due to anticipated variability between trials regarding patient populations, interventions, and concomitant regimens. To assess the robustness of the results, analyses were also performed using a fixed effect model.
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	01 March 2003
Date authors' conclusions section amended	Information not supplied by author
Contact address	Dr Bodil Als-Nielsen Cochrane Hepato-Biliary Group Copenhagen Trial Unit, Centre for Clinical Intervention Research H:S Rigshospitalet, Dep. 7102 Blegdamsvej 9 Copenhagen DK-2100 DENMARK E-mail: bodil.als@dadlnet.dk Tel: +45 3545 7169 Fax: +45 3545 7101
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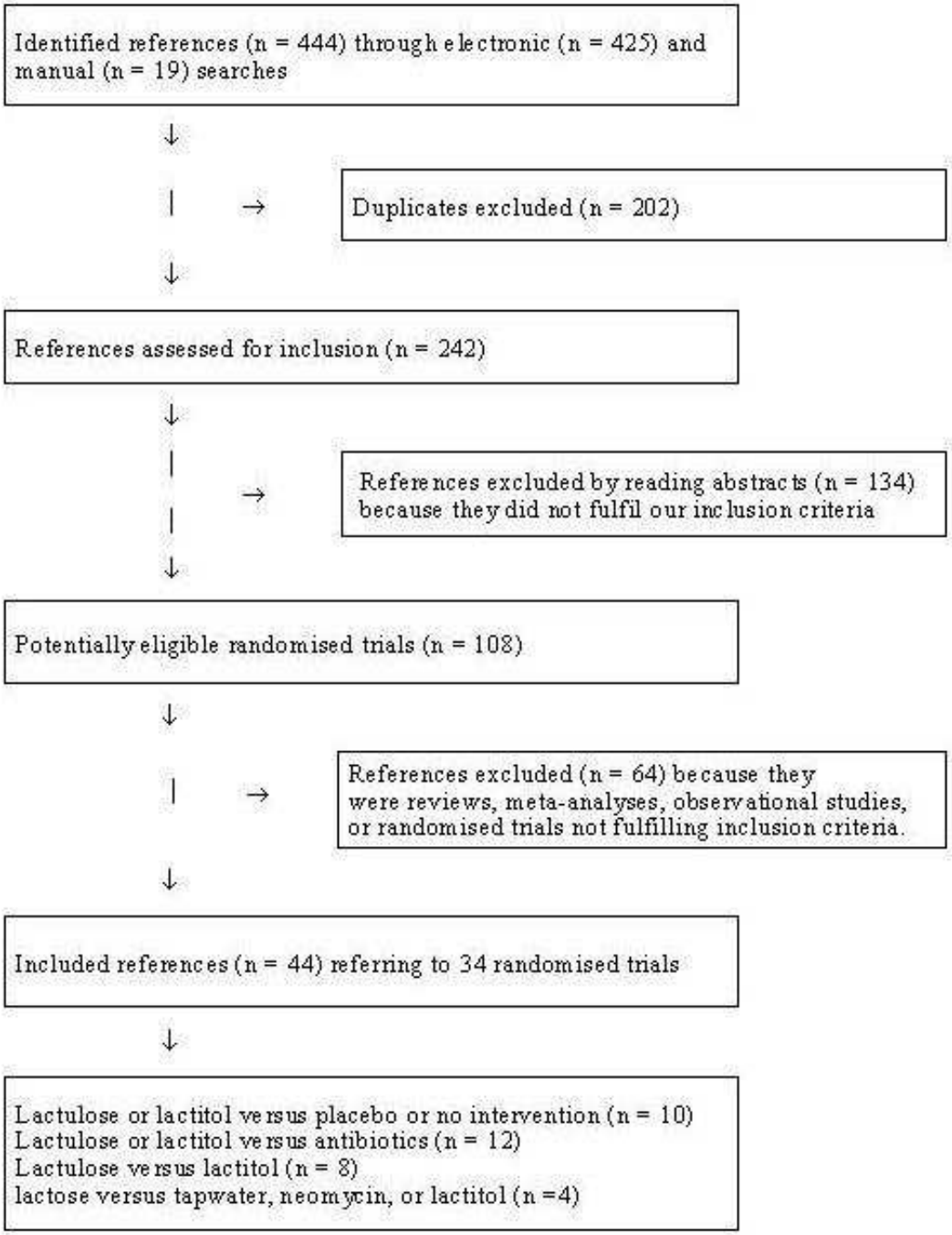
GRAPHS AND OTHER TABLES

Figure 01.



Analysis 01.01. Comparison 01 Lactulose or lactitol versus placebo or no intervention, Outcome 01 Number of patients without improvement of hepatic encephalopathy

Review: Nonabsorbable disaccharides for hepatic encephalopathy

Comparison: 01 Lactulose or lactitol versus placebo or no intervention

Outcome: 01 Number of patients without improvement of hepatic encephalopathy

Study	Lactulose/lactitol n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Dhiman 2000 - SHE	6/14	12/12		19.4	0.43 [0.23, 0.78]
Germain 1973 - CHE	4/9	3/9		6.2	1.33 [0.41, 4.33]
Li 1999 - SHE	22/48	27/38		37.8	0.65 [0.45, 0.93]
Simmons 1970 - AHE	4/14	5/12		7.4	0.69 [0.24, 1.99]
Uribe 1987a - AHE	0/10	4/5		1.2	0.06 [0.00, 0.95]
Watanabe 1997 - SHE	12/22	11/14		28.0	0.69 [0.43, 1.11]
Total (95% CI)	117	90		100.0	0.62 [0.46, 0.84]

Total events: 48 (Lactulose/lactitol), 62 (Control)

Test for heterogeneity chi-square=6.22 df=5 p=0.29 I?? =19.6%

Test for overall effect z=3.08 p=0.002

Analysis 01.02. Comparison 01 Lactulose or lactitol versus placebo or no intervention, Outcome 02 All-cause mortality

Review: Nonabsorbable disaccharides for hepatic encephalopathy

Comparison: 01 Lactulose or lactitol versus placebo or no intervention

Outcome: 02 All-cause mortality

Study	Lactulose/lactitol n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Dhiman 2000 - SHE	2/14	1/12		53.5	1.71 [0.18, 16.65]
× Germain 1973 - CHE	0/9	0/9		0.0	Not estimable
× Simmons 1970 - AHE	0/14	0/12		0.0	Not estimable
Uribe 1987a - AHE	0/10	3/5		46.5	0.08 [0.00, 1.27]
Total (95% CI)	47	38		100.0	0.41 [0.02, 8.68]

Total events: 2 (Lactulose/lactitol), 4 (Control)

Test for heterogeneity chi-square=2.90 df=1 p=0.09 I?? =65.6%

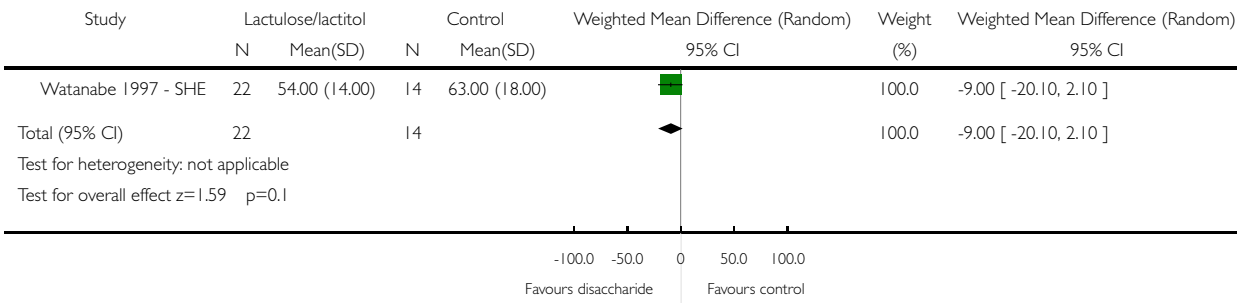
Test for overall effect z=0.58 p=0.6

Analysis 01.03. Comparison 01 Lactulose or lactitol versus placebo or no intervention, Outcome 03 Number connection test (seconds)

