H.11 Management of an episode of acute hepatic encephalopathy

Study	Abid 2011[3]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	N/A (n=120)
Countries and setting	Conducted in Pakistan; setting: secondary care
Line of therapy	First line
Duration of study	Intervention + follow up: Until discharge or death
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Cirrhosis diagnosed on the basis of clinical findings, ultrasonic and/or histologic basis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	(1) Diagnosis of cirrhosis. (2) Aged >18 years with hepatic encephalopathy grades 1 to 4. (3) Patients were grouped as minimal hepatic encephalopathy if NCT-A completion took >30 seconds and no other sign of encephalopathy. (4) Hyperammonaemia. (5) With/without a single reversible precipitating factor of hepatic encephalopathy (for example constipation, hypokalaemia, urinary tract infection, respiratory tract infection, spontaneous bacterial peritonitis, dehydration)
Exclusion criteria	Hepatocellular carcinoma; severe septicaemia with compromised haemodynamic status; active GI bleeding; hepatorenal syndrome; acute superimposed liver injury; advanced cardiac/pulmonary disease; end-stage renal failure; patients taking sedatives/anti-depressants/benzodiazepines; patients with chronic hepatic encephalopathy on metronidazole/lactulose prior to admission
Recruitment/selection of patients	Patients admitted to the hospital via outpatient clinic or emergency room were assessed at randomisation
Age, gender and ethnicity	Age - mean (SD): 57 (11). Gender (M:F): 62/58. Ethnicity: Not reported.
Further population details	1. Grade of acute hepatic encephalopathy: Not applicable/not stated/unclear. 2. Severity of the underlying liver disease: Child-Pugh B or C.
Indirectness of population	No indirectness
Interventions	(n=60) Intervention 1: l-Ornithine-l-aspartate (LOLA). IV administration of 20 g (4 ampoules of 10 ml each) mixed in 250 ml of 5% dextrose, daily over 4 hours for 3 consecutive days. Duration: 3 days. Concurrent medication/care: Lactulose + Metronidazole + Any necessary concomitant medications for the treatment of precipitating factor(s). (n=60) Intervention 2: Placebo. IV administration of 20 g (4 ampoules of 10 ml distilled water) mixed in 250 ml of 5% dextrose, appearance indistinguishable from LOLA, daily over 4 hours for 3 consecutive days. Duration: 3 days.

Study	Abid 2011[3]
	Concurrent medication/care: Lactulose + Metronidazole + Any necessary concomitant medications for the treatment of precipitating factor(s)
Funding	Study funded by industry (Unrestricted grant from Brookes Pharmaceutical Pakistan)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: L-ORNITHINE-L-ASPARTATE (LOLA) versus PLACEBO

Protocol outcome 1: Survival at end of study
- Actual outcome: Mortality (includes 12/120 patients with minimal hepatic encephalopathy, 6 in each arm) during inpatient stay; Group 1: 4/60, Group 2: 7/60; risk of bias: low; indirectness of outcome: serious indirectness

Protocol outcome 2: No improvement in hepatic encephalopathy (improvement defined as a partial or complete resolution of clinical symptoms of hepatic encephalopathy. Some studies may assess improvement using electrophysiological or psychometrical testing, PSE score, or blood plasma ammonia levels) at end of study
- Actual outcome: Complete improvement defined as improvement of 2 grades from baseline (West Haven Grade I-IV hepatic encephalopathy only, 12 patients with minimal hepatic encephalopathy not included in analysis) at 3 days; Group 1: 45/54, Group 2: 25/54; risk of bias: low; indirectness of outcome: no indirectness
- Actual outcome: Partial improvement defined as improvement of 1 grade from baseline (West Haven Grade I-IV hepatic encephalopathy only, 12 patients with minimal hepatic encephalopathy not included in analysis) at 3 days; Group 1: 4/54, Group 2: 19/54; risk of bias: low; indirectness of outcome: no indirectness
- Actual outcome: No improvement/deterioration in hepatic encephalopathy grade (West Haven Grade I-IV hepatic encephalopathy only, 12 patients with minimal hepatic encephalopathy not included in analysis) at 3 days; Group 1: 5/54, Group 2: 10/54; risk of bias: low; indirectness of outcome: no indirectness
- Actual outcome: SUBGROUP DATA (Grade I and II). Complete improvement defined as improvement of 2 grades from baseline (West Haven Grade I-IV hepatic encephalopathy only, 12 patients with minimal hepatic encephalopathy not included in analysis) at 3 days; Group 1: 25/29, Group 2: 10/27; risk of bias: low; indirectness of outcome: no indirectness
- Actual outcome: SUBGROUP DATA (Grade III and IV). Complete improvement defined as improvement of 2 grades from baseline (West Haven Grade I-IV hepatic encephalopathy only, 12 patients with minimal hepatic encephalopathy not included in analysis) at 3 days; Group 1: 20/25, Group 2: 15/27; risk of bias: low; indirectness of outcome: no indirectness
- Actual outcome: SUBGROUP DATA (Grade I and II). Partial improvement defined as improvement of 1 grade from baseline (West Haven Grade I-IV hepatic encephalopathy only, 12 patients with minimal hepatic encephalopathy not included in analysis) at 3 days; Group 1: 2/29, Group 2: 14/27; risk of bias: low; indirectness of outcome: no indirectness
- Actual outcome: SUBGROUP DATA (Grade III and IV). Partial improvement defined as improvement of 1 grade from baseline (West Haven Grade I-IV hepatic encephalopathy only, 12 patients with minimal hepatic encephalopathy not included in analysis) at 3 days; Group 1: 2/25, Group 2: 5/27; risk of bias: low; indirectness of outcome: no indirectness
- Actual outcome: SUBGROUP DATA (Grade I and II). No improvement/deterioration in hepatic encephalopathy grade (West Haven Grade I-IV hepatic encephalopathy only, 12 patients with minimal hepatic encephalopathy not included in analysis) at 3 days; Group 1: 2/29, Group 2: 3/27; risk of bias: low; indirectness of outcome: no

Study	Abid 2011[3]
indirectness - Actual outcome: SUBGROUP DATA (Grade III and IV.) No improvement/deterioration in hepatic encephalopathy grade (West Haven Grade I-IV hepatic encephalopathy only, 12 patients with minimal hepatic encephalopathy not included in analysis) at 3 days; Group 1: 3/25, Group 2: 7/27; risk of bias: low; indirectness of outcome: no indirectness Protocol outcome 3: Discharge from hospital at end of study - Actual outcome: Median duration of hospitalisation (includes 12/120 patients with minimal hepatic encephalopathy, 6 in each arm); other: median (range). LOLA=96 hours (range 48–574) versus placebo = 96 hours (range 90–240); p = 0.025; risk of bias: low; indirectness of outcome: serious indirectness Protocol outcome 4: Adverse events (diarrhoea, flatulence, abdominal pain, nausea, GI bleeding, renal failure) at end of study - Actual outcome: Adverse drug reactions (includes 12/120 patients with minimal hepatic encephalopathy, 6 in each arm) at 3 days; Group 1: 0/60, Group 2: 0/60; risk of bias: low; indirectness of outcome: serious indirectness	
Protocol outcomes not reported by the study	Quality of life at end of study

Study	Ahmad 2008[5]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	N/A (n=80)
Countries and setting	Conducted in Pakistan; setting: secondary care
Line of therapy	First line
Duration of study	Intervention time: 5 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Cirrhosis was diagnosed on the basis of clinical, laboratory and ultrasonographic features
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	(1) Adult with diagnosis of cirrhosis. (2) Clinically overt encephalopathy (West Haven 1-4) developed spontaneously without any precipitating factor. (3) Hyperammonaemia.
Exclusion criteria	Existence of specified precipitating factors; mental state grade IV hepatic encephalopathy; active & major complications of portal hypertension; acute superimposed liver injury; hepatocellular carcinoma; serious non-hepatic diseases (for example heart/respiratory/renal failure); presence of infections other than spontaneous bacterial

Study	Ahmad 2008[5]
	peritonitis necessitating antibiotic therapy.
Recruitment/selection of patients	Unclear
Age, gender and ethnicity	Age – mean (SD): intervention 51.7 (10.8) versus control 52.0 (11.7). Gender (M:F): 59/21. Ethnicity: Not reported.
Further population details	1. Grade of acute hepatic encephalopathy: Grade 1–2 (82.5% grade I or II; 17.5% grade III). 2. Severity of the underlying liver disease: Child-Pugh B or C (only 2.5% were Child Pugh A).
Extra comments	The participants had hepatic encephalopathy of I to III.
Indirectness of population	No indirectness
Interventions	(n=40) Intervention 1: l-Ornithine-l-aspartate (LOLA). IV of 20 g (4 ampoules of 10 ml each) in 250 ml of 5% dextrose; administered daily over 4 hours for 5 consecutive days. Duration: 5 days. Concurrent medication/care: Lactulose + Metronidazole (n=40) Intervention 2: Placebo. IV of 20 g (4 ampoules of 10 ml distilled water) in 250 ml of 5% dextrose; administered daily over 4 hours for 5 consecutive days. Duration: 5 days. Concurrent medication/care: Lactulose + Metronidazole
Funding	Equipment/drugs provided by industry (Brookes Pharmaceutical Pakistan provided the intervention medication)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: L-ORNITHINE-L-ASPARTATE (LOLA) versus PLACEBO Protocol outcome 1: Survival at end of study - Actual outcome: In-hospital mortality at 5 days; Group 1: 2/40, Group 2: 4/40; risk of bias: very high; indirectness of outcome: no indirectness Protocol outcome 2: No improvement in hepatic encephalopathy (improvement defined as a partial or complete resolution of clinical symptoms of hepatic encephalopathy. Some studies may assess improvement using electrophysiological or psychometrical testing, PSE score, or blood plasma ammonia levels) at end of study - Actual outcome: Number of participants who achieved hepatic encephalopathy grade 0 at 5 days; Group 1: 37/40, Group 2: 31/40; risk of bias: very high; indirectness of outcome: no indirectness Protocol outcome 3: Adverse events (diarrhoea, flatulence, abdominal pain, nausea, GI bleeding, renal failure) at end of study - Actual outcome: Adverse reactions to medicine (nausea/vomiting) at 5 days; Group 1: 1/40, Group 2: 0/40; risk of bias: very high; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Quality of life at end of study; discharge from hospital at end of study

