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Antibiotic treatment for spontaneous bacterial peritonitis in people with decompensated liver cirrhosis: a network meta-analysis (Review)

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[Intervention Review]

Antibiotic treatment for spontaneous bacterial peritonitis in people with decompensated liver cirrhosis: a network meta-analysis

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ABSTRACT

Background

Approximately 2.5% of all hospitalisations in people with cirrhosis are for spontaneous bacterial peritonitis (SBP). Antibiotics, in addition to supportive treatment (fluid and electrolyte balance, treatment of shock), form the mainstay treatments of SBP. Various antibiotics are available for the treatment of SBP, but there is uncertainty regarding the best antibiotic for SBP.

Objectives

To compare the benefits and harms of different antibiotic treatments for spontaneous bacterial peritonitis (SBP) in people with decompensated liver cirrhosis.

Search methods

We searched CENTRAL, MEDLINE, Embase, Science Citation Index Expanded, World Health Organization International Clinical Trials Registry Platform, and trials registers until November 2018 to identify randomised clinical trials on people with cirrhosis and SBP.

Selection criteria

We included only randomised clinical trials (irrespective of language, blinding, or publication status) in adults with cirrhosis and SBP. We excluded randomised clinical trials in which participants had previously undergone liver transplantation.

Data collection and analysis

Two review authors independently identified eligible trials and collected data. The outcomes for this review included mortality, serious adverse events, any adverse events, resolution of SBP, liver transplantation, and other decompensation events. We performed a network meta-analysis with OpenBUGS using Bayesian methods and calculated the odds ratio, rate ratio, and hazard ratio with 95% credible

intervals (CrIs) based on an available-case analysis, according to the National Institute of Health and Care Excellence (NICE) Decision Support Unit guidance.

Main results

We included a total of 12 trials (1278 participants; 13 antibiotics) in the review. Ten trials (893 participants) were included in one or more outcomes in the review. The trials that provided the information included patients having cirrhosis with or without other features of decompensation of varied aetiologies. The follow-up in the trials ranged from one week to three months. All the trials were at high risk of bias. Only one trial was included under each comparison for most of the outcomes. Because of these reasons, there is very low certainty in all the results. The majority of the randomised clinical trials used third-generation cephalosporins, such as intravenous ceftriaxone, cefotaxime, or ciprofloxacin as one of the interventions.

Overall, approximately 75% of trial participants recovered from SBP and 25% of people died within three months. There was no evidence of difference in any of the outcomes for which network meta-analysis was possible: mortality (9 trials; 653 participants), proportion of people with any adverse events (5 trials; 297 participants), resolution of SBP (as per standard definition, 9 trials; 873 participants), or other features of decompensation (6 trials; 535 participants). The effect estimates in the direct comparisons (when available) were very similar to those of network meta-analysis. For the comparisons where network meta-analysis was not possible, there was no evidence of difference in any of the outcomes (proportion of participants with serious adverse events, number of adverse events, and proportion of participants requiring liver transplantation). Due to the wide CrIs and the very low-certainty evidence for all the outcomes, significant benefits or harms of antibiotics are possible.

None of the trials reported health-related quality of life, number of serious adverse events, or symptomatic recovery from SBP.

Funding: the source of funding for two trials were industrial organisations who would benefit from the results of the trial; the source of funding for the remaining 10 trials was unclear.

Authors' conclusions

Short-term mortality after SBP is about 25%. There is significant uncertainty about which antibiotic therapy is better in people with SBP.

We need adequately powered randomised clinical trials, with adequate blinding, avoiding post-randomisation dropouts (or performing intention-to-treat analysis), and using clinically important outcomes, such as mortality, health-related quality of life, and adverse events.

PLAIN LANGUAGE SUMMARY

Antibiotic treatment for spontaneous bacterial peritonitis in people with advanced liver disease

What is the aim of this Cochrane Review?

To find out the best available antibiotic for spontaneous bacterial peritonitis (fluid collection in the tummy (abdomen), infected with bacteria) in people with advanced liver disease (liver cirrhosis, or late stage scarring of the liver with complications). The abnormal buildup of fluid in people with liver cirrhosis is called ascites. Sometimes, this fluid may get infected with bacteria, with no obvious source of infection. This is called 'spontaneous bacterial peritonitis'. The main treatment of spontaneous bacterial peritonitis is antibiotics, but it is unclear which antibiotic is best for treating it. The authors collected and analysed all relevant studies to answer this question and found 12 randomised clinical trials (participants receive the treatment based on methods similar to a coin toss; this is to ensure that the people who receive the different treatments are similar in all aspects except the treatment, so that any differences in the results between the treatments can be attributed to the treatment rather than differences in the type of people who received the treatment). During the analysis of data, authors used standard Cochrane techniques, which allows comparison of two treatments at a time. Authors also used advanced techniques, that allows comparison of many treatments at the same time (usually referred as 'network meta-analysis' or 'multiple treatment comparisons'). The aim is to gather reliable evidence on the relative benefits and harms of the different antibiotics.