Review: Nonabsorbable disaccharides for hepatic encephalopathy

Comparison: 01 Lactulose or lactitol versus placebo or no intervention

Outcome: 03 Number connection test (seconds)

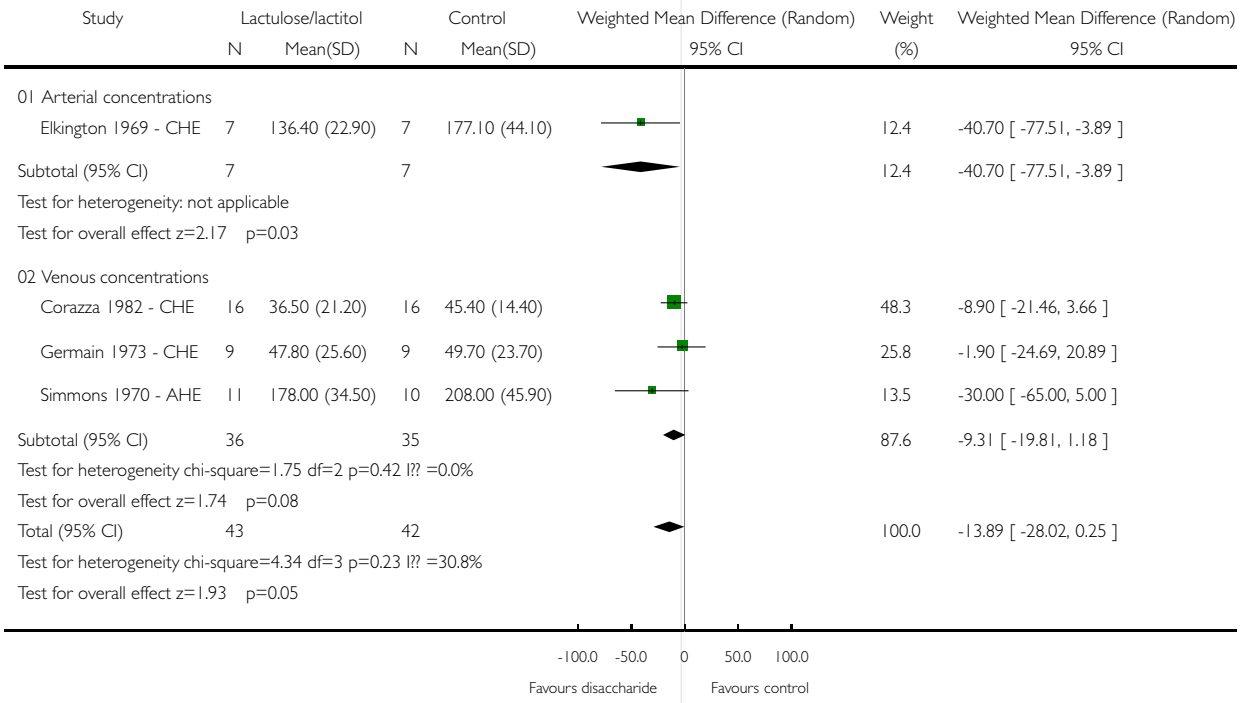


Analysis 01.04. Comparison 01 Lactulose or lactitol versus placebo or no intervention, Outcome 04 Ammonia (µg/dl)

Review: Nonabsorbable disaccharides for hepatic encephalopathy

Comparison: 01 Lactulose or lactitol versus placebo or no intervention

Outcome: 04 Ammonia (??g/dl)



Analysis 02.01. Comparison 02 Sensitivity analyses - lactulose or lactitol versus placebo or no intervention, Outcome 01 Methodological quality - number of patients without improvement of hepatic encephalopathy

Review: Nonabsorbable disaccharides for hepatic encephalopathy

Comparison: 02 Sensitivity analyses - lactulose or lactitol versus placebo or no intervention

Outcome: 01 Methodological quality - number of patients without improvement of hepatic encephalopathy

Study	Lactulose/lactitol n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 High quality					
Germain 1973 - CHE	4/9	3/9		6.2	1.33 [0.41, 4.33]
Simmons 1970 - AHE	4/14	5/12		7.4	0.69 [0.24, 1.99]
Subtotal (95% CI)	23	21		13.6	0.92 [0.42, 2.04]
Total events: 8 (Lactulose/lactitol), 8 (Control)					
Test for heterogeneity chi-square=0.67 df=1 p=0.41 I?? =0.0%					
Test for overall effect z=0.19 p=0.8					
02 Low quality					
Dhiman 2000 - SHE	6/14	12/12		19.4	0.43 [0.23, 0.78]
Li 1999 - SHE	22/48	27/38		37.8	0.65 [0.45, 0.93]
Watanabe 1997 - SHE	12/22	11/14		28.0	0.69 [0.43, 1.11]
Uribe 1987a - AHE	0/10	4/5		1.2	0.06 [0.00, 0.95]
Subtotal (95% CI)	94	69		86.4	0.57 [0.40, 0.83]
Total events: 40 (Lactulose/lactitol), 54 (Control)					
Test for heterogeneity chi-square=4.69 df=3 p=0.20 I?? =36.1%					
Test for overall effect z=2.98 p=0.003					
Total (95% CI)	117	90		100.0	0.62 [0.46, 0.84]
Total events: 48 (Lactulose/lactitol), 62 (Control)					
Test for heterogeneity chi-square=6.22 df=5 p=0.29 I?? =19.6%					
Test for overall effect z=3.08 p=0.002					

Analysis 02.02. Comparison 02 Sensitivity analyses - lactulose or lactitol versus placebo or no intervention, Outcome 02 Form of hepatic encephalopathy - number of patients without improvement of hepatic encephalopathy

Review: Nonabsorbable disaccharides for hepatic encephalopathy

Comparison: 02 Sensitivity analyses - lactulose or lactitol versus placebo or no intervention

Outcome: 02 Form of hepatic encephalopathy - number of patients without improvement of hepatic encephalopathy