Study	Cerra 1983[21]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	1 (n=22)
Countries and setting	Conducted in USA; setting: Department of Surgery, University of Minnesota Hospital, Minneapolis
Line of therapy	First line
Duration of study	Intervention + follow up: 4–14 days with a follow-up period of at least 7 days after study or until death or discharge
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Cirrhosis proven by clinical evaluation or biopsy studies. Patients were screened by means of a history, physical examination, mental status exam, EEG and metabolic and laboratory data.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Men and women aged 18–85 with chronic hepatic disease and at least acute grade 2 encephalopathy who were judged to require parenteral nutritional support
Exclusion criteria	Acute viral hepatitis, hepatorenal syndrome, significant GI bleeding, non-hepatic coma, need for fluid restriction
Age, gender and ethnicity	Age – mean (SD): BCAA: 56 (3); neomycin: 55 (3). Gender (M:F): 75% male. Ethnicity: not reported.
Further population details	1. Grade of acute hepatic encephalopathy: Not applicable/not stated/unclear. 2. Severity of the underlying liver disease: not applicable/not stated/unclear.
Extra comments	Nine patients had portocaval shunts. A neurologic examination was done daily. EEGs were planned on days 0, 2, 4, 6 and 10. Only data from the first 7 days of the study were reported so as to maintain statistically valid samples. No patients crossed over.
Indirectness of population	Serious indirectness: Approximately 50–60% patients had failed to improve encephalopathy over at least 48 hours
Interventions	(n=12) Intervention 1: Branch chain amino acids – IV branch chain amino acids. F080 (BCAA-enriched solution, 36% equimolar (HeparAmine, 8% amino acid injection, American McGaw) low in aromatic acids and methionine in 25% dextrose) plus placebo tablets matching the appearance of neomycin. Duration 4–14 days with a follow-up period of at least 7 days after the study or until death or discharge. To complete the study, a patient had to finish the first 4 days of therapy with complete data. Concurrent medication/care: All other therapy was allowed as clinically indicated with the exception of sedatives, lactulose or levodopa. Oral protein was restricted for the first 6 days of the study or until encephalopathy cleared. (n=10) Intervention 2: Oral non-absorbable antibiotics – neomycin. Four grams per day given orally or by nasogastric tube in 4 divided doses daily. Duration 4–14 days with a follow-up period of at least 7 days after the study or until

Study	Cerra 1983[21]
	death or discharge. To complete the study, a patient had to finish the first 4 days of therapy with complete data. Concurrent medication/care: All other therapy was allowed as clinically indicated with the exception of sedatives, lactulose or levodopa. Oral protein was restricted for the first 6 days of the study or until encephalopathy cleared.
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV BRANCH CHAIN AMINO ACIDS versus NEOMYCIN Protocol outcome 1: Survival at end of study - Actual outcome: Mortality at study plus follow-up; Group 1: 2/12, Group 2: 4/10; risk of bias: high; indirectness of outcome: no indirectness Protocol outcome 2: No improvement in hepatic encephalopathy (improvement defined as a partial or complete resolution of clinical symptoms of hepatic encephalopathy. Some studies may assess improvement using electrophysiological or psychometrical testing, PSE score, or blood plasma ammonia levels) at end of study - Actual outcome: Patients whose encephalopathy improved to grade 0 at study plus follow-up; Group 1: 5/9, Group 2: 2/8; risk of bias: high; indirectness of outcome: no indirectness - Actual outcome: Patients whose encephalopathy improved to grade 0–1 at study plus follow-up; Group 1: 8/9, Group 2: 6/8; risk of bias: high; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Quality of life at end of study; discharge from hospital at end of study; adverse events (diarrhoea, flatulence, abdominal pain, nausea, GI bleeding, renal failure) at end of study

Study	Cerra 1985[20]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	1 (n=75)
Countries and setting	Conducted in USA; setting: Eight centres participated in the study. Three centres equally contributed 70% of the patients. The remaining patients were distributed among the remaining 5 centres.
Line of therapy	First line
Duration of study	Intervention + follow up: Up to 14 days, with a follow-up period of at least 7 days post-study, or until death or discharge

Study	Cerra 1985[20]
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: 'For most patients that diagnosis was cirrhosis'. 65–75% of the patients in each group had this diagnosis made by biopsy, the rest by clinical criteria.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Males and females between 18 and 85 years with chronic hepatic disease and at least acute grade 2 encephalopathy
Exclusion criteria	Acute viral hepatitis, acute fulminant hepatitis, hepatorenal syndrome, significant GI bleeding, non-hepatic coma, patients requiring severe fluid restriction
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age – mean (SD): intervention: 53 (2), control: 53 (2). Gender (M:F): intervention: 80% male, control: 93% male. Ethnicity: not reported.
Further population details	1. Grade of acute hepatic encephalopathy: not applicable/not stated/unclear. 2. Severity of the underlying liver disease: not applicable/not stated/unclear
Extra comments	The patients were screened by history and physical examination, electroencephalogram and by metabolic laboratory data. Encephalopathy was graded by a trained independent observer on a scale of 0–4.
Indirectness of population	Serious indirectness: Approximately 75% patients had failed to improve encephalopathy over at least 48 hours
Interventions	(n=40) Intervention 1: Branch chain amino acids – IV branch chain amino acids. F080 - BCAA solution low in aromatic amino acids and methionine (Hepatamine, McGaw laboratories) in 25% dextrose, given via central vein catheter, plus placebo tablets matching the appearance of neomycin and given on the same dosing schedule. F080 contained 36% of the amino acids as the BCAA leucine, isoleucine and valine in essentially equimolar amounts; methionine, phenylalanine and glycine were decreased as compared to conventional solutions and arginine and alanine were somewhat increased. Day 1: 1.5 litres of solution; days 2–6: 2 litres of solution and up to a maximum of 3 litres per day thereafter. Duration: up to 14 days. To complete the study, the patient had to finish the first 4 days of therapy with complete data. Concurrent medication/care: All other therapy was allowed as clinically indicated with the exception of sedatives, lactulose or L-dopa. Oral intake was restricted until hepatic encephalopathy cleared, after which oral intake was allowed as tolerated. (n=35) Intervention 2: Oral non-absorbable antibiotics – neomycin. Four grams of enteral neomycin daily along with 25% dextrose by central venous catheter in 4 divided doses. Duration: up to 14 days. To complete the study, the patient had to finish the first 4 days of therapy with complete data. Concurrent medication/care: All other therapy was allowed as clinically indicated with the exception of sedatives, lactulose or L-dopa. Oral intake was restricted until hepatic encephalopathy cleared, after which oral intake was allowed as tolerated.

Study	Cerra 1985[20]
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV BRANCH CHAIN AMINO ACIDS versus NEOMYCIN Protocol outcome 1: Survival at end of study - Actual outcome: Death during treatment; Group 1: 14/40, Group 2: 22/35; risk of bias: high; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Quality of life at end of study; No improvement in hepatic encephalopathy (improvement defined as a partial or complete resolution of clinical symptoms of hepatic encephalopathy. Some studies may assess improvement using electrophysiological or psychometrical testing, PSE score, or blood plasma ammonia levels) at end of study; discharge from hospital at end of study; adverse events (diarrhoea, flatulence, abdominal pain, nausea, GI bleeding, renal failure) at end of study

Study	Fiaccadori 1984[41]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	N/A (n=48)
Countries and setting	Conducted in Italy; setting: unclear
Line of therapy	First line
Duration of study	Intervention time: 7 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosis of cirrhosis based on clinical and laboratory data and confirmed in all cases but one by liver biopsy
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	(1) Presence of liver cirrhosis. (2) Presence of hepatic encephalopathy. (3) No evidence of hepatorenal syndrome.
Exclusion criteria	Not given
Recruitment/selection of patients	Patients consecutively admitted to the study group's departments and selected according to the criteria
Age, gender and ethnicity	Age - other: mean=50.8. Gender (M:F): 35/13. Ethnicity: Not reported.