Date of literature search
November 2018.

Key messages
None of the studies were conducted without flaws, and because of the very low certainty in the results, the authors cannot suggest which antibiotic, given alone or in combination to remove the bacteria from one's tummy, is better or worse than other antibiotics in the treatment of spontaneous bacterial peritonitis.

The funding source was unclear in 10 studies; industrial organisations funded two studies.

What was studied in the review?

This review studied people, of any sex, age, and origin, with advanced liver disease due to various causes, and who had developed spontaneous bacterial peritonitis. People were administered different antibiotics for the treatment of spontaneous bacterial peritonitis. The authors excluded studies with liver transplanted participants and bacterial peritonitis due to other causes. The participants' age, when

reported, ranged from 42 to 60 years. The number of females, when reported, ranged from 18 to 42 out of 100. The administered antibiotic groups were cephalosporins, penicillins, and quinolones. The review authors wanted to gather and analyse data on death, quality of life, serious and non-serious complications, time to liver transplantation (replacement of a diseased liver with a healthy one), time until disappearance of spontaneous bacterial peritonitis, and disappearance of symptoms.

What were the main results of the review?

The 12 studies included a small number of participants (1278 participants). The study data were sparse; 10 studies with 893 participants provided data for analyses. Follow-up in the trials ranged from one week to three months. The review shows the following.

- Out of the 13 different antibiotics compared in the trials, ceftriaxone and cefotaxime administered into the vein, were most commonly used.

- The type of antibiotic provided may make no difference to the number or percentage of people with serious complications or with any complications; number of (any) complications per person; percentage of people undergoing liver transplantation; or who recovered from spontaneous bacterial peritonitis as per laboratory tests, or other complications of liver cirrhosis.

- Twenty-five out of every 100 people died within three months, and 75 out of every 100 people recovered from spontaneous bacterial peritonitis.

- None of the trials reported health-related quality of life, number of serious adverse events, or symptomatic recovery from spontaneous bacterial peritonitis.

- We have very low confidence in the overall results. Whether some antibiotics may cause important or less important benefits or harms compared to others when given to people with advanced liver disease and spontaneous bacterial peritonitis is questionable.

- We need data from trials of proper design and quality in order to be able to clarify the best antibiotic for spontaneous bacterial peritonitis.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

Antibiotic treatment for spontaneous bacterial peritonitis in people with decompensated liver cirrhosis

Patient or population: people with cirrhosis and spontaneous bacterial peritonitis

Settings: secondary or tertiary care

Intervention: various interventions

Comparison: ceftriaxone

Follow-up period: 1 week to 3 months

Network geometry plots: Figure 1

Interventions	Relative effect (95% CrI)	Anticipated absolute effect* (95% CrI)			Certainty of evidence	Ranking**
		Ceftriaxone	Various interventions	Difference		
All-cause mortality Total studies: 7 Total participants: 458						
Cefotaxime (1 RCT; 37 participants)	**HR 0.56** (0.11 to 2.28) Network estimate	**263 per 1000**	**146 per 1000** (28 to 599)	**117 fewer per 1000** (235 fewer to 336 more)	**Very low**[a,b,c]	-
Ciprofloxacin (1 RCT; 35 participants)	**HR 0.65** (0.12 to 2.72) Network estimate	**263 per 1000**	**171 per 1000** (31 to 717)	**92 fewer per 1000** (232 fewer to 454 more)	**Very low**[a,b,c]	-
Ceftazidime (No direct RCT)	**HR 1.15** (0.17 to 6.37) Network estimate	**263 per 1000**	**301 per 1000** (45 to 1000)	**38 more per 1000** (218 fewer to 737 more)	**Very low**[a,b,c]	-
Amikacin (No direct RCT)	**HR 0.76** (0.09 to 5.90) Network estimate	**263 per 1000**	**201 per 1000** (24 to 1000)	**62 fewer per 1000** (239 fewer to 737 more)	**Very low**[a,b,c]	-
Cefixime	**HR 1.26** (0.26 to 6.90)	**263 per 1000**	**331 per 1000** (68 to 1000)	**68 more per 1000** (195 fewer to 737 more)	**Very low**[a,b,c]	-