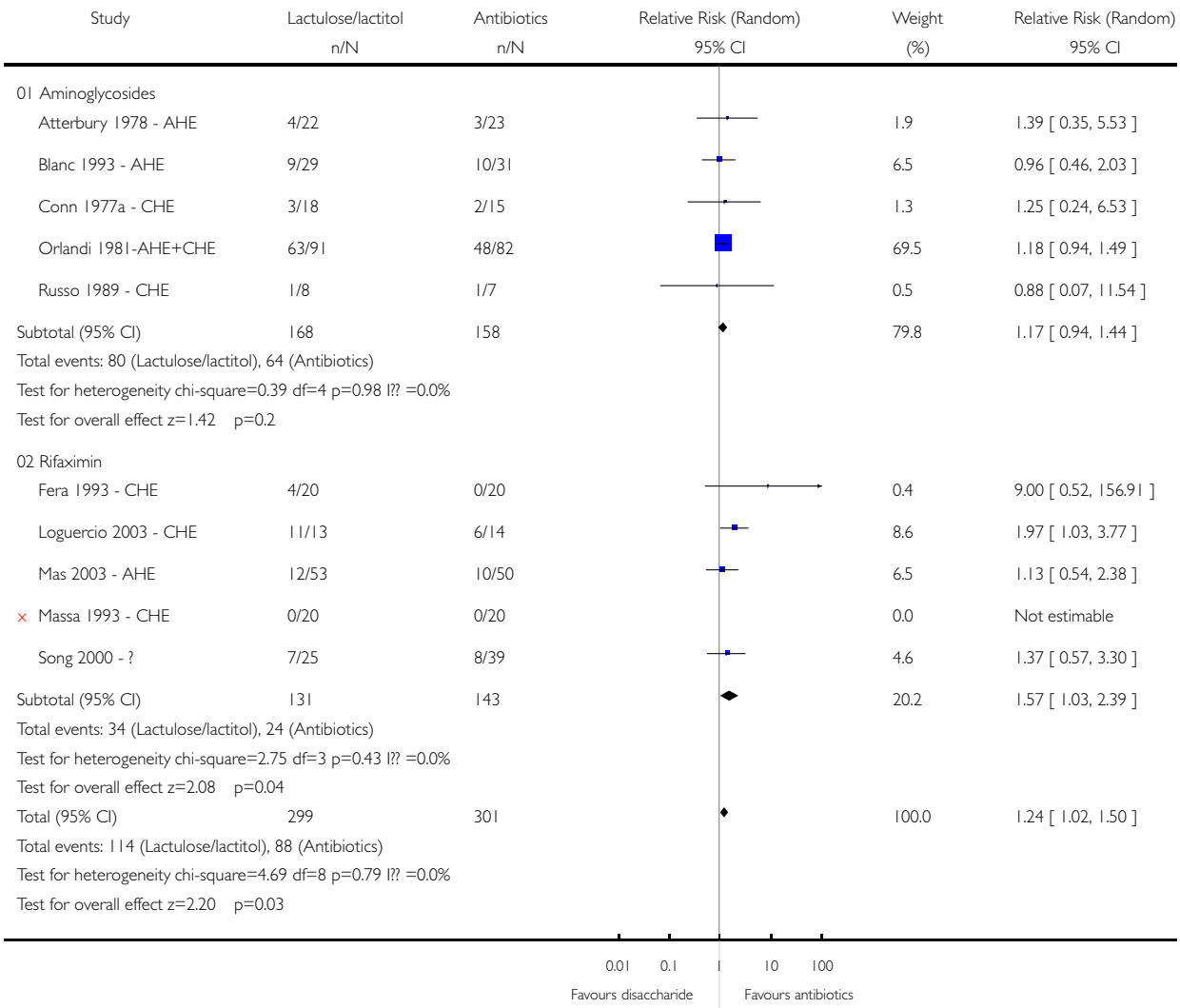
Study	Lactulose/lactitol n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 Acute hepatic encephalopathy					
Simmons 1970 - AHE	4/14	5/12		7.4	0.69 [0.24, 1.99]
Uribe 1987a - AHE	0/10	4/5		1.2	0.06 [0.00, 0.95]
Subtotal (95% CI)	24	17		8.6	0.27 [0.02, 3.28]
Total events: 4 (Lactulose/lactitol), 9 (Control)					
Test for heterogeneity chi-square=3.02 df=1 p=0.08 I?? =66.8%					
Test for overall effect z=1.02 p=0.3					
02 Chronic hepatic encephalopathy					
Germain 1973 - CHE	4/9	3/9		6.2	1.33 [0.41, 4.33]
Subtotal (95% CI)	9	9		6.2	1.33 [0.41, 4.33]
Total events: 4 (Lactulose/lactitol), 3 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.48 p=0.6					
03 Subclinical hepatic encephalopathy					
Dhiman 2000 - SHE	6/14	12/12		19.4	0.43 [0.23, 0.78]
Li 1999 - SHE	22/48	27/38		37.8	0.65 [0.45, 0.93]
Watanabe 1997 - SHE	12/22	11/14		28.0	0.69 [0.43, 1.11]
Subtotal (95% CI)	84	64		85.2	0.61 [0.47, 0.79]
Total events: 40 (Lactulose/lactitol), 50 (Control)					
Test for heterogeneity chi-square=1.69 df=2 p=0.43 I?? =0.0%					
Test for overall effect z=3.69 p=0.0002					
Total (95% CI)	117	90		100.0	0.62 [0.46, 0.84]
Total events: 48 (Lactulose/lactitol), 62 (Control)					
Test for heterogeneity chi-square=6.22 df=5 p=0.29 I?? =19.6%					
Test for overall effect z=3.08 p=0.002					

Analysis 03.01. Comparison 03 Lactulose or lactitol versus antibiotics, Outcome 01 Number of patients without improvement of hepatic encephalopathy

Review: Nonabsorbable disaccharides for hepatic encephalopathy

Comparison: 03 Lactulose or lactitol versus antibiotics

Outcome: 01 Number of patients without improvement of hepatic encephalopathy



Analysis 03.02. Comparison 03 Lactulose or lactitol versus antibiotics, Outcome 02 All-cause mortality

Review: Nonabsorbable disaccharides for hepatic encephalopathy

Comparison: 03 Lactulose or lactitol versus antibiotics

Outcome: 02 All-cause mortality

Study	Lactulose/lactitol n/N	Antibiotics n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 Aminoglycosides					
Blanc 1993 - AHE	4/29	4/31		23.1	1.07 [0.29, 3.88]
Orlandi 1981-AHE+CHE	11/91	12/82		66.1	0.83 [0.39, 1.77]
Subtotal (95% CI)	120	113		89.2	0.88 [0.46, 1.70]
Total events: 15 (Lactulose/lactitol), 16 (Antibiotics)					
Test for heterogeneity chi-square=0.11 df=1 p=0.74 I?? =0.0%					
Test for overall effect z=0.37 p=0.7					
02 Rifaximin					
Loguercio 2003 - CHE	0/13	1/14		4.0	0.36 [0.02, 8.06]
Mas 2003 - AHE	2/53	1/50		6.8	1.89 [0.18, 20.17]
× Massa 1993 - CHE	0/20	0/20		0.0	Not estimable
Subtotal (95% CI)	86	84		10.8	1.03 [0.16, 6.76]
Total events: 2 (Lactulose/lactitol), 2 (Antibiotics)					
Test for heterogeneity chi-square=0.70 df=1 p=0.40 I?? =0.0%					
Test for overall effect z=0.03 p=1					
Total (95% CI)	206	197		100.0	0.90 [0.48, 1.67]
Total events: 17 (Lactulose/lactitol), 18 (Antibiotics)					
Test for heterogeneity chi-square=0.83 df=3 p=0.84 I?? =0.0%					
Test for overall effect z=0.34 p=0.7					