Study	Fiaccadori 1984[41]
Further population details	1. Grade of acute hepatic encephalopathy: Not applicable/not stated/unclear. 2. Severity of the underlying liver disease: not applicable/not stated/unclear.
Extra comments	23 out of 48 (47.9%) of the participants had had previous episodes of hepatic encephalopathy
Indirectness of population	No indirectness
Interventions	(n=16) Intervention 1: Non-absorbable disaccharides – lactulose enema. Administered via a nasogastric tube or enema, at 150 to 300 mg per day. Duration: 7 days. Concurrent medication/care: Hypertonic glucose (30%) solution administered through a catheter in the subclavian vein at 1.35 ml/minute for 24 hours. (n=16) Intervention 2: Branch chain amino acids – IV branch chain amino acids. BS 666 infusion lasted for 12 hours with protein intake of around 0.8 to 1g/kg/body weight/day. Duration: 7 days. Concurrent medication/care: Hypertonic glucose (30%) solution administered through a catheter in the subclavian vein at 1.35 ml/minute for 24 hours. (n=16) Intervention 3: Branch chain amino acids – IV branch chain amino acids. BS 666 infusion lasted for 12 hours with protein intake of around 0.8 to 1g/kg/body weight/day + lactulose administered via a nasogastric tube or enema, at 150 to 300 mg per day. Duration: 7 days. Concurrent medication/care: Hypertonic glucose (30%) solution administered through a catheter in the subclavian vein at 1.35ml/minute for 24 hours.
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LACTULOSE ENEMA versus IV BRANCH CHAIN AMINO ACIDS

Protocol outcome 1: No improvement in hepatic encephalopathy (improvement defined as a partial or complete resolution of clinical symptoms of hepatic encephalopathy. Some studies may assess improvement using electrophysiological or psychometrical testing, PSE score, or blood plasma ammonia levels) at end of study
- Actual outcome: The number of participants that came out of coma by the seventh day; Group 1: 5/8, Group 2: 15/16; risk of bias: very high; indirectness of outcome: no indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LACTULOSE ENEMA versus IV BRANCH CHAIN AMINO ACIDS + LACTULOSE

Protocol outcome 1: No improvement in hepatic encephalopathy (improvement defined as a partial or complete resolution of clinical symptoms of hepatic encephalopathy. Some studies may assess improvement using electrophysiological or psychometrical testing, PSE score, or blood plasma ammonia levels) at end of study

Study	Fiaccadori 1984[41]
- Actual outcome: The number of participants that came out of coma by the seventh day; Group 1: 5/8, Group 2: 16/16; risk of bias: very high; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Survival at end of study; quality of life at end of study; discharge from hospital at end of study; adverse events (diarrhoea, flatulence, abdominal pain, nausea, GI bleeding, renal failure) at end of study

Study	Gyr 1996[59]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	N/A (n=49)
Countries and setting	Conducted in multiple countries; setting: secondary care
Line of therapy	First line
Duration of study	Intervention + follow up: 12 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Hospitalised patients having chronic liver failure with mild to moderate degree of PSE (stage I-III or clinical PSE score 3-14)
Exclusion criteria	Acute fulminant liver failure; coma at any point of the study; metabolic coma other than due to liver failure; hepatitis superimposed on cirrhosis; liver tumours; severe cerebral atrophy as assessed by cranial computer aided tomography; and psychiatric disease except PSE; patients who reported to have taken psychotropic medication (including benzodiazepines)
Recruitment/selection of patients	Unclear
Age, gender and ethnicity	Age – mean (SD): Intervention 55.5 (9.4) versus control 53.6 (10.3). Gender (M:F): 34/15. Ethnicity: Not reported.
Further population details	1. Grade of acute hepatic encephalopathy: not applicable/not stated/unclear (West Haven stage not reported). 2. Severity of the underlying liver disease: Child-Pugh B or C (Only 4% Child Pugh A).
Extra comments	Portal systemic encephalopathy (PSE) episodes resulting from common precipitating situations such as severe bleeding and infection were excluded, resulting in a selection of patients with apparently more spontaneous and stable PSE in chronic liver disease.

Study	Gyr 1996[59]
Indirectness of population	No indirectness
Interventions	(n=28) Intervention 1: IV benzodiazepine antagonist – Flumazenil. [1] Three sequential bolus injections of flumazenil (0.4, 0.8, then 1 mg) at one-minute intervals. [2] IV infusions of flumazenil at 1 mg/hour for 3 hours. Duration: 3 hours. Concurrent medication/care: saline, glucose, lactulose, potassium and vitamin K were allowed as additional treatments. (n=21) Intervention 2: Placebo. [1] Three sequential bolus injections of placebo (0.4, 0.8, then 1 mg) at one-minute intervals. [2] IV infusions of placebo at 1 mg/hour for 3 hours. Duration: 3 hours. Concurrent medication/care: saline, glucose, lactulose, potassium and vitamin K were allowed as additional treatments.
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FLUMAZENIL versus PLACEBO Protocol outcome 1: Survival at end of study - Actual outcome: death (from respiratory failure) during the observation period at 3 hour treatment period + 5 hour post-treatment observation period; Group 1: 0/28, Group 2: 1/21; risk of bias: very high; indirectness of outcome: no indirectness - Actual outcome: death following the study (considered not related to study medication) at within 4 weeks following the study; Group 1: 4/28, Group 2: 5/21; risk of bias: very high; indirectness of outcome: no indirectness Protocol outcome 2: No improvement in hepatic encephalopathy (improvement defined as a partial or complete resolution of clinical symptoms of hepatic encephalopathy. Some studies may assess improvement using electrophysiological or psychometrical testing, PSE score, or blood plasma ammonia levels) at end of study - Actual outcome: Number of patients with clinically relevant response (improvement of at least 2 points in PSE score from baseline, PSE score on a 0–16 scale, better indicated by lower values) at 3 hour treatment period + 5 hour post-treatment observation period; Group 1: 7/28, Group 2: 0/21; risk of bias: very high; indirectness of outcome: no indirectness Protocol outcome 3: Adverse events (diarrhoea, flatulence, abdominal pain, nausea, GI bleeding, renal failure) at end of study - Actual outcome: Adverse events at 3 hour treatment period + 5 hour post-treatment observation period; Group 1: 4/28, Group 2: 0/21; risk of bias: very high; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Quality of life at end of study; discharge from hospital at end of study

Study	Hassanein 2007[61]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	N/A (n=70)
Countries and setting	Conducted in multiple countries; setting: tertiary care centres
Line of therapy	First line
Duration of study	Intervention + follow up: Maximum of 5 days of treatment (study period); patients followed up to 180 days after the end of the study period
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Cirrhosis was determined by medical history, and confirmed clinically, biochemically and radiologically
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients 18 years of age or older, presenting with manifestations of cirrhosis and hepatic encephalopathy grade 3 or 4
Exclusion criteria	Active haemorrhage; haemodynamic instability; acute cardiopulmonary complications; pregnancy; active renal replacement therapy; presenting with drug intoxication/irreversible brain damage/non-hepatic causes of altered mental status; acute liver failure; hepatocellular carcinoma; liver transplant recipient
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age – mean (range): intervention 49 (20–67) versus control 56 (32–76); p=0.019. Gender (M:F): 39/31. Ethnicity: Not reported.
Further population details	1. Grade of acute hepatic encephalopathy: Grade 3–4 (III: 56%; IV: 44%). 2. Severity of the underlying liver disease: Child-Pugh B or C (All Child-Pugh C [range 10–15]).
Indirectness of population	Serious indirectness: Medium time to randomisation from first presentation with severe hepatic encephalopathy was 2 days. In the meantime, patients were managed with their respective local standards of care for hepatic encephalopathy.
Interventions	(n=39) Intervention 1: MARS. Extracorporeal albumin dialysis (ECAD) using molecular absorbent recirculating system (MARS; Teraklin AG, Germany) with standard medical therapy (SMT). Treatments done every day for 6 hours for 5 days or until a 2-grade improvement in hepatic encephalopathy (West Haven). SMT included treatment of the precipitating event of the acute episode of hepatic encephalopathy; oral lactulose titrated to achieve 2–3 daily bowel movements, oral neomycin or metronidazole and daily zinc sulphate. Duration: 5 days. Concurrent medication/care: Most patients received systemic antibiotics.

Study	Hassanein 2007[61]
	(n=31) Intervention 2: No treatment. Standard medical therapy: included treatment of the precipitating event of the acute episode of hepatic encephalopathy; oral lactulose titrated to achieve 2–3 daily bowel movements, oral neomycin or metronidazole and daily zinc sulphate. Duration: 5 days. Concurrent medication/care: Most patients received systemic antibiotics
Funding	Study funded by industry (Grants from Teraklin AG; Rostock & Gambro Renal Products)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MARS + SMT versus STANDARD MEDICAL THERAPY Protocol outcome 1: Survival at end of study - Actual outcome: death at 5 days; Group 1: 5/39, Group 2: 5/31; risk of bias: low; indirectness of outcome: no indirectness Protocol outcome 2: No improvement in hepatic encephalopathy (improvement defined as a partial or complete resolution of clinical symptoms of hepatic encephalopathy. Some studies may assess improvement using electrophysiological or psychometrical testing, PSE score, or blood plasma ammonia levels) at end of study - Actual outcome: Responder (people with an improvement of hepatic encephalopathy by 2 grades at any time during the 5-day study period) at 5 days; Group 1: 24/39, Group 2: 12/30; risk of bias: high; indirectness of outcome: no indirectness Protocol outcome 3: Adverse events (diarrhoea, flatulence, abdominal pain, nausea, GI bleeding, renal failure) at end of study - Actual outcome: serious adverse events at 5 days; Group 1: 20/39, Group 2: 8/31; risk of bias: low; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Quality of life at end of study; discharge from hospital at end of study

Study	hepatic encephalopathyLP (Hepatic Encephalopathy: Lactulose versus Polyethylene Glycol 3350-Electrolyte Solution) study trial: Rahimi 2014[105]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	N/A (n=50)
Countries and setting	Conducted in USA
Line of therapy	First line
Duration of study	Intervention + follow up: Until discharge from hospital or death