(1 RCT; 38 participants)	Network estimate					
Cefonicid (1 RCT; 60 participants)	**HR 1.30** (0.52 to 3.24) Network estimate	**263 per 1000**	**341 per 1000** (138 to 853)	**78 more per 1000** (126 fewer to 590 more)	**Very low**[a,b,c]	-
Meropenem plus daptomycin (No direct RCT)	**HR 0.64** (0.05 to 6.13) Network estimate	**263 per 1000**	**169 per 1000** (14 to 1000)	**94 fewer per 1000** (249 fewer to 737 more)	**Very low**[a,b,c]	-
Ofloxacin (No direct RCT)	**HR 0.56** (0.09 to 2.93) Network estimate	**263 per 1000**	**147 per 1000** (23 to 770)	**116 fewer per 1000** (240 fewer to 507 more)	**Very low**[a,b,c]	-
Health-related quality of life						
None of the trials reported this outcome						
Serious adverse events (proportion of participants)						
None of the trials with ceftriaxone as control group reported this outcome						
Serious adverse events (number of events per participant)						
None of the trials reported this outcome						
Adverse events (proportion of participants) **Total studies: 5** **Total participants: 297**						
Cefotaxime (1 RCT; 37 participants)	**OR 0.64** (0.15 to 2.62) Network estimate	**67 per 1000**	**44 per 1000** (10 to 157)	**23 fewer per 1000** (56 fewer to 91 more)	**Very low**[a,b,c]	-
Ciprofloxacin (1 RCT; 35 participants)	**OR 1.02** (0.24 to 4.16) Network estimate	**67 per 1000**	**68 per 1000** (17 to 229)	**1 more per 1000** (50 fewer to 162 more)	**Very low**[a,b,c]	-
Ceftazidime (No direct RCT)	**OR 1.97** (0.38 to 10.18) Network estimate	**67 per 1000**	**123 per 1000** (27 to 421)	**57 more per 1000** (40 fewer to 354 more)	**Very low**[a,b,c]	-
Amikacin (No direct RCT)	**OR 0.69** (0.04 to 10.94)	**67 per 1000**	**47 per 1000** (3 to 439)	**20 fewer per 1000** (64 fewer to 372 more)	**Very low**[a,b,c]	-

	Network estimate					
Cefonicid (1 RCT; 60 participants)	**OR 1.00** (0.10 to 10.16) Network estimate	**67 per 1000**	**67 per 1000** (7 to 420)	**0 fewer per 1000** (60 fewer to 354 more)	**Very low**[a,b,c]	-
Meropenem plus daptomycin (No direct RCT)	**OR 1.20** (0.10 to 13.53) Network estimate	**67 per 1000**	**79 per 1000** (7 to 491)	**12 more per 1000** (60 fewer to 425 more)	**Very low**[a,b,c]	-
Adverse events (number of events per participant)						
None of the trials with ceftriaxone as control group reported this outcome						
Liver transplantation						
None of the trials with ceftriaxone as control group reported this outcome						
Spontaneous bacterial peritonitis (symptomatic)						
None of the trials reported this outcome						
Spontaneous bacterial peritonitis (as per definition used for spontaneous bacterial peritonitis) **Total studies: 7** **Total participants: 638**						
Cefotaxime (1 RCT; 37 participants)	**HR 0.90** (0.42 to 1.86) Network estimate	**733 per 1000**	**661 per 1000** (308 to 1000)	**73 fewer per 1000** (425 fewer to 267 more)	**Very low**[a,b,c]	-
Ciprofloxacin (2 RCT; 275 participants)	**HR 0.93** (0.69 to 1.25) Network estimate	**733 per 1000**	**679 per 1000** (504 to 916)	**54 fewer per 1000** (230 fewer to 183 more)	**Very low**[a,b,c]	-
Ceftazidime (No direct RCT)	**HR 0.97** (0.55 to 1.72) Network estimate	**733 per 1000**	**713 per 1000** (403 to 1000)	**21 fewer per 1000** (330 fewer to 267 more)	**Very low**[a,b,c]	-
Amikacin (No direct RCT)	**HR 0.54** (0.17 to 1.62) Network estimate	**733 per 1000**	**393 per 1000** (126 to 1000)	**340 fewer per 1000** (608 fewer to 267 more)	**Very low**[a,b,c]	-
Cefixime	**HR 0.78** (0.32 to 1.90)	**733 per 1000**	**575 per 1000** (232 to 1000)	**159 fewer per 1000** (501 fewer to 267 more)	**Very low**[a,b,c]	-