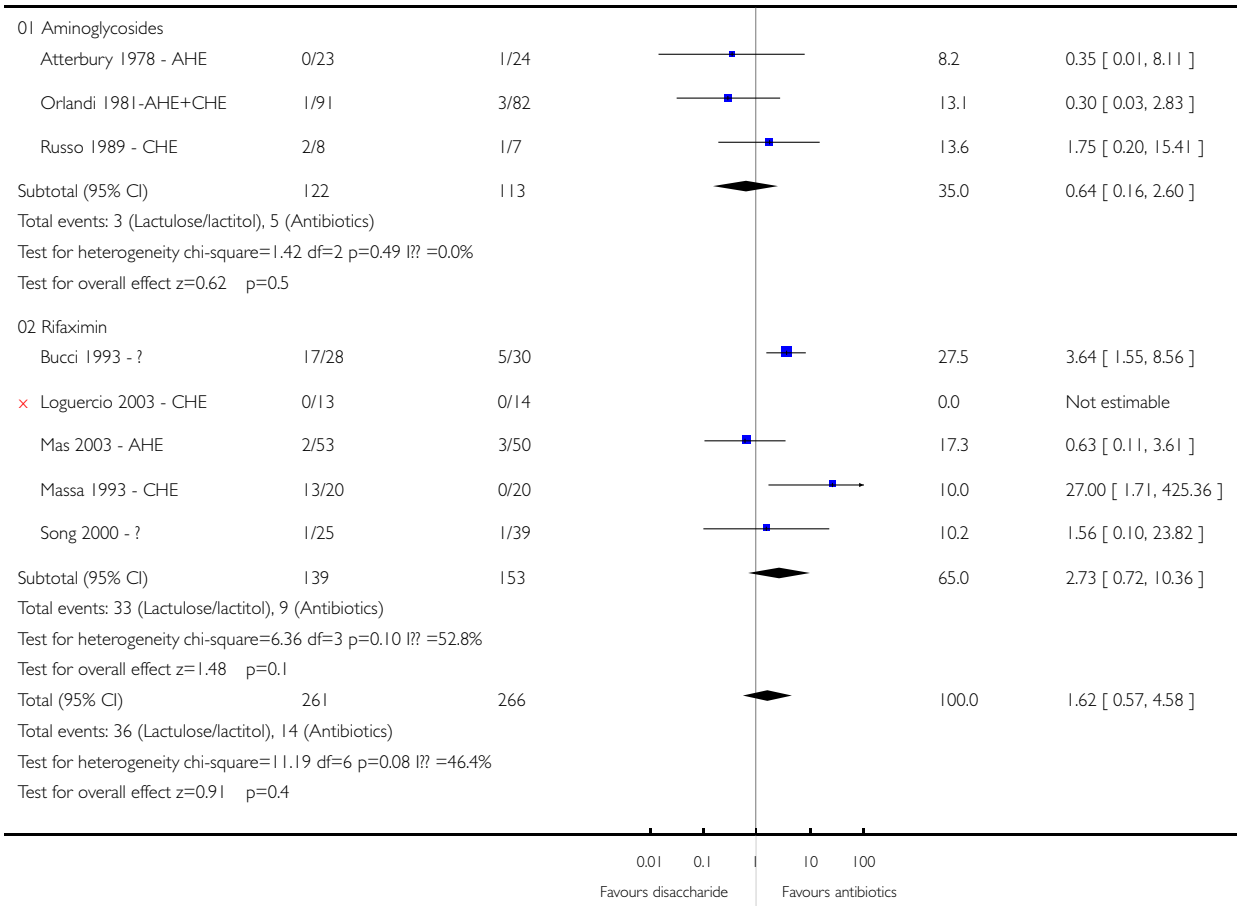
Analysis 03.03. Comparison 03 Lactulose or lactitol versus antibiotics, Outcome 03 Adverse events

Review: Nonabsorbable disaccharides for hepatic encephalopathy

Comparison: 03 Lactulose or lactitol versus antibiotics

Outcome: 03 Adverse events

Study	Lactulose/lactitol n/N	Antibiotics n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 Aminoglycosides					
Atterbury 1978 - AHE	0/23	1/24		8.2	0.35 [0.01, 8.11]
Orlandi 1981-AHE+CHE	1/91	3/82		13.1	0.30 [0.03, 2.83]
Russo 1989 - CHE	2/8	1/7		13.6	1.75 [0.20, 15.41]
Subtotal (95% CI)	122	113		35.0	0.64 [0.16, 2.60]
Total events: 3 (Lactulose/lactitol), 5 (Antibiotics)					
Test for heterogeneity chi-square=1.42 df=2 p=0.49 I?? =0.0%					
Test for overall effect z=0.62 p=0.5					
02 Rifaximin					
Bucci 1993 - ?	17/28	5/30		27.5	3.64 [1.55, 8.56]
× Loguercio 2003 - CHE	0/13	0/14		0.0	Not estimable
Mas 2003 - AHE	2/53	3/50		17.3	0.63 [0.11, 3.61]
Massa 1993 - CHE	13/20	0/20		10.0	27.00 [1.71, 425.36]
Song 2000 - ?	1/25	1/39		10.2	1.56 [0.10, 23.82]
Subtotal (95% CI)	139	153		65.0	2.73 [0.72, 10.36]
Total events: 33 (Lactulose/lactitol), 9 (Antibiotics)					
Test for heterogeneity chi-square=6.36 df=3 p=0.10 I?? =52.8%					
Test for overall effect z=1.48 p=0.1					
Total (95% CI)	261	266		100.0	1.62 [0.57, 4.58]
Total events: 36 (Lactulose/lactitol), 14 (Antibiotics)					
Test for heterogeneity chi-square=11.19 df=6 p=0.08 I?? =46.4%					
Test for overall effect z=0.91 p=0.4					