Study	hepatic encephalopathyLP (Hepatic Encephalopathy: Lactulose versus Polyethylene Glycol 3350-Electrolyte Solution) study trial: Rahimi 2014[105]
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Cirrhosis was defined by clinical features, including a history consistent with chronic liver disease (CLD) as well as documented complication of CLD and/or imaging results consistent with cirrhosis and/or liver histologic findings consistent with cirrhosis.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	(1) Age 18 to 80 years; (2) Diagnosis of cirrhosis from any cause; (3) Presence of any grade of hepatic encephalopathy; (4) Availability of a legally authorised representative (LAR) for interview and consent.
Exclusion criteria	(1) Acute liver failure, defined as coagulopathy with any degree of altered mental status in the absence of underlying CLD; (2) Altered mental status from a cause other than hepatic encephalopathy; (3) Treatment with rifaximin or neomycin within the previous 7 days; (4) Receipt of more than 1 dose of lactulose prior to consent; (5) Lack of an LAR to provide consent; (5) Refusal of consent by the LAR; (6) Previous participation in the present study; (7) Haemodynamic instability treated with vasopressors; (8) Pregnancy; (9) Being a prisoner.
Recruitment/selection of patients	As a person with cirrhosis and altered mental status with a suspected hepatic encephalopathy presented at the ED of the hospital (study site) between January 2011 and June 2012, their LAR was approached and interviewed to seek consent for study participation.
Age, gender and ethnicity	Age – mean (SD): 56 (9). Gender (M:F): 31/19. Ethnicity: White Hispanic 70%; White non-Hispanic 20%; African American 8%; Asian 1%.
Further population details	1. Grade of acute hepatic encephalopathy: Not applicable/not stated/unclear. 2. Severity of the underlying liver disease: Not applicable/not stated/unclear
Indirectness of population	No indirectness: Previous episodes of hepatic encephalopathy for the participants are unknown
Interventions	(n=25) Intervention 1: Polyethylene gycol electrolyte solution, PEG 3350. Four litres of PEG administered orally or via nasogastric tube in a single dose over 4 hours. After PEG administration, no lactulose (or other potential hepatic encephalopathy therapy) was allowed for 24 hours. After 24 hours, participants were allowed to receive lactulose per the standard care. Duration: 4 hours. Concurrent medication/care: N/A. (n=25) Intervention 2: Non-absorbable disaccharides – oral lactulose. 20 to 30 g administered orally or by nasogastric tube (3 or more doses within 24 hours) or 200 g by rectal tube if oral intake was not possible or inadequate. Duration: 24 hours. Concurrent medication/care: N/A.
Funding	Academic or government funding (National Institutes of Health [NIH] grant; NIH National Center for Advancing

Study	hepatic encephalopathyLP (Hepatic Encephalopathy: Lactulose versus Polyethylene Glycol 3350-Electrolyte Solution) study trial: Rahimi 2014[105]
	Translational Sciences grant)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: POLYETHYLENE GLYCOL ELECTROLYTE SOLUTION, PEG 3350 versus ORAL LACTULOSE Protocol outcome 1: Survival at end of study - Actual outcome: Death at 24 hours; Group 1: 1/25, Group 2: 2/25; risk of bias: low; indirectness of outcome: no indirectness Protocol outcome 2: No improvement in hepatic encephalopathy (improvement defined as a partial or complete resolution of clinical symptoms of hepatic encephalopathy. Some studies may assess improvement using electrophysiological or psychometrical testing, PSE score, or blood plasma ammonia levels) at end of study - Actual outcome: Improvement of one or more in hepatic encephalopathy grade at 24 hours (hepatic encephalopathy scoring algorithm score) at 24 hours; Group 1: 21/25, Group 2: 13/25; risk of bias: low; indirectness of outcome: no indirectness - Actual outcome: Time to hepatic encephalopathy resolution (defined as an improvement to grade 0, or two days at grade 1 after an initial improvement of at least one grade); HR 1.76 (95% CI 0.97 to 3.18) calculated – from curve + numbers at risk; risk of bias: low; indirectness of outcome: no indirectness - Actual outcome: No improvement of hepatic encephalopathy scoring algorithm grade at 24 hours; Group 1: 2/23, Group 2: 12/25; risk of bias: high; indirectness of outcome: no indirectness Protocol outcome 3: Discharge from hospital at end of study - Actual outcome: Overall length of stay; Group 1: mean 4 days (SD 3); n=25, Group 2: mean 8 days (SD 12); n=25; risk of bias: low; indirectness of outcome: no indirectness Protocol outcome 4: Adverse events (diarrhoea, flatulence, abdominal pain, nausea, GI bleeding, renal failure) at end of study - Actual outcome: Number of adverse events (none considered definitely or probably related to the study interventions) at 24 hours; Group 1: 3/25, Group 2: 5/25; risk of bias: low; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Quality of life at end of study

Study	Laccetti 2000[73]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	N/A (n=54)

Study	Laccetti 2000[73]
Countries and setting	Conducted in Italy; Setting: Hospital emergency department
Line of therapy	1st line
Duration of study	Intervention + follow up: 24 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: The diagnosis of liver cirrhosis were made by pertinent clinical, laboratory and morphological procedures performed during previous hospitalisation.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with a diagnosis of liver cirrhosis who presented with hepatic encephalopathy in the ED or developed hepatic encephalopathy during their hospital stay: of those, only individuals with chronic liver failure and more severe stages of hepatic encephalopathy (stages III-IV) were included.
Exclusion criteria	People with alcoholic liver cirrhosis
Recruitment/selection of patients	Unclear
Age, gender and ethnicity	Age - Mean (SD): Intervention 59.6 (6) versus Control 57.7 (5.4). Gender (M:F): 29/25. Ethnicity: Not stated
Further population details	1. Grade of acute hepatic encephalopathy : Grade 3-4 (Grade I and II excluded). 2. Severity of the underlying liver disease : Not applicable / Not stated / Unclear (Only mean Child Pugh score reported).
Indirectness of population	No indirectness: Patients with alcoholic liver cirrhosis were excluded to avoid bias by neurological and psychiatric signs due to chronic or acute ethanol abuse.
Interventions	(n=28) Intervention 1: IV benzodiazepine antagonist - Flumazenil. 2mg in 50ml saline at 10ml/min. Duration 5 minutes. Concurrent medication/care: Conventional treatment similar for both groups (the following additional treatments were permitted: saline, glucose, lactulose enemas, BCAAs) (n=26) Intervention 2: Placebo. IV placebo 2mg in 50ml saline at 10ml/min. Duration 5 minutes. Concurrent medication/care: Conventional treatment similar for both groups (the following additional treatments were permitted: saline, glucose, lactulose enemas, BCAAs)
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FLUMAZENIL versus PLACEBO Protocol outcome 1: Survival at End of study	

Study	Laccetti 2000[73]
- Actual outcome: Mortality at 24 hours; Group 1: 6/28, Group 2: 5/26; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: No improvement in hepatic encephalopathy (improvement defined as a partial or complete resolution of clinical symptoms of hepatic encephalopathy. Some studies may assess improvement using electrophysiological or psychometrical testing, PSE score, or blood plasma ammonia levels) at End of study - Actual outcome: Improvement in neurological status (Increase in Glasgow coma score by 3 points) at 24 hours; Group 1: 22/28, Group 2: 14/26; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Adverse events (diarrhoea, flatulence, abdominal pain, nausea, GI bleeding, renal failure) at End of study - Actual outcome: Side effects at 24 hours; Group 1: 0/28, Group 2: 0/26; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at End of study; Discharge from hospital at End of study

Study	Loguercio 1987[81]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in Italy; Setting: Institute of General Medicine and clinical methodology, the faculty of medicine and surgery, University of Naples, Italy
Line of therapy	1st line
Duration of study	Intervention + follow up: 10 days treatment and a further 10 days follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Conn and Lieberthal method
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Cirrhotic patients
Exclusion criteria	nr
Recruitment/selection of patients	nr
Age, gender and ethnicity	Age - Median (range): Enterococcus group: 58 (25-66), 57 (35-68). Gender (M:F): Enterococcus group: 13M/7F, lactulose group: 13M/F. Ethnicity: nr
Further population details	1. Grade of acute hepatic encephalopathy : Not applicable / Not stated / Unclear (West Haven criteria not used). 2.