(1 RCT; 38 participants)	Network estimate					
Meropenem plus daptomycin (No direct RCT)	**HR 1.29** (0.43 to 3.92) Network estimate	**733 per 1000**	**944 per 1000** (315 to 1000)	**211 more per 1000** (419 fewer to 267 more)	**Very low**[a,b,c]	-
Ofloxacin (No direct RCT)	**HR 1.12** (0.45 to 2.70) Network estimate	**733 per 1000**	**825 per 1000** (330 to 1000)	**91 more per 1000** (404 fewer to 267 more)	**Very low**[a,b,c]	-
Other features of decompensation (per participant) **Total studies: 5** **Total participants: 360**						
Cefotaxime (1 RCT; 37 participants)	**Rate ratio 1.22** (0.43 to 3.53) Network estimate	**368 per 1000**	**449 per 1000** (160 to 1301)	**80 more per 1000** (209 fewer to 933 more)	**Very low**[a,b,c]	-
Ciprofloxacin (1 RCT; 35 participants)	**Rate ratio 1.01** (0.32 to 3.16) Network estimate	**368 per 1000**	**373 per 1000** (119 to 1164)	**4 more per 1000** (249 fewer to 795 more)	**Very low**[a,b,c]	-
Ceftazidime (No direct RCT)	**Rate ratio 1.43** (0.40 to 5.19) Network estimate	**368 per 1000**	**527 per 1000** (147 to 1911)	**159 more per 1000** (222 fewer to 1542 more)	**Very low**[a,b,c]	-
Amikacin (No direct RCT)	**Rate ratio 1.28** (0.11 to 15.66) Network estimate	**368 per 1000**	**471 per 1000** (40 to 5769)	**103 more per 1000** (329 fewer to 5400 more)	**Very low**[a,b,c]	-
Meropenem plus daptomycin (No direct RCT)	**Rate ratio 2.19** (0.49 to 9.49) Network estimate	**368 per 1000**	**807 per 1000** (179 to 3495)	**438 more per 1000** (189 fewer to 3127 more)	**Very low**[a,b,c]	-
Ofloxacin (No direct RCT)	**Rate ratio 1.12** (0.31 to 4.09) Network estimate	**368 per 1000**	**412 per 1000** (113 to 1508)	**44 more per 1000** (255 fewer to 1139 more)	**Very low**[a,b,c]	-

*Anticipated absolute effect. Anticipated absolute effect compares two risks by calculating the difference between the risks of the intervention group with the weighted median risk of the control group.

**Ranking is not provided as the median rank was not 1 for at least one of the ranking positions for each intervention for the outcome.

CrI: credible interval; **HR:** hazard ratio; **OR:** odds ratio; **RCT**: randomised clinical trial