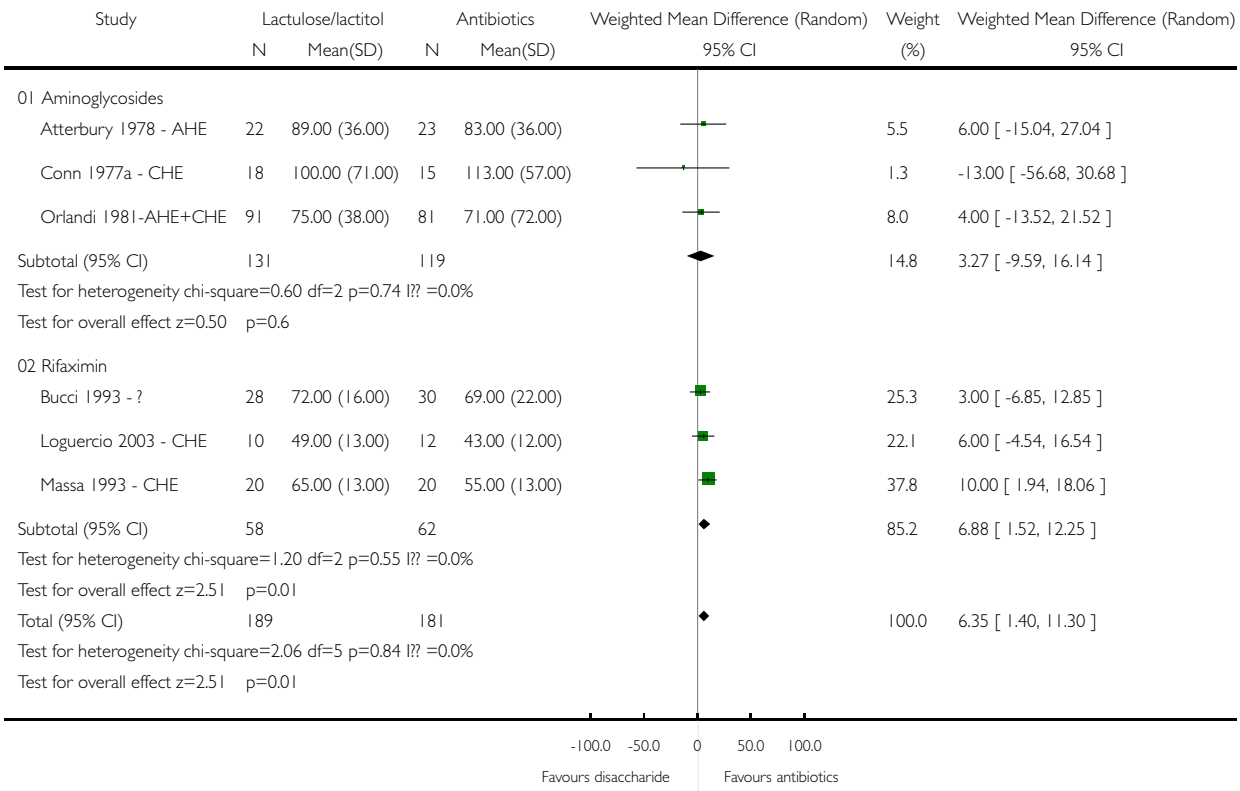


Analysis 03.04. Comparison 03 Lactulose or lactitol versus antibiotics, Outcome 04 Number connection test (seconds)

Review: Nonabsorbable disaccharides for hepatic encephalopathy

Comparison: 03 Lactulose or lactitol versus antibiotics

Outcome: 04 Number connection test (seconds)



Analysis 03.05. Comparison 03 Lactulose or lactitol versus antibiotics, Outcome 05 Ammonia (µg/dl)

Review: Nonabsorbable disaccharides for hepatic encephalopathy

Comparison: 03 Lactulose or lactitol versus antibiotics

Outcome: 05 Ammonia (??g/dl)

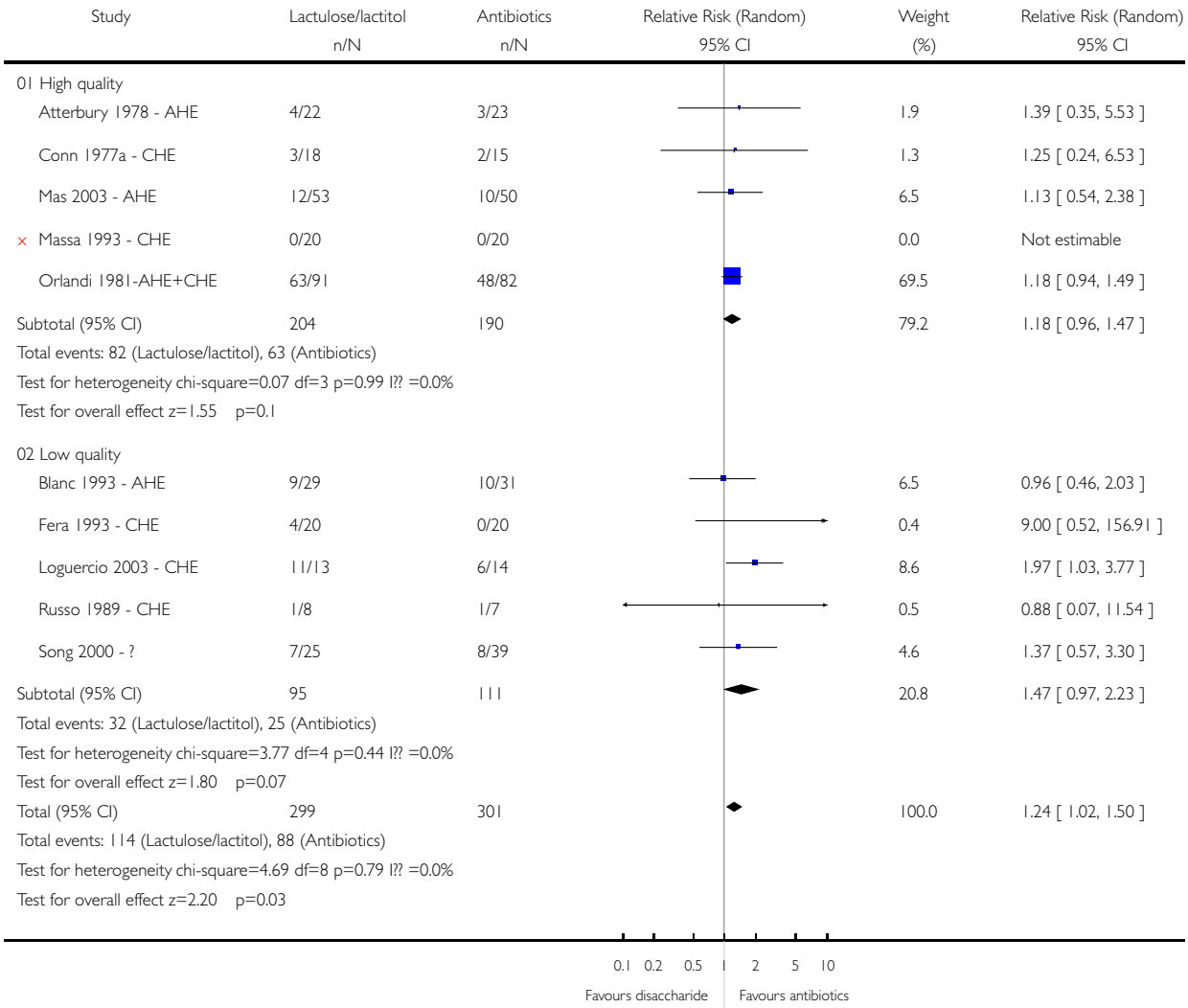
Study	Lactulose/lactitol N	Lactulose/lactitol Mean(SD)	Antibiotics N	Antibiotics Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
01 Aminoglycosides							
Atterbury 1978 - AHE	22	188.60 (54.00)	23	171.40 (40.00)		2.0	17.20 [-10.66, 45.06]
Conn 1977a - CHE	18	209.00 (25.00)	15	205.00 (58.00)		1.5	4.00 [-27.54, 35.54]
Festi 1993 - CHE	12	47.00 (6.00)	9	45.00 (7.00)		46.8	2.00 [-3.70, 7.70]
Orlandi 1981-AHE+CHE	91	79.00 (57.00)	82	86.00 (45.00)		6.5	-7.00 [-22.23, 8.23]
Russo 1989 - CHE	8	84.00 (41.00)	7	70.00 (38.00)		0.9	14.00 [-26.00, 54.00]
Subtotal (95% CI)	151		136			57.8	1.75 [-3.38, 6.87]
Test for heterogeneity chi-square=2.84 df=4 p=0.59 I?? =0.0%							
Test for overall effect z=0.67 p=0.5							
02 Rifaximin (venous concentration)							
Bucci 1993 - ?	28	79.30 (23.00)	30	74.30 (7.00)		19.3	5.00 [-3.88, 13.88]
Loguercio 2003 - CHE	10	109.00 (15.00)	12	105.00 (16.00)		9.0	4.00 [-8.98, 16.98]
Massa 1993 - CHE	20	74.00 (13.00)	20	62.00 (20.00)		13.9	12.00 [1.55, 22.45]
Subtotal (95% CI)	58		62			42.2	7.09 [1.09, 13.09]
Test for heterogeneity chi-square=1.28 df=2 p=0.53 I?? =0.0%							
Test for overall effect z=2.32 p=0.02							
Total (95% CI)	209		198			100.0	4.00 [0.10, 7.90]
Test for heterogeneity chi-square=5.88 df=7 p=0.55 I?? =0.0%							
Test for overall effect z=2.01 p=0.04							