Study	Loguercio 1987[81]
	Severity of the underlying liver disease : Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Oral probiotics . Enterococcus strain SF68 (Bioflorin) is a lactic acid bacteria. Two capsules, three times per day after meals, each capsule containing at least 75 x 10^6 cells. Duration 10 days. Concurrent medication/care: none (n=20) Intervention 2: Non-absorbable disaccharides - oral lactulose. Lactulose (30ml, four times per day after meals). Duration 10 days. Concurrent medication/care: none
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ORAL PROBIOTICS versus ORAL LACTULOSE Protocol outcome 1: No improvement in hepatic encephalopathy (improvement defined as a partial or complete resolution of clinical symptoms of hepatic encephalopathy. Some studies may assess improvement using electrophysiological or psychometrical testing, PSE score, or blood plasma ammonia levels) at End of study - Actual outcome: Improvement in hepatic encephalopathy symptoms at Day 10; Group 1: 15/19, Group 2: 14/19; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: Adverse events (diarrhoea, flatulence, abdominal pain, nausea, GI bleeding, renal failure) at End of study - Actual outcome: Meteroism, abdominal pain, diarrhoea, hyperammonaemia, worsening of hepatic encephalopathy, constipation at 20 days; Group 1: 1/16, Group 2: 8/15; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Survival at End of study; Quality of life at End of study; Discharge from hospital at End of study

Study	Mas 2003[87]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	N/A (n=103)
Countries and setting	Conducted in Spain; setting: secondary care
Line of therapy	First line

Study	Mas 2003[87]
Duration of study	Intervention time: 5 to 10 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: After hospital admission, patients underwent detailed physical, neurological and psychometric assessment
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Consecutive cirrhotic patients with an acute hepatic encephalopathy episode, diagnosed in specified 13 hospitals in Spain from November 1995 to December 1997 with clinical, psychometric and electroencephalographic evidence of grade I-III hepatic encephalopathy of <2 days duration and PSE index >0.
Exclusion criteria	Major psychiatric illness; chronic renal and/or respiratory insufficiency; intercurrent infections; known hypersensitivity to rifamycin antibiotics and/or to disaccharides; patients having received treatment with sedatives or antibiotics within 7 days before inclusion; pregnant or lactating women; and patients who did not fulfill protocol requirements.
Recruitment/selection of patients	Consecutive patients fulfilling criteria
Age, gender and ethnicity	Age – mean (SD): Intervention 61.6 (9.7) versus control 62.9 (0.6). Gender (M:F): 72/31. Ethnicity: Not reported.
Further population details	1. Grade of acute hepatic encephalopathy: Not applicable/not stated/unclear (West Haven Criteria not reported). 2. Severity of the underlying liver disease: not applicable/not stated/unclear.
Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: Oral non-absorbable antibiotics – rifaximin. Two 200 mg rifaximin tablets taken orally or via nasogastric tube, every 8 hours. Duration: maximum of 10 days. Concurrent medication/care: 20 g placebo sachet dissolved in 100 ml of water, given orally or via nasogastric tube, every 8 hours. (n=53) Intervention 2: Non-absorbable disaccharides – oral lactitol. One 20 g lactitol sachet dissolved in 100 ml of water given orally or via nasogastric tube, every 8 hours. Duration: maximum of 10 days. Concurrent medication/care: two tablets of placebo, externally indistinguishable from the rifaximin tablets, every 8 hours.
Funding	Study funded by industry (the study was supported by a grant given by Zambon S.A. [Spain], and the interventional drugs were provided by Alfa Wassermann Pharmaceutical Company [Italy])

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RIFAXIMIN versus LACTITOL

Protocol outcome 1: Survival at end of study
- Actual outcome: Death considered unrelated to the study medication within 28 days of the last dose; Group 1: 1/50, Group 2: 2/53; risk of bias: low; indirectness of

Study	Mas 2003[87]
outcome: no indirectness Protocol outcome 2: No improvement in hepatic encephalopathy (improvement defined as a partial or complete resolution of clinical symptoms of hepatic encephalopathy. Some studies may assess improvement using electrophysiological or psychometrical testing, PSE score, or blood plasma ammonia levels) at end of study - Actual outcome: Unchanged/failure (hepatic encephalopathy clinical syndrome not improved and blood ammonia levels not decreased/increase in blood ammonia, increase in PSE index and/or a shift to a higher stage of hepatic encephalopathy) – this is versus a resolution or improvement in hepatic encephalopathy clinical stage or blood ammonia at post-treatment; Group 1: 9/50, Group 2: 10/53; risk of bias: low; indirectness of outcome: no indirectness Protocol outcome 3: Adverse events (diarrhoea, flatulence, abdominal pain, nausea, GI bleeding, renal failure) at end of study - Actual outcome: Adverse events at post-treatment; Group 1: 3/50, Group 2: 2/53; risk of bias: low; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Quality of life at end of study; discharge from hospital at end of study

Study	Paik 2005[97]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	N/A (n=54)
Countries and setting	Conducted in South Korea; setting: secondary care
Line of therapy	First line
Duration of study	Intervention time: 7 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosis of cirrhosis based on clinical and laboratory findings
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Hospital inpatients with episodic hepatic encephalopathy affected by decompensated liver cirrhosis
Exclusion criteria	Age <18 years; presence of a major neuropsychiatric illness; presence of intestinal obstruction or IBD; hypersensitivity to rifamycin/diasaccharides; a serum creatinine level > twice normal; received loop diuretics/antacids/cathartics within 12-hour period before study commencement; on antibiotics during preceding 7 days; previously treated with encephalopathy-causing agents
Recruitment/selection of patients	Unclear

Study	Paik 2005[97]
Age, gender and ethnicity	Age – mean (SD): Intervention 56.2 (7.1) versus control 54.9 (6.6). Gender (M:F): 37/17. Ethnicity: Korean 100%.
Further population details	1. Grade of acute hepatic encephalopathy: Not applicable/not stated/unclear (West Haven criteria not reported). 2. Severity of the underlying liver disease : Child-Pugh B or C.
Extra comments	The participants showed signs of the first to third degree hepatic encephalopathy, according to Conn's modification of Parsons-Smith classification, and had serum ammonia levels >75 µmol/L. Of the 64 participants, 26 (40.6%) had "acute hepatic encephalopathy" and 38 (59.4%) had "recurrent hepatic encephalopathy".
Indirectness of population	No indirectness
Interventions	(n=32) Intervention 1: Oral non-absorbable antibiotics – rifaximin. 1200 mg per day in 3 divided doses. Duration: 7 days. Concurrent medication/care: Not reported. (n=22) Intervention 2: Non-absorbable disaccharides – oral lactulose. Lactulose syrup, 90 ml per day. Duration: 7 days. Concurrent medication/care: Not reported.
Funding	Equipment/drugs provided by industry (Ajou Pharmaceutical, Co. Ltd. Korea supplied rifaximin and lactulose)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RIFAXIMIN versus ORAL LACTULOSE Protocol outcome 1: No improvement in hepatic encephalopathy (improvement defined as a partial or complete resolution of clinical symptoms of hepatic encephalopathy. Some studies may assess improvement using electrophysiological or psychometrical testing, PSE score, or blood plasma ammonia levels) at end of study - Actual outcome: Improvement in hepatic encephalopathy grade at 7 days; Group 1: 26/32, Group 2: 16/22; risk of bias: high; indirectness of outcome: no indirectness - Actual outcome: Improvement in hepatic encephalopathy index (taking into account hepatic encephalopathy grade, number connection test [NCT], blood ammonia and severity of flapping tremor) at 7 days; Group 1: 27/32, Group 2: 21/22; risk of bias: high; indirectness of outcome: no indirectness Protocol outcome 2: Adverse events (diarrhoea, flatulence, abdominal pain, nausea, GI bleeding, renal failure) at end of study - Actual outcome: Adverse effects at 7 days; Group 1: 1/32, Group 2: 1/22; risk of bias: high; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Survival at end of study; quality of life at end of study; discharge from hospital at end of study

Study (subsidiary papers)	Rossi-fanelli 1982[111] (Rossi fanelli 1986[109], Rossi 1984[110])
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	(n=34)
Countries and setting	Conducted in Italy; setting: secondary care
Line of therapy	First line
Duration of study	Intervention + follow up: Until 10 days after the start of therapy
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	(1) Presence of liver cirrhosis, diagnosed on clinical, biochemical and histological findings; (2) Presence of hepatic coma (grade 3–4 hepatic encephalopathy) assessed by 2 independent observers according to the classification of Adams & Foley as reported by Fischer et al.; (3) Absence of signs of hepatorenal syndrome assessed according to the criteria established at the symposium held in Sassari.
Exclusion criteria	Not reported
Recruitment/selection of patients	Consecutive patients fulfilling the inclusion criteria between August 1979 and June 1980
Age, gender and ethnicity	Age – other: Mean age only: Intervention=57 versus control=60.8. Gender (M:F): 21/13. Ethnicity: Not reported.
Further population details	1. Grade of acute hepatic encephalopathy: Grade 3–4. 2. Severity of the underlying liver disease: Not applicable/ not stated/unclear
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Branch chain amino acids – IV branch chain amino acids. BS 692 (leucine 1.1%, isoleucine 0.9%, valine 0,8% in 20% dextrose): 60 ml/hour for the first 24 hours, and 80 ml/hour thereafter until 48 hours after mental recovery. Duration: Up to 48 hours (following this, patients who did not recover underwent a combination treatment). Concurrent medication/care: None. (n=20) Intervention 2: Non-absorbable disaccharides – oral lactulose. Lactulose via (1) nasogastric tube: 30–40 g every 4 hours until catharsis, thereafter, the dose adjusted to ensure 2 bowel movements/day. Or (2) via rectal route for patients who could not receive lactulose orally: 200–300 g/day intermittent enemas. Duration: Until 48 hours (following this, patients who did not recover underwent a combination treatment). Concurrent medication/care:

Study (subsidiary papers)	Rossi-fanelli 1982[111] (Rossi fanelli 1986[109], Rossi 1984[110])
	Dextrose in isocaloric amounts and at the same rate as Group A.
Funding	Academic or government funding (Ministry of Health, Rome, Italy)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV BRANCH CHAIN AMINO ACIDS versus ORAL LACTULOSE Protocol outcome 1: Survival at end of study - Actual outcome: Number of deaths up to 10 days after mental recovery; Group 1: 4/17, Group 2: 5/17; risk of bias: low; indirectness of outcome: no indirectness Protocol outcome 2: No improvement in hepatic encephalopathy (improvement defined as a partial or complete resolution of clinical symptoms of hepatic encephalopathy. Some studies may assess improvement using electrophysiological or psychometrical testing, PSE score, or blood plasma ammonia levels) at end of study - Actual outcome: Mean time of arousal; Group 1: mean 27.6 hours (SD 26.7); n=17, Group 2: mean 31.5 hours (SD 18.1); n=17; risk of bias: low; indirectness of outcome: no indirectness - Actual outcome: Responsive: number of participants achieving complete mental recovery (consciousness regained and returned to grade 0 hepatic encephalopathy) ; Group 1: 12/17, Group 2: 8/17; risk of bias: low; indirectness of outcome: no indirectness - Actual outcome: Unresponsive: number of participants achieving complete mental recovery (consciousness regained and returned to grade 0 hepatic encephalopathy) ; Group 1: 5/17, Group 2: 9/17; risk of bias: low; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Quality of life at end of study; discharge from hospital at end of study; adverse events (diarrhoea, flatulence, abdominal pain, nausea, GI bleeding, renal failure) at end of study

Study	Sharma 2013[128]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	N/A (n=120)
Countries and setting	Conducted in India; setting: tertiary care
Line of therapy	First line
Duration of study	Intervention + follow up: Treatment was given until complete recovery of hepatic encephalopathy or a maximum of 10 days. Patients were followed till they were discharged or died during their hospital stay
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosis of cirrhosis was based on laboratory tests, endoscopic

Study	Sharma 2013[128]
	evidence, sonographic findings, and liver histology if available.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients at a tertiary care centre aged 18 to 80 years with liver cirrhosis and overt hepatic encephalopathy
Exclusion criteria	Serum creatinine >1.5 mg/dL on admission; active alcohol intake <4 weeks before present episode; other metabolic encephalopathies; hepatocellular carcinoma; degenerative central nervous system disease or major psychiatric illness; and significant comorbidity
Recruitment/selection of patients	Unclear
Age, gender and ethnicity	Age – mean (SD): 39.4 (9.6). Gender (M:F): 89:31. Ethnicity: Not reported.
Further population details	1. Grade of acute hepatic encephalopathy: Grade 3–4 (81.7% had grade 3 or 4 on admission, 18.3% grade 2). 2. Severity of the underlying liver disease: Child-Pugh B or C.
Extra comments	The mean age of the participants is relatively younger than that seen in other studies
Indirectness of population	Serious indirectness: 18 patients were on regular lactulose for prophylaxis of hepatic encephalopathy
Interventions	(n=63) Intervention 1: Oral non-absorbable antibiotics – rifaximin. One 400 mg capsule, 3 times a day. Duration: Until complete recovery of hepatic encephalopathy or a maximum of 10 days if no recovery; discharge from hospital; or death. Concurrent medication/care: Lactulose 30 to 60 ml, 3 times a day. (n=57) Intervention 2: Non-absorbable disaccharides – oral lactulose. Lactulose via nasogastric tube, 30 to 60 ml, 3 times a day. Duration: Until complete recovery of hepatic encephalopathy or a maximum of 10 days if no recovery; discharge from hospital; or death. Concurrent medication/care: Placebo capsule resembling rifaximin, 3 times a day.
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RIFAXIMIN + LACTULOSE versus ORAL LACTULOSE

Protocol outcome 1: Survival at end of study
- Actual outcome: Mortality; Group 1: 15/63, Group 2: 28/57; risk of bias: low; indirectness of outcome: no indirectness

Protocol outcome 2: No improvement in hepatic encephalopathy (improvement defined as a partial or complete resolution of clinical symptoms of hepatic encephalopathy. Some studies may assess improvement using electrophysiological or psychometrical testing, PSE score, or blood plasma ammonia levels) at end of study

Study	Sharma 2013[128]
- Actual outcome: Number of participants achieving complete reversal of hepatic encephalopathy (according to West Haven criteria) at within 10 days; Group 1: 48/63, Group 2: 29/57; risk of bias: low; indirectness of outcome: no indirectness Protocol outcome 3: Discharge from hospital at end of study - Actual outcome: Length of hospital stay; Group 1: mean 5.8 days (SD 3.4); n=63, Group 2: mean 8.2 days (SD 4.6); n=57; risk of bias: low; indirectness of outcome: no indirectness Protocol outcome 4: Adverse events (diarrhoea, flatulence, abdominal pain, nausea, GI bleeding, renal failure) at end of study - Actual outcome: Side effects related to study medications; Group 1: 12/63, Group 2: 10/57; risk of bias: low; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Quality of life at end of study

Study	Strauss 1986[140]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	1 (n=29)
Countries and setting	Conducted in Brazil; setting: Hospital Heliopolis and Hospital Municipal, Sao Paulo, Brazil
Line of therapy	First line
Duration of study	Intervention: Neomycin group received intervention until 2 days after complete recovery of consciousness, the enriched branched chain amino acid group received the intervention until complete recovery of consciousness.
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: 'mainly on a histological basis'
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Diagnosed cirrhosis. Hepatic encephalopathy characterised as a disturbance of consciousness assessed semiquantitatively as grades I to IV.
Exclusion criteria	If previous to randomisation, a specific treatment for the hepatic encephalopathy (neomycin, lactulose or L-dopa) had already been started.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age – range: 28–67. Gender (M:F): 26 men, 3 women. Ethnicity: Not reported.
Further population details	1. Grade of acute hepatic encephalopathy: Grade 1–2 (22/32 were grade 1 or 2, the other 10 were grade 3). 2.

Study	Strauss 1986[140]
	Severity of the underlying liver disease: Not applicable/not stated/unclear.
Extra comments	Patients were treated equally for precipitating factors of the exogenous encephalopathy. Diuretics were always withdrawn and gastrointestinal bleeding due to oesophageal varices was treated with Sungstaken-Blakemore balloon and blood transfusion. Potassium was supplemented if necessary and laxatives were used only in obstipated patients. Infections were treated with antibiotics, mainly ampicillin (1–4 g orally) or according to specific antibiograms.
Indirectness of population	No indirectness
Interventions	(n=16) Intervention 1: Branch chain amino acids – IV branch chain amino acids. F080, which contains higher percentages of branched chain amino acids and reduced amounts of aromatic amino acids. Continuous intravenous administration of 60 g of protein equivalent in 24 hours. A hypertonic glucose solution was given simultaneously, according to the needs of the patient. Duration: Until recovery. Concurrent medication/care: Grades I and II were allowed to eat, receiving initially a diet of 10 g protein. Fluid and electrolyte supplementation were made according to each patient's needs. As the patient improved, dietary protein was increased (20 g every second day) while the parenteral solution was decreased until its total withdrawal after complete recovery of consciousness. (n=16) Intervention 2: Oral non-absorbable antibiotics – neomycin. 1 g of neomycin sulphate orally every four hours. Intestinal cleansing was performed every 12 hours, with a litre of water and 2 g of neomycin. As patients improved, dietary protein was increased (20 g every second day) while the dosage of neomycin was decreased (2 g every second day) until its total withdrawal after two days of complete recovery of consciousness. Duration: Until recovery. Concurrent medication/care: Grades I and II were allowed to eat, receiving initially a diet of 10 g protein. Fluid and electrolyte supplementation were made according to each patient's needs. As the patient improved, dietary protein was increased (20 g every second day) while the parenteral solution was decreased until its total withdrawal after complete recovery of consciousness.
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV BRANCH CHAIN AMINO ACIDS versus NEOMYCIN

Protocol outcome 1: Survival at end of study
- Actual outcome: Mortality during treatment; Group 1: 2/16, Group 2: 2/16; risk of bias: high; indirectness of outcome: no indirectness

Protocol outcome 2: No improvement in hepatic encephalopathy (improvement defined as a partial or complete resolution of clinical symptoms of hepatic encephalopathy. Some studies may assess improvement using electrophysiological or psychometrical testing, PSE score, or blood plasma ammonia levels) at end of study

Study	Strauss 1986[140]
- Actual outcome: Time to recovery during treatment; Group 1: mean 33.4 hours (SD 21.1); n=14, Group 2: mean 70.8 hours (SD 28.8); n=14; risk of bias: high; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Quality of life at end of study; discharge from hospital at end of study; adverse events (diarrhoea, flatulence, abdominal pain, nausea, GI bleeding, renal failure) at end of study

Study	Strauss 1992[141]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	1 (n=39)
Countries and setting	Conducted in Brazil; setting: hospital
Line of therapy	First line
Duration of study	Intervention + follow up: Patients followed up and analysed for mortality for 1 year after discharge
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: histopathological and/or clinical-biochemical diagnosis of hepatic cirrhosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Define
Exclusion criteria	Define
Recruitment/selection of patients	January 1986 to December 1990
Age, gender and ethnicity	Age – mean (SD): 49.23 (11.39). Gender (M:F): 34/5. Ethnicity: not reported.
Further population details	1. Grade of acute hepatic encephalopathy: Grade 1–2 (majority grade I or II [I: 41.0%; II: 23.1%; III: 35.9%; IV: 0%]). 2. Severity of the underlying liver disease: Child-Pugh B or C (12.8% CPB and 87.2% CPC).
Extra comments	8 of the 39 patients randomised had previous episodes of hepatic encephalopathy (but people with chronic hepatic encephalopathy or on specific treatment for hepatic encephalopathy at the time of randomisation or in the week before it were excluded)
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Oral non-absorbable antibiotics – neomycin. Neomycin sulphate 1 g every 4 hours (6 g/day; oral for grades I and II, by nasogastric tube for grades II and IV) and 2 g in 500 ml of tepid water every 12 hours for