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

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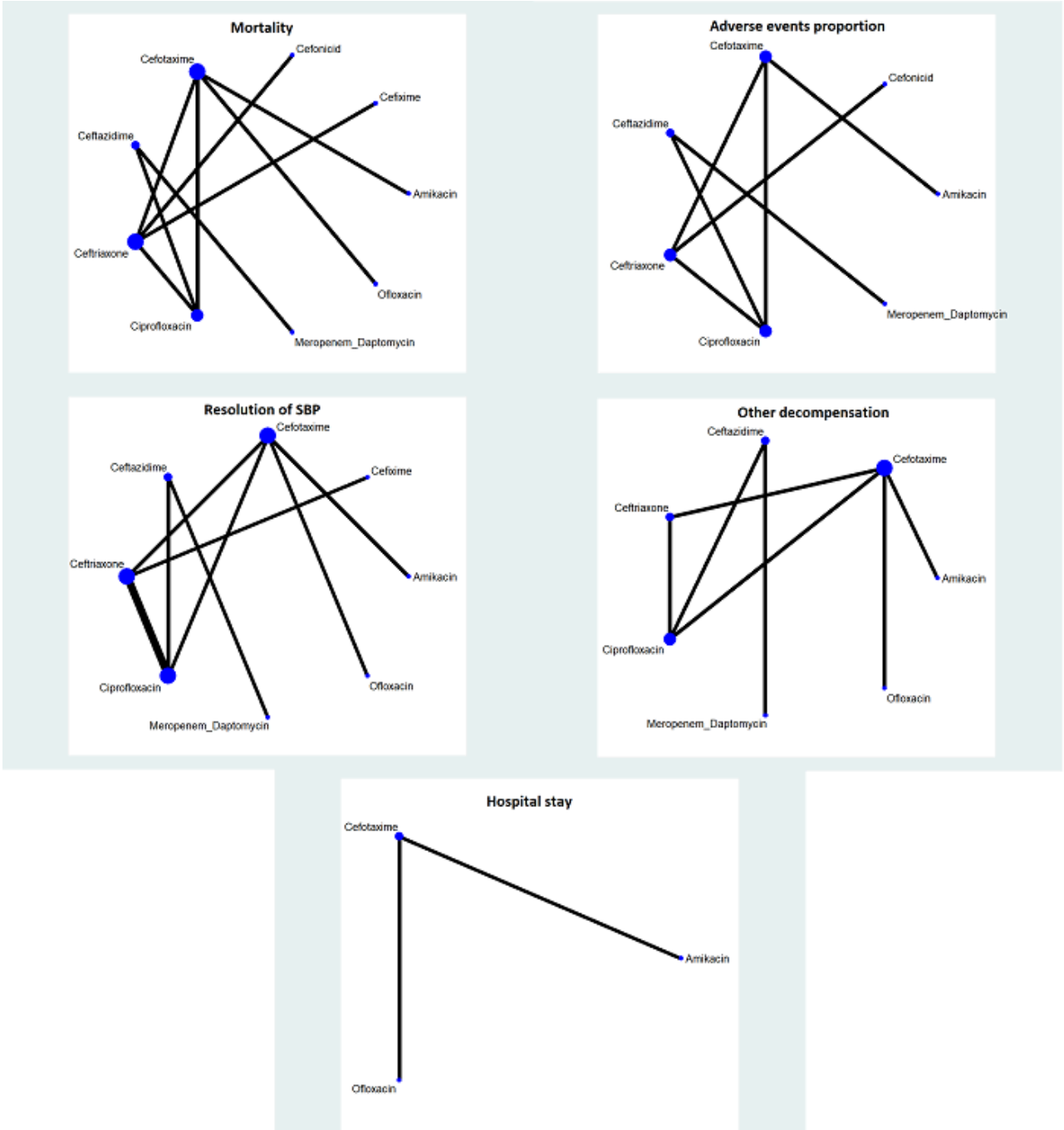
[a]The trial(s) included in the analysis was/were at high risk of bias (downgraded 1 level).
[b]The sample size was small (downgraded 1 level).
[c]The credible intervals were wide (includes clinical benefit and harms) (downgraded 1 level).

Figure 1. The network plots showing the outcomes for which network meta-analysis was performed. The size of the node (circle) provides a measure of the number of trials in which the particular intervention was included as one of the intervention groups. The thickness of the line provides a measure of the number of direct comparisons between two nodes (interventions).



Summary of findings 2.

Antibiotic treatment for spontaneous bacterial peritonitis in people with decompensated liver cirrhosis

Patient or population: people with cirrhosis and spontaneous bacterial peritonitis

Settings: secondary or tertiary care

Intervention: various interventions

Comparison: ceftriaxone

Follow-up period: 1 week to 3 months

Network geometry plots: Figure 1

Outcomes	Cefotaxime		Ciprofloxacin	
All-cause mortality				
Ceftriaxone 263 per 1000 (26.3%)	**HR 0.56** (0.11 to 2.28) **Network estimate**	**117 fewer per 1000** (235 fewer to 336 more)	**HR 0.65** (0.12 to 2.72) **Network estimate**	**92 fewer per 1000** (232 fewer to 454 more)
	Very low[1,2,3]		**Very low**[1,2,3]	
Rank*: -	**Rank: -**		**Rank: -**	
	Based on 37 participants (1 RCT)		Based on 35 participants (1 RCT)	
Adverse events (proportion of participants)				
Ceftriaxone 67 per 1000 (6.7%)	**OR 0.64** (0.15 to 2.62) **Network estimate**	**23 fewer per 1000** (56 fewer to 91 more)	**OR 1.02** (0.24 to 4.16) **Network estimate**	**1 more per 1000** (50 fewer to 162 more)
	Very low[1,2,3]		**Very low**[1,2,3]	
Rank: -	**Rank: -**		**Rank: -**	
	Based on 37 participants (1 RCT)		Based on 35 participants (1 RCT)	
Spontaneous bacterial peritonitis (as per definition used for spontaneous bacterial peritonitis)				