Analysis 04.01. Comparison 04 Sensitivity analyses - lactulose or lactitol versus antibiotics, Outcome 01 Methodological quality - number of patients without improvement of hepatic encephalopathy

Review: Nonabsorbable disaccharides for hepatic encephalopathy

Comparison: 04 Sensitivity analyses - lactulose or lactitol versus antibiotics

Outcome: 01 Methodological quality - number of patients without improvement of hepatic encephalopathy

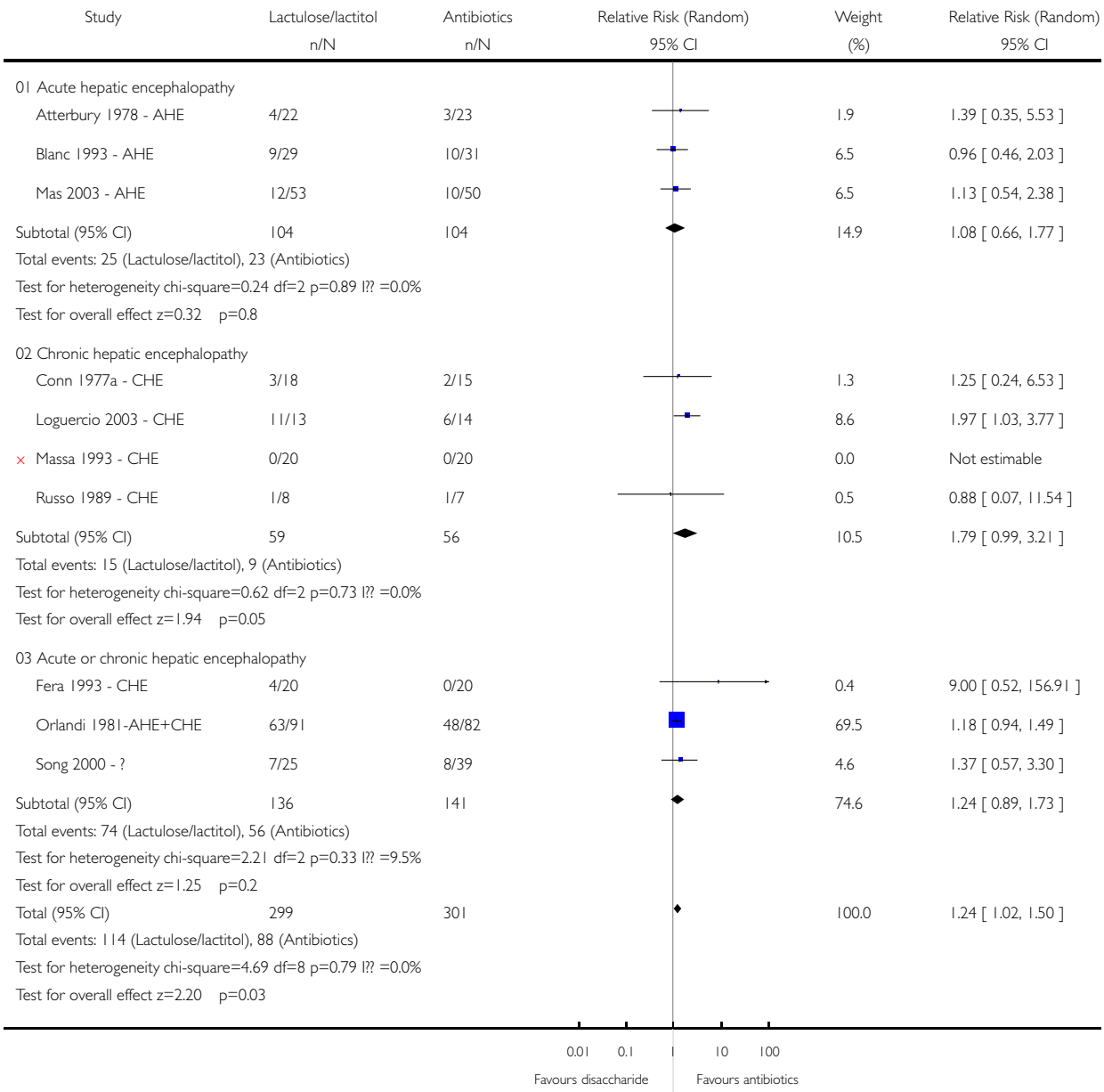


Analysis 04.02. Comparison 04 Sensitivity analyses - lactulose or lactitol versus antibiotics, Outcome 02 Form of hepatic encephalopathy - number of patients without improvement of hepatic encephalopathy

Review: Nonabsorbable disaccharides for hepatic encephalopathy

Comparison: 04 Sensitivity analyses - lactulose or lactitol versus antibiotics

Outcome: 02 Form of hepatic encephalopathy - number of patients without improvement of hepatic encephalopathy



Analysis 05.01. Comparison 05 Lactulose versus lactitol, Outcome 01 Number of patients without improvement of hepatic encephalopathy

Review: Nonabsorbable disaccharides for hepatic encephalopathy

Comparison: 05 Lactulose versus lactitol

Outcome: 01 Number of patients without improvement of hepatic encephalopathy

Study	Lactulose n/N	Lactitol n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Heredia 1987 - AHE	4/20	3/20		12.1	1.33 [0.34, 5.21]
Morgan 1987a - AHE	4/13	5/15		19.1	0.92 [0.31, 2.73]
Pai 1995 - AHE	4/22	4/23		14.2	1.05 [0.30, 3.67]
Riggio 1989-CHE+SHE	9/15	8/16		54.6	1.20 [0.63, 2.28]
Total (95% CI)	70	74		100.0	1.13 [0.71, 1.82]
Total events: 21 (Lactulose), 20 (Lactitol)					
Test for heterogeneity chi-square=0.24 df=3 p=0.97 I?? =0.0%					
Test for overall effect z=0.52 p=0.6					

Analysis 05.02. Comparison 05 Lactulose versus lactitol, Outcome 02 All-cause mortality

Review: Nonabsorbable disaccharides for hepatic encephalopathy

Comparison: 05 Lactulose versus lactitol

Outcome: 02 All-cause mortality

Study	Lactulose n/N	Lactitol n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Heredia 1987 - AHE	4/20	3/20		100.0	1.33 [0.34, 5.21]
× Morgan 1987a - AHE	0/13	0/15		0.0	Not estimable
Total (95% CI)	33	35		100.0	1.33 [0.34, 5.21]
Total events: 4 (Lactulose), 3 (Lactitol)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.41 p=0.7					

Analysis 05.03. Comparison 05 Lactulose versus lactitol, Outcome 03 Adverse events