Study	Strauss 1992[141]
	intestinal cleansing. Patients in grades III and IV also received 60 g/day of an enriched solution of BCAAs (Portamin) with IV hypertonic glucose. When improvement to grade 0 hepatic encephalopathy observed, neomycin decreased to 2 g each second day (and if BCAAs given, decreased by 20 g every other day). Duration: unclear. Concurrent medication/care: Grade I and II hepatic encephalopathy: oral diet continued but protein restricted to 10 g/day; Grade III and IV hepatic encephalopathy: IV administration of necessary calories. When improvement to grade 0 hepatic encephalopathy observed, dietary protein increased to 20 g/day. (n=19) Intervention 2: Placebo. Patients in grades III and IV also received 60 g/day of an enriched solution of BCAAs (Portamin) with IV hypertonic glucose. When improvement to grade 0 hepatic encephalopathy observed, if BCAAs given, decreased by 20 g every other day. Duration: Unclear. Concurrent medication/care: Grade I and II hepatic encephalopathy: Oral diet continued but protein restricted to 10 g/day; Grade III and IV hepatic encephalopathy: IV administration of necessary calories. When improvement to grade 0 hepatic encephalopathy observed, dietary protein increased to 20 g/day.
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NEOMYCIN versus PLACEBO Protocol outcome 1: Survival at end of study - Actual outcome: Therapeutic failure and death at fifth day of treatment; Group 1: 2/20, Group 2: 2/19; risk of bias: high; indirectness of outcome: no indirectness Protocol outcome 2: No improvement in hepatic encephalopathy (improvement defined as a partial or complete resolution of clinical symptoms of hepatic encephalopathy. Some studies may assess improvement using electrophysiological or psychometrical testing, PSE score, or blood plasma ammonia levels) at end of study - Actual outcome: Time until regression to grade 0 hepatic encephalopathy; Group 1: mean 36.11 hours (SD 23.04); n=20, Group 2: mean 49.47 hours (SD 21.92); n=19; risk of bias: high; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Quality of life at end of study; discharge from hospital at end of study; adverse events (diarrhoea, flatulence, abdominal pain, nausea, GI bleeding, renal failure) at end of study

Study	Sushma 1992[143]
Study type	RCT (patient randomised; parallel)

Study	Sushma 1992[143]
Number of studies (number of participants)	N/A (n=74)
Countries and setting	Conducted in India; setting: secondary care
Line of therapy	First line
Duration of study	Intervention + follow up: Until recovery or death
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosis of cirrhosis was made by liver biopsy or clinical criteria when liver biopsy was not possible
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Diagnosis of cirrhosis or had had a surgical portal-systemic anastomosis; hepatic encephalopathy of <7 days
Exclusion criteria	Treatment with lactulose for 24 hours or more before entry into the study or had active GI bleeding; history of neurological disease other than hepatic encephalopathy; refusal to enter study by the responsible next of kin
Recruitment/selection of patients	Consecutive patients with cirrhosis and hepatic encephalopathy admitted to the gastroenterology ward of a hospital
Age, gender and ethnicity	Age – mean (SD): Intervention 35.6 (18.4) versus control 37.9 (12.8). Gender (M:F): 56/18. Ethnicity: Not reported.
Further population details	1. Grade of acute hepatic encephalopathy: Not applicable/not stated/unclear. 2. Severity of the underlying liver disease: Not applicable/not stated/unclear.
Extra comments	Four out of the 74 patients had had portacaval shunt prior to entering the study. Out of these, 2 had cirrhosis and 2 had non-cirrhotic fibrosis.
Indirectness of population	No indirectness
Interventions	(n=38) Intervention 1: Sodium benzoate. Administered orally or via a nasogastric tube (if necessary), 5 mg twice daily (each dose dissolved in 30 ml of tap water). Duration: Until clinical recovery. Concurrent medication/care: Standard treatment for acute hepatic encephalopathy: twice daily bowel washes with tap water, maintenance of fluid and electrolyte levels, intake of at least 800 calories/day, restriction of oral intake of proteins to 20 mg/day in whom oral intake was possible. (n=36) Intervention 2: Non-absorbable disaccharides – oral lactulose. Administered orally or via a nasogastric tube (if necessary), initially at 30 ml every 8 hours, then adjusted to once in 24 hours to achieve 3 semi-formed stools/day. Duration: Until clinical recovery. Concurrent medication/care: Standard treatment for acute hepatic encephalopathy: twice daily bowel washes with tap water, maintenance of fluid and electrolyte levels, intake of at least 800 calories/day, restriction of oral intake of proteins to 20 mg/day in whom oral intake was possible.

Study	Sushma 1992[143]
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SODIUM BENZOATE versus ORAL LACTULOSE Protocol outcome 1: Survival at end of study - Actual outcome: Mortality during treatment; Group 1: 8/38, Group 2: 7/36; risk of bias: low; indirectness of outcome: no indirectness Protocol outcome 2: No improvement in hepatic encephalopathy (improvement defined as a partial or complete resolution of clinical symptoms of hepatic encephalopathy. Some studies may assess improvement using electrophysiological or psychometrical testing, PSE score, or blood plasma ammonia levels) at end of study - Actual outcome: Mean duration of therapy before complete clinical recovery at N/A; Group 1: mean 11.6 days (SD 6.4); n=38, Group 2: mean 12.8 days (SD 9.1); n=36; risk of bias: low; indirectness of outcome: no indirectness - Actual outcome: Number of participants with complete response (recovery to normal mental status with no evidence of asterixis); Group 1: 30/38, Group 2: 29/36; risk of bias: low; indirectness of outcome: no indirectness - Actual outcome: Number of participants who continued in grade 1+ mental status despite therapy for 21 days at 21 days; Group 1: 3/38, Group 2: 1/36; risk of bias: low; indirectness of outcome: no indirectness Protocol outcome 3: Adverse events (diarrhoea, flatulence, abdominal pain, nausea, GI bleeding, renal failure) at end of study - Actual outcome: Number of complications at during treatment; Group 1: 35/38, Group 2: 30/36; risk of bias: low; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Quality of life at end of study; discharge from hospital at end of study

Study	Uribe 1981[154]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	N/A (n=18)
Countries and setting	Conducted in Mexico; setting: hospital
Line of therapy	First line
Duration of study	Intervention time: Treatment continued until 48 hours after recovery then study was concluded
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: biopsy-proven cirrhosis
Stratum	Overall

Study	Uribe 1981[154]
Subgroup analysis within study	Not applicable
Inclusion criteria	Cirrhosis; developed within 24 hours an acute episode of hepatic encephalopathy (at least grade 2+ severity) plus 2 of the following abnormalities: arterial ammonia levels above 120ug% (normal <90ug%); abnormal slow waves in the EEG as blindly judged by a neurologist; time taken to perform an NCT at least double the normal range (>60 s, normal is >30 s) or patient unable to perform the test due to mental confusion or coma.
Exclusion criteria	Use of analgesics of sedatives; presented with acute renal failure; required or had ingested antibiotics; presented with active bleeding; presented with anorectal disease; had a history of previous neurological disease other than hepatic encephalopathy; no consent to participate from relatives.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age – mean (SD): Neomycin: 55 (9); Lactose: 51 (11). Gender (M:F): 6/12. Ethnicity: Not reported.
Further population details	1. Grade of acute hepatic encephalopathy: Not applicable/not stated/unclear (West Haven criteria not reported). 2. Severity of the underlying liver disease: Not applicable/not stated/unclear
Indirectness of population	No indirectness
Interventions	(n=8) Intervention 1: Non-absorbable disaccharides – lactulose enema. 1 litre lactose (20%) enema. Duration: Until 48 hours after recovery. Concurrent medication/care: 2 placebo tablets which looked identical to neomycin tablets Comments: This is lactose and not lactulose. (n=10) Intervention 2: Oral non-absorbable antibiotics – neomycin. Two 0.5 g neomycin tablets. Duration: Until 48 hours after recovery. Concurrent medication/care: 1 litre starch (10%) enema bottled in identical containers as lactose enema.
Funding	Academic or government funding (Grants from Consejo Nacional de Ciencia y Tecnologia; Academia Nacional de Medicina, Chinoin Award)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LACTOSE ENEMA versus NEOMYCIN

Protocol outcome 1: Survival at end of study
- Actual outcome: Mortality within 1 month from the end of the study; Group 1: 1/8, Group 2: 1/10; risk of bias: high; indirectness of outcome: no indirectness

Protocol outcome 2: No improvement in hepatic encephalopathy (improvement defined as a partial or complete resolution of clinical symptoms of hepatic encephalopathy. Some studies may assess improvement using electrophysiological or psychometrical testing, PSE score, or blood plasma ammonia levels) at end of study

Study	Uribe 1981[154]
- Actual outcome: Clinical-biochemical improvement (improvement of 1 grade in mental state [Conn's grading 0–4], a reduction of 30 s in time taken to perform the number connection test [NCT] and ammonia reduction of 50ug%); Group 1: 7/8, Group 2: 7/10; risk of bias: high; indirectness of outcome: no indirectness Protocol outcome 3: Adverse events (diarrhoea, flatulence, abdominal pain, nausea, GI bleeding, renal failure) at end of study - Actual outcome: Treatment side effects; Group 1: 0/8, Group 2: 0/10; risk of bias: high; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Quality of life at end of study; discharge from hospital at end of study