Ceftriaxone 733 per 1000 (73.3%)	**HR 0.90** (0.42 to 1.86) **Network estimate**	**73 fewer per 1000** (425 fewer to 267 more)	**HR 0.93** (0.69 to 1.25) **Network estimate**	**54 fewer per 1000** (230 fewer to 183 more)
	Very low[1,2,3]		**Very low**[1,2,3]	
Rank: -	**Rank: -**		**Rank: -**	
	Based on 37 participants (1 RCT)		Based on 275 participants (2 RCT)	
Other features of decompensation (per participant)				
Ceftriaxone 368 per 1000 (36.8 per 100 participants)	**Rate ratio 1.22** (0.43 to 3.53) Network estimate	**80 more per 1000** (209 fewer to 933 more)	**Rate ratio 1.01** (0.32 to 3.16) Network estimate	**4 more per 1000** (249 fewer to 795 more)
	Very low[1,2,3]		**Very low**[1,2,3]	
Rank: -	**Rank: -**		**Rank: -**	
	Based on 37 participants (1 RCT)		Based on 35 participants (1 RCT)	

*Ranking is not provided as the median rank was not 1 for at least one of the ranking positions for each intervention for the outcome.

CrI: credible interval; **HR:** hazard ratio; **OR:** odds ratio; **RCT**: randomised clinical trial

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

[a]The trial(s) included in the analysis was/were at high risk of bias (downgraded one level).
[b]The sample size was small (downgraded one level).
[c]The credible intervals were wide (includes clinical benefit and harms) (downgraded one level).

BACKGROUND

Description of the condition

Liver cirrhosis

The liver is a complex organ with multiple functions, including metabolism of carbohydrates, fats, proteins, and drugs; it also has synthetic, storage, digestive, excretory, and immunological functions (Read 1972). Liver cirrhosis is a liver disease in which the normal microcirculation, the gross vascular anatomy, and the hepatic architecture have been variably destroyed and altered, with fibrous septa surrounding regenerated or regenerating parenchymal nodules (Tsochatzis 2014; NCBI 2018a). The major causes of liver cirrhosis include excessive alcohol consumption, viral hepatitis, non-alcohol-related fatty liver disease, autoimmune liver disease, and metabolic liver disease (Williams 2014; Ratib 2015; Setiawan 2016). The global prevalence of liver cirrhosis is difficult to estimate as most estimates correspond to chronic liver disease (which includes liver fibrosis and liver cirrhosis). In studies from the USA, the prevalence of chronic liver disease varies between 0.3% and 2.1% (Scaglione 2015; Setiawan 2016); in the UK, the prevalence was 0.1% in one study (Fleming 2008). In 2010, liver cirrhosis caused an estimated 2% of all global deaths, equivalent to one million deaths (Mokdad 2014). There is an increasing trend of cirrhosis-related deaths in some countries, like the UK, while there is a decreasing trend in other countries, for example France (Mokdad 2014; Williams 2014). The major cause of complications and deaths in people with liver cirrhosis is due to the development of clinically significant portal hypertension - hepatic venous pressure gradient at least 10 mmHg (de Franchis 2015). Some of the clinical features of decompensation include jaundice, coagulopathy, ascites, variceal bleeding, hepatic encephalopathy, and renal failure (de Franchis 2015; McPherson 2016; EASL 2018). Decompensated cirrhosis is the most common indication for liver transplantation (Merion 2010; Adam 2012).

Spontaneous bacterial peritonitis (SBP)

Ascites is accumulation of free fluid in the abdomen (peritoneal cavity) (NCBI 2018b), and is a feature of liver decompensation (Tsochatzis 2017; EASL 2018). Approximately 20% of people with cirrhosis have ascites (D'Amico 2014). Approximately 1% to 4% of people with cirrhosis develop ascites each year (D'Amico 2006; D'Amico 2014). Ascites is the first sign of liver decompensation in about one-third of people with compensated liver cirrhosis (D'Amico 2014). When the ascitic fluid is infected with bacteria, it is called 'spontaneous bacterial peritonitis' (SBP). Due to the poor sensitivity of ascitic fluid culture, SBP is diagnosed by a polymorphonuclear (PMN) leukocyte count of more than 250 per mm^3 in the ascitic fluid (Rimola 2000; EASL 2018). In the presence of haemorrhagic ascites (ascites with red blood cell count of more than 10,000 per mm^3), one PMN leukocyte count should be subtracted for every 250 red blood cells to account for the presence of blood in the ascitic fluid (Rimola 2000). People with SBP may or may not display symptoms of peritonitis, such as abdominal pain fever,chills, and hypotension (Rimola 2000; Nousbaum 2007; EASL 2010).

The overall incidence and prevalence of SBP in people with cirrhosis is difficult to estimate. Approximately 2.5% of all hospitalisations in people with cirrhosis are for SBP (Devani 2017). The prevalence of SBP in patients with cirrhosis and ascites undergoing paracentesis varies from 0.5% to 8.7% (Nousbaum 2007; Castellote 2008; Khan 2009; Cadranel 2013). The incidence of SBP in people with decompensated liver cirrhosis is about 20% over a period of one to 12 months (Saab 2009).