Review: Nonabsorbable disaccharides for hepatic encephalopathy

Comparison: 05 Lactulose versus lactitol

Outcome: 03 Adverse events

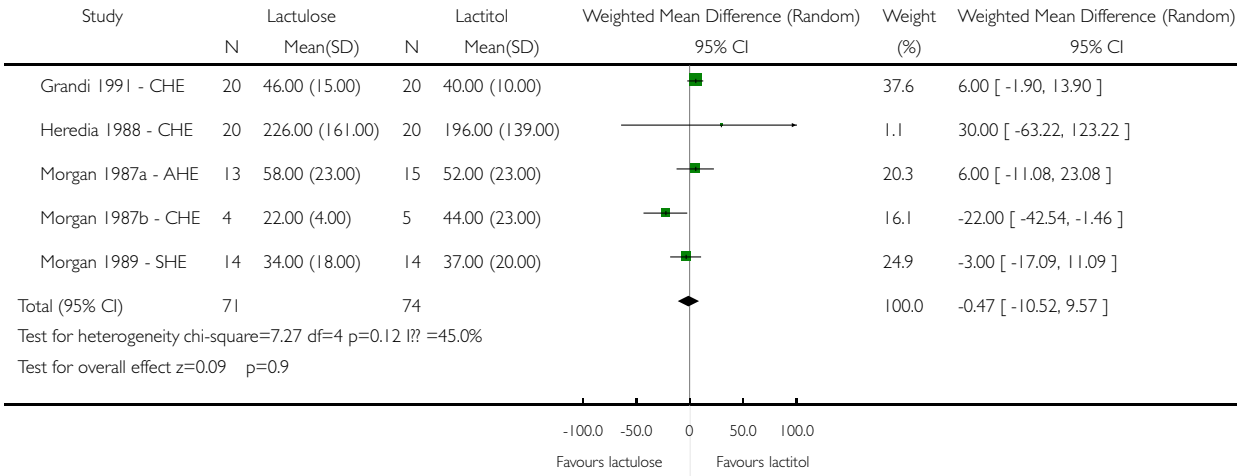
Study	Lactulose n/N	Lactitol n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 Parallel trials					
× Heredia 1987 - AHE	0/20	0/20		0.0	Not estimable
Pai 1995 - AHE	7/22	0/23		1.7	15.65 [0.95, 258.68]
Riggio 1989-CHE+SHE	7/15	3/16		8.2	2.49 [0.78, 7.90]
Subtotal (95% CI)	57	59		9.9	4.27 [0.70, 26.03]
Total events: 14 (Lactulose), 3 (Lactitol)					
Test for heterogeneity chi-square=1.72 df=1 p=0.19 I?? =41.7%					
Test for overall effect z=1.57 p=0.1					
02 Cross-over trials (summary results from both treatment periods)					
Grandi 1991 - CHE	5/40	9/40		10.2	0.56 [0.20, 1.51]
Heredia 1988 - CHE	18/20	12/20		27.6	1.50 [1.02, 2.21]
Morgan 1987b - CHE	9/9	8/9		34.1	1.13 [0.89, 1.42]
Morgan 1989 - SHE	8/14	8/14		18.1	1.00 [0.53, 1.90]
Subtotal (95% CI)	83	83		90.1	1.15 [0.87, 1.52]
Total events: 40 (Lactulose), 37 (Lactitol)					
Test for heterogeneity chi-square=4.63 df=3 p=0.20 I?? =35.2%					
Test for overall effect z=0.97 p=0.3					
Total (95% CI)	140	142		100.0	1.24 [0.85, 1.80]
Total events: 54 (Lactulose), 40 (Lactitol)					
Test for heterogeneity chi-square=10.73 df=5 p=0.06 I?? =53.4%					
Test for overall effect z=1.12 p=0.3					

Analysis 05.04. Comparison 05 Lactulose versus lactitol, Outcome 04 Number connection test (seconds)

Review: Nonabsorbable disaccharides for hepatic encephalopathy

Comparison: 05 Lactulose versus lactitol

Outcome: 04 Number connection test (seconds)

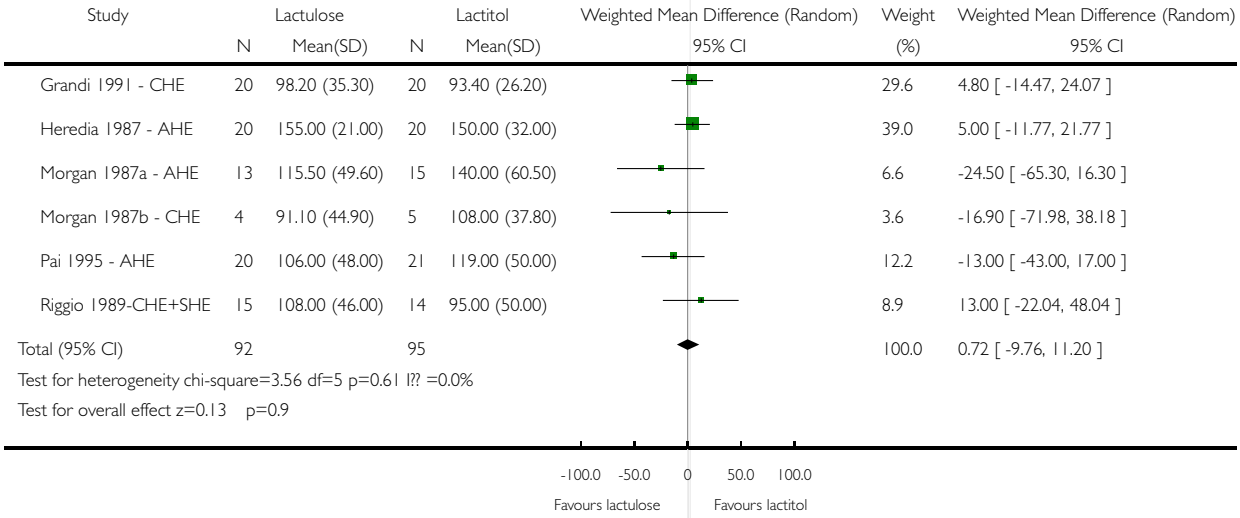


Analysis 05.05. Comparison 05 Lactulose versus lactitol, Outcome 05 Ammonia (µg/dl)

Review: Nonabsorbable disaccharides for hepatic encephalopathy

Comparison: 05 Lactulose versus lactitol

Outcome: 05 Ammonia (??g/dl)



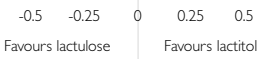
Analysis 05.06. Comparison 05 Lactulose versus lactitol, Outcome 06 PSE Index after treament

Review: Nonabsorbable disaccharides for hepatic encephalopathy

Comparison: 05 Lactulose versus lactitol

Outcome: 06 PSE Index after treament

Study	Lactulose N	Lactulose Mean(SD)	Lactitol N	Lactitol Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
01 Parallel trials							
Morgan 1987a - AHE	13	0.19 (0.09)	15	0.19 (0.14)		22.1	0.00 [-0.09, 0.09]
Morgan 1987b - CHE	4	0.07 (0.03)	5	0.17 (0.14)		10.3	-0.10 [-0.23, 0.03]
Pai 1995 - AHE	20	0.38 (0.12)	21	0.34 (0.16)		22.0	0.04 [-0.05, 0.13]
Riggio 1989-CHE+SHE	15	0.20 (0.12)	16	0.20 (0.10)		27.0	0.00 [-0.08, 0.08]
Subtotal (95% CI)	52		57			81.5	0.00 [-0.05, 0.04]
Test for heterogeneity chi-square=3.23 df=3 p=0.36 I?? =7.2%							
Test for overall effect z=0.10 p=0.9							
02 Cross-over trials							
Heredia 1988 - CHE	20	0.29 (0.19)	20	0.26 (0.10)		18.5	0.03 [-0.06, 0.12]
Subtotal (95% CI)	20		20			18.5	0.03 [-0.06, 0.12]
Test for heterogeneity: not applicable							
Test for overall effect z=0.62 p=0.5							
Total (95% CI)	72		77			100.0	0.00 [-0.04, 0.04]
Test for heterogeneity chi-square=3.59 df=4 p=0.46 I?? =0.0%							
Test for overall effect z=0.20 p=0.8							