Study	Uribe 1987[155]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	1 (n=15 [placebo arm discontinued, trial continued to recruit 45 people for lactitol versus lactose comparison])
Countries and setting	Conducted in Switzerland; setting: not reported
Line of therapy	First line
Duration of study	Intervention time: Response-dependent
Method of assessment of guideline condition	Method of assessment /diagnosis not stated: Cirrhosis diagnosis method unclear
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Cirrhosis; development within 24 hour of an acute episode of PSE, characterized by encephalopathy of at least Grade 2+ severity (3) plus two of the following abnormalities-(i) arterial ammonia levels above 120 µg% (n ≤ 90 µg%); (ii) abnormal slow waves in the electroencephalogram, and (iii) protracted performance of a number connection test (NCT) of at least double the normal time (n <30 s) or inability to perform the test due to mental confusion or coma. PSE could be precipitated by nitrogenous substances (dietary proteins, use of diuretics or idiopathic [endogenous] factors).
Exclusion criteria	(i) Required or had received systemic or rectal antibiotics; (ii) presented with active gastrointestinal bleeding; (iii) presented with anorectal disease; (iv) had a history of previous neurological disease other than PSE, or (v) the relatives refused to sign a consent form.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age – other: not reported. Gender (M:F): not reported. Ethnicity: not reported.
Further population details	1. Grade of acute hepatic encephalopathy: Not applicable/not stated/unclear (at least grade 2+). 2. Severity of the

Study	Uribe 1987[155]
	underlying liver disease: Not applicable/not stated/unclear
Indirectness of population	No indirectness
Interventions	(n=10) Intervention 1: Non-absorbable disaccharides – lactulose enema. 20% lactitol enema (Lactitol, Laboratories Zyma SA, Nyon, Switzerland). Duration variable and response-dependent. Concurrent medication/care: not reported. (n=5) Intervention 2: Placebo. Tap water enema at a dose of 1 litre three times daily. Duration variable and response-dependent. Concurrent medication/care: not reported.
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LACTITOL ENEMA versus PLACEBO Protocol outcome 1: Survival at end of study - Actual outcome: Mortality at variable and response-dependent; Group 1: 0/10, Group 2: 3/5; risk of bias: very high; indirectness of outcome: no indirectness Protocol outcome 2: No improvement in hepatic encephalopathy (improvement defined as a partial or complete resolution of clinical symptoms of hepatic encephalopathy. Some studies may assess improvement using electrophysiological or psychometrical testing, PSE score, or blood plasma ammonia levels) at end of study - Actual outcome: Therapeutic response (defined as (i) sustained improvement of one grade in mental state during ≤48 hours or (ii) improvement of more than two grades in mental state) at variable and response-dependent; Group 1: 10/10, Group 2: 1/5; risk of bias: very high; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Quality of life at end of study; discharge from hospital at end of study; adverse events (diarrhoea, flatulence, abdominal pain, nausea, GI bleeding, renal failure) at end of study

Study	Vilstrup 1990[156]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	N/A (n=77)
Countries and setting	Conducted in Denmark; setting: secondary care
Line of therapy	First line
Duration of study	Intervention time: Until recovery or death

Study	Vilstrup 1990[156]
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Cirrhosis and hepatic encephalopathy Grade II/III/IV, according to the Fogarty classification
Exclusion criteria	Non-hepatic encephalopathy or psychosis including drug effects; lack of central venous access; oliguria that rendered the planned regimens impossible; malignancy with an expected life span of <1 year
Recruitment/selection of patients	Consecutive patients fulfilling the inclusion criteria in 3 hospitals
Age, gender and ethnicity	Age – M=mean (SD): Intervention 55 (9) versus control 56 (12). Gender (M:F): 47/18. Ethnicity: Not reported.
Further population details	1. Grade of acute hepatic encephalopathy: Not applicable/not stated/unclear. 2. Severity of the underlying liver disease: Not applicable/not stated/unclear.
Indirectness of population	No indirectness
Interventions	(n=38) Intervention 1: Branch chain amino acids – IV branch chain amino acids. IV BCAA (8%) via central venous lines by infusion pumps at 12.5 ml/kg/day throughout day and night. Duration: Up to recovery or death (maximum of 16 days treatment). Concurrent medication/care: Glucose (50%) 12.5 ml/kg/day + Lactulose syrup 60 ml/day + Cimetidine 200 to 400mg/day + Minerals + Vitamins + other medications according to needs. (n=39) Intervention 2: Placebo. Glucose (8%) 12.5 ml/kg/day in bottles that look identical to those for BCAA. Duration: Up to recovery or death (maximum of 16 days treatment). Concurrent medication/care: Glucose (50%) 12.5 ml/kg/day + Lactulose syrup 60 ml/day + Cimetidine 200 to 400 mg/day + Minerals + Vitamins + other medications according to needs.
Funding	Academic or government funding (Grants from the Borgen Foundation, the Danish Medical Research Council, the Ebba Celinder's Foundation, and the Johann and Hanne Weimann, nee Seedorff's Foundation)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV BRANCH CHAIN AMINO ACIDS versus GLUCOSE

Protocol outcome 1: Survival at end of study
- Actual outcome: Number of participants who died at 16 days; Group 1: 11/32, Group 2: 10/33; risk of bias: low; indirectness of outcome: no indirectness

Protocol outcome 2: No improvement in hepatic encephalopathy (improvement defined as a partial or complete resolution of clinical symptoms of hepatic encephalopathy. Some studies may assess improvement using electrophysiological or psychometrical testing, PSE score, or blood plasma ammonia levels) at end of

Study	Vilstrup 1990[156]
study - Actual outcome: Number of participants who woke up (to hepatic encephalopathy grade 0 or I by Fogarty classification) at 16 days; Group 1: 17/32, Group 2: 17/33; risk of bias: low; indirectness of outcome: no indirectness - Actual outcome: Number of participants who had treatment failures other than death (hepatic encephalopathy deeper than grade I [Fogarty classification] after 16 days despite other improvements defined as failure) at 16 days; Group 1: 4/32, Group 2: 6/33; risk of bias: low; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Quality of life at end of study; discharge from hospital at end of study; adverse events (diarrhoea, flatulence, abdominal pain, nausea, GI bleeding, renal failure) at end of study

Study	Wahren 1983[157]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	1 (n=50)
Countries and setting	Conducted in France, Sweden; setting: five medical centres
Line of therapy	First line
Duration of study	Intervention + follow up: A maximum of 5 days intervention. Last blood collected the morning after the end of the intervention.
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: EEG and neurological examinations
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Clinical and laboratory evidence of cirrhosis verified histologically by liver biopsy, autopsy, angiography, laparoscopy, laparotomy
Exclusion criteria	Patients with severe respiratory failure, septic shock or uremia
Recruitment/selection of patients	17 from Paris, 12 from Marseille, 7 from Montpellier, 7 from Lille, 7 from Stockholm
Age, gender and ethnicity	Age – mean (SD): BCAA: 59 (2), placebo: 52 (2). Gender (M:F): BCAA group: 13 male, 12 female. Placebo group: 15 male, 10 female. Ethnicity: Not reported.
Extra comments	Grade of hepatic encephalopathy at baseline. BCAA: grade II: 1, grade III: 10, grade IVa-IVc: 14. Placebo: grade II: 1, grade III: 8, grade IVa-IVc: 16 EEG grade IVa-IVdat baseline. 40% in BCAA group, 82% in placebo group.
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Branch chain amino acids – IV branch chain amino acids. 20 g/litre in a solution containing 70% leucine, 20% valine, 10% isoleucine, in 5% glucose. 20 hours per day. Duration: Given until 1 day after hepatic encephalopathy had improved to grade 0 or 1, for a maximum of 5 days. Concurrent medication/care: Five patients in this group also received conventional therapy involving lactulose and/or neomycin. Four patients received antibiotics. (n=25) Intervention 2: Placebo. 5% glucose given 20 hours per day. Duration: Given until 1 day after hepatic encephalopathy had improved to grade 0 or 1, for a maximum of 5 days. Concurrent medication/care: Three patients in this group also received conventional therapy involving lactulose and/or neomycin. Seven patients received antibiotics.
Funding	Study funded by industry (Industry, medical research council and a charity)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV BRANCH CHAIN AMINO ACIDS versus PLACEBO Protocol outcome 1: Survival at end of study - Actual outcome: Mortality during treatment at 5 days; Group 1: 10/25, Group 2: 5/25; risk of bias: High; indirectness of outcome: no indirectness Protocol outcome 2: No improvement in hepatic encephalopathy (improvement defined as a partial or complete resolution of clinical symptoms of hepatic encephalopathy. Some studies may assess improvement using electrophysiological or psychometrical testing, PSE score, or blood plasma ammonia levels) at end of study - Actual outcome: Positive response to treatment at 5 days; Group 1: 10/20, Group 2: 11/22; risk of bias: high; indirectness of outcome: no indirectness - Actual outcome: No response to treatment at 5 days; Group 1: 7/20, Group 2: 7/22; risk of bias: high; indirectness of outcome: no indirectness - Actual outcome: Negative response to treatment at 5 days; Group 1: 3/20, Group 2: 4/22; risk of bias: high; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Quality of life at end of study; discharge from hospital at end of study; adverse events (diarrhoea, flatulence, abdominal pain, nausea, GI bleeding, renal failure) at end of study