The short-term mortality (that is, death within 30 days of diagnosis or death in hospital) after SBP is about 15% to 40% (Khan 2009; Tandon 2011; Devani 2017). In addition, SBP is associated with significant resource utilisation; a study conducted in the USA showed that the average length of hospital stay was approximately six days and the average hospital costs per patient were approximately USD 17,000 (Devani 2017).

Pathophysiology of SBP

Increased bacterial translocation (gut bacteria or bacterial products migrating outside the intestinal lumen) and decreased local and systemic immune responses in patients having cirrhosis are believed to be the cause of SBP (Bernardi 2010).

Description of the intervention

Antibiotics, in addition to supportive treatment (fluid and electrolyte balance, treatment of shock) form the mainstay treatment of SBP. There are various classes of antibiotics available for the treatment of SBP. If bacteria can be cultured from the ascitic fluid, antibiotic therapy can be based on the susceptibility of the bacteria to different antibiotics (EASL 2010; Runyon 2013; EASL 2018). However, bacteria can be cultured only in 40% to 60% of people with SBP (Rimola 2000; EASL 2010). Therefore, empirical antibiotic treatment is used in the majority of people with SBP (EASL 2010; Runyon 2013; EASL 2018). The major classes of empirical antibiotics used in the treatment of SBP include third-generation cephalosporins, such as ceftriaxone, cefotaxime, and - less commonly - penicillins, such as amoxicillin/clavulanic acid, and fluoroquinolones, such as ciprofloxacin (in people who have not taken fluoroquinolones for prophylaxis of SBP) (EASL 2010; Runyon 2013; EASL 2018).

How the intervention might work

Different antibiotic classes have different mechanisms of action to kill bacteria (bactericidal effect) or reduce their growth (bacteriostatic effect). Penicillins and cephalosporins inhibit bacterial cell wall synthesis (Yocum 1980; Yotsuji 1988). Fluoroquinolones are type II topoisomerase inhibitors; type II topoisomerases at appropriate levels are required for normal cellular processes, and altering their levels leads to bacterial cell death (Aldred 2014). Other antibiotics act via bacteriostatic effects.

Why it is important to do this review

SBP is associated with significant short-term mortality (Khan 2009; Tandon 2011; Devani 2017). It is important to provide optimal empirical treatment to people with SBP while waiting for the results of ascitic fluid culture and sensitivity (susceptibility of bacteria to the specific antibiotic) to improve their survival. Bacteria can be cultured only in 40% to 60% of people with SBP (Rimola 2000; EASL 2010). Several different antibiotic treatments are available, but their relative efficacy and the optimal combination are not known. There has been one Cochrane Review on the role of antibiotics in patients with cirrhosis and SBP (Chavez-Tapia 2009); however, there have been no previous network meta-analyses on the topic. Network meta-analysis allows for a combination of direct

and indirect evidence, and the ranking of different interventions for different outcomes (Salanti 2011; Salanti 2012). With this systematic review and network meta-analysis, we aim to provide the best level of evidence for the benefits and harms of different antibiotic treatments for SBP in people with decompensated liver cirrhosis.

OBJECTIVES

To compare the benefits and harms of different antibiotic treatments for spontaneous bacterial peritonitis (SBP) in people with decompensated liver cirrhosis.

METHODS

Criteria for considering studies for this review

Types of studies

We considered only randomised clinical trials for this network meta-analysis, irrespective of language, publication status, or date of publication. We excluded studies with a quasi-randomised design or non-randomised design because of the risk of bias in such studies. Inclusion of indirect observational evidence could weaken our network meta-analysis, but this could also be viewed as a strength for assessing rare adverse events. It is well established that exclusion of non-randomised studies increases the focus on potential benefits and reduces the focus on the risks of serious adverse events and those of any adverse events. However, due to the exponentially increased amount of work required for non-randomised studies, we planned to register and perform a new systematic review and meta-analysis of non-randomised studies for adverse events, if there was uncertainty in the balance of benefits and harms of effective treatment(s). We did not perform this because of the findings of the review.

Types of participants

We included randomised clinical trials with adult participants with decompensated liver cirrhosis, who are undergoing treatment for spontaneous bacterial peritonitis (SBP). We excluded randomised clinical trials in which participants have previously undergone liver transplantation, have SBP due to other causes, or have secondary peritonitis (i.e. peritonitis due to hollow viscus perforation or inflammation of other intra-abdominal organs, such as appendicitis or pancreatitis).