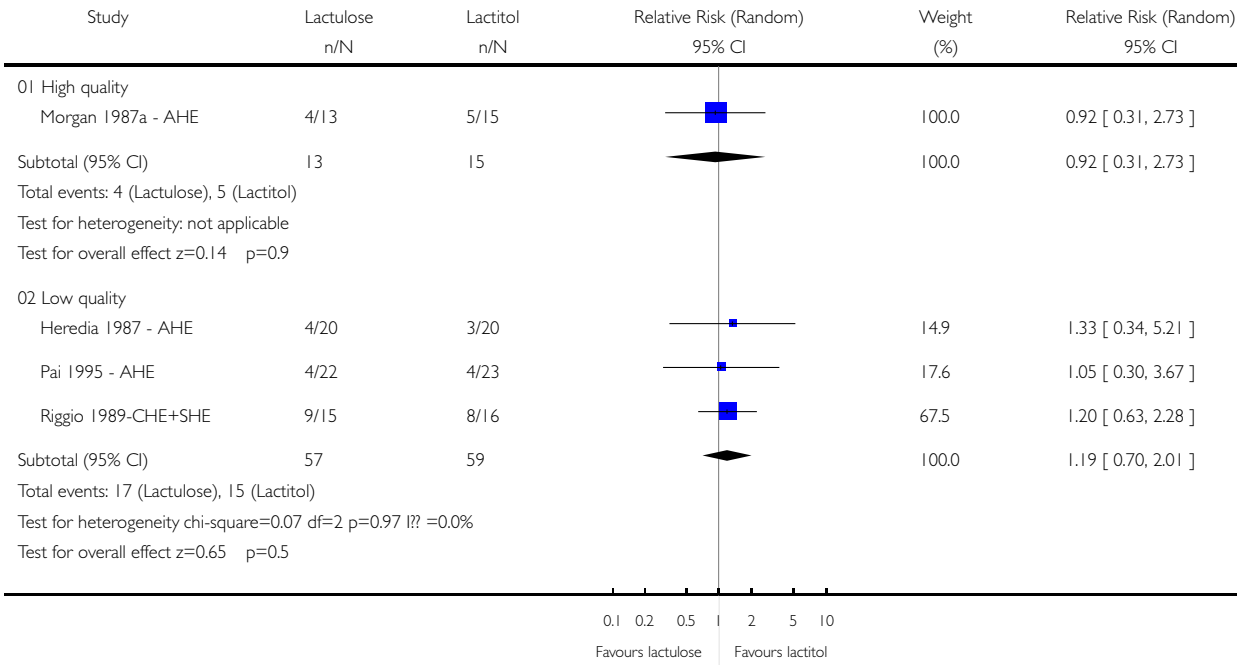


Analysis 06.01. Comparison 06 Sensitivity analyses - lactulose versus lactitol, Outcome 01 Methodological quality - number of patients without improvement of hepatic encephalopathy

Review: Nonabsorbable disaccharides for hepatic encephalopathy

Comparison: 06 Sensitivity analyses - lactulose versus lactitol

Outcome: 01 Methodological quality - number of patients without improvement of hepatic encephalopathy



Analysis 06.02. Comparison 06 Sensitivity analyses - lactulose versus lactitol, Outcome 02 Form of hepatic encephalopathy - number of patients without improvement of hepatic encephalopathy

Review: Nonabsorbable disaccharides for hepatic encephalopathy

Comparison: 06 Sensitivity analyses - lactulose versus lactitol

Outcome: 02 Form of hepatic encephalopathy - number of patients without improvement of hepatic encephalopathy

Study	Lactulose n/N	Lactitol n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 Acute hepatic encephalopathy					
Heredia 1987 - AHE	4/20	3/20		12.1	1.33 [0.34, 5.21]
Morgan 1987a - AHE	4/13	5/15		19.1	0.92 [0.31, 2.73]
Pai 1995 - AHE	4/22	4/23		14.2	1.05 [0.30, 3.67]
Subtotal (95% CI)	55	58		45.4	1.06 [0.52, 2.14]
Total events: 12 (Lactulose), 12 (Lactitol)					
Test for heterogeneity chi-square=0.17 df=2 p=0.92 I?? =0.0%					
Test for overall effect z=0.16 p=0.9					
02 Chronic hepatic encephalopathy					
Riggio 1989-CHE+SHE	9/15	8/16		54.6	1.20 [0.63, 2.28]
Subtotal (95% CI)	15	16		54.6	1.20 [0.63, 2.28]
Total events: 9 (Lactulose), 8 (Lactitol)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.56 p=0.6					
Total (95% CI)	70	74		100.0	1.13 [0.71, 1.82]
Total events: 21 (Lactulose), 20 (Lactitol)					
Test for heterogeneity chi-square=0.24 df=3 p=0.97 I?? =0.0%					
Test for overall effect z=0.52 p=0.6					

Analysis 07.01. Comparison 07 Additional analyses of lactose versus tapwater, neomycin, or lactitol, Outcome 01 Number of patients without improvement of hepatic encephalopathy

Review: Nonabsorbable disaccharides for hepatic encephalopathy

Comparison: 07 Additional analyses of lactose versus tapwater, neomycin, or lactitol

Outcome: 01 Number of patients without improvement of hepatic encephalopathy

Study	lactose n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 Lactose versus tapwater					
Uribe 1987a - AHE	2/5	4/5		100.0	0.50 [0.16, 1.59]
Subtotal (95% CI)	5	5		100.0	0.50 [0.16, 1.59]
Total events: 2 (lactose), 4 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.17 p=0.2					
02 Lactose versus neomycin					
Uribe 1981 - AHE	1/8	3/10		100.0	0.42 [0.05, 3.28]
Subtotal (95% CI)	8	10		100.0	0.42 [0.05, 3.28]
Total events: 1 (lactose), 3 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.83 p=0.4					
03 Lactose versus lactitol					
Uribe 1987a - AHE	5/18	3/22		41.9	2.04 [0.56, 7.39]
Uribe 1987b - CHE	9/10	10/10		58.1	0.90 [0.73, 1.11]
Subtotal (95% CI)	28	32		100.0	1.27 [0.27, 6.03]
Total events: 14 (lactose), 13 (Control)					
Test for heterogeneity chi-square=5.87 df=1 p=0.02 I?? =83.0%					
Test for overall effect z=0.30 p=0.8					

Analysis 07.02. Comparison 07 Additional analyses of lactose versus tapwater, neomycin, or lactitol, Outcome 02 Adverse events

Review: Nonabsorbable disaccharides for hepatic encephalopathy

Comparison: 07 Additional analyses of lactose versus tapwater, neomycin, or lactitol

Outcome: 02 Adverse events

Study	Lactose n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 Lactose versus lactitol					
Uribe 1987b - CHE	6/18	7/18		100.0	0.86 [0.36, 2.05]
Total (95% CI)	18	18		100.0	0.86 [0.36, 2.05]
Total events: 6 (Lactose), 7 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.35 p=0.7