Types of interventions

We included any of the following different antibiotic interventions for comparison with one another, either alone or in combination.

- Cephalosporins
- Penicillins
- Quinolones
- Other classes of antibiotics

We did not include trials evaluating interventions targeted at fluid and electrolyte balance, or the treatment of shock. However, we included trials in which such cointerventions are administered equally in all the intervention arms.

We evaluated the plausibility of the transitivity assumption (the assumption that participants included in the different trials with different treatments can be considered to be a part of a multiarm randomised clinical trial and could potentially have been randomised to any of the interventions) (Salanti 2012), by looking at the inclusion and exclusion criteria in the studies. In other words, any participant that meets the inclusion criteria is, in principle, equally likely to be randomised to any of the above eligible interventions. This necessitates that information on potential effect modifiers, such as the presence of other features of decompensation (hepatorenal syndrome, hepatic encephalopathy, or variceal bleeding) are the same across trials. Since, there was no concern about the transitivity assumption, we did not perform a separate meta-analysis for people with cirrhosis and SBP versus without other features of decompensation.

Types of outcome measures

Primary outcomes

- All-cause mortality at maximal follow-up (time to death)
- Health-related quality of life using a validated scale, such as the EQ-5D or 36-Item Short Form Health Survey (SF-36) (EuroQol 2018; Optum 2018), at maximal follow-up
- Serious adverse events (during or within 6 months after cessation of the intervention). We defined a serious adverse event as any event that would increase mortality; is life-threatening; requires hospitalisation; results in persistent or significant disability; is a congenital anomaly/birth defect; or any important medical event that might jeopardise the person or require intervention to prevent it (ICH-GCP 1997). However, none of the authors defined serious adverse events. Therefore, we used the definitions provided by trial authors for serious adverse events (as indicated in the protocol).
  - Proportion of participants with one or more serious adverse event(s)
  - Number of serious adverse events per participant

Secondary outcomes

- Any adverse event (during or within 6 months after cessation of the intervention): we defined an adverse event as any untoward medical occurrence, not necessarily having a causal relationship with the intervention, but resulting in a dose reduction or discontinuation of intervention (any time after commencement of the intervention) (ICH-GCP 1997). However, none of the authors defined 'adverse event'. Therefore, we used the definitions provided by trial authors for adverse events (as indicated in the protocol).
  - Proportion of participants with one or more adverse event
  - Number of any adverse events per participant
- Time to liver transplantation (maximal follow-up)
- Time to resolution of spontaneous bacterial peritonitis (SBP) (however defined by study authors at maximal follow-up)
  - Symptomatic recovery
  - Recovery according to definitions used for SBP
- Number of other decompensation episodes (maximal follow-up)

Exploratory outcomes

- Length of hospital stay (all hospital admissions until maximal follow-up)
- Number of days of lost work (in people who work) (maximal follow-up)
- Treatment costs (including the cost of the treatment and any resulting complications)

We have chosen outcomes based on their importance to patients in a survey related to research priorities for people with liver diseases (Gurusamy 2019), based on feedback of the patient and public representative of this project, and based on an online survey about the outcomes promoted through the Cochrane Consumer Network.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, MEDLINE Ovid, Embase Ovid, and Science Citation Index Expanded (Web of Science) from inception to 10 November 2018, without applying any language restrictions (Royle 2003). We searched for all possible comparisons formed by the interventions of interest. To identify further ongoing or completed trials, we also searched clinicaltrials.gov, and the World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch/) which included various trial registers, including ISRCTN and ClinicalTrials.gov on 10 November 2018. We also searched the European Medical Agency (EMA) (www.ema.europa.eu/ema/), and US Food and Drug Administration (FDA) registries (www.fda.gov), for randomised clinical trials on 10 November 2018. The search strategies are provided in Appendix 1.

Searching other resources

We searched the references of the identified trials and the existing Cochrane Review on antibiotic treatments in liver cirrhosis to identify additional trials for inclusion (Chavez-Tapia 2009).

Data collection and analysis

Selection of studies

Two review authors (KG and LP) independently identified trials for inclusion by screening the titles and abstracts, and sought full-text articles for any references identified by at least one of the review authors for potential inclusion. We selected trials for inclusion based on the full-text articles. We provided the list of references that we excluded and the reasons for their exclusion in the 'Characteristics of excluded studies' table. We also planned to list any ongoing trials identified primarily through the search of the clinical trial registers for further follow-up. We resolved any discrepancies through discussion.

Data extraction and management

Two review authors (KG and LP) independently extracted the following data in a piloted Microsoft Excel-based data extraction form (after translation of non-English articles).

- Outcome data (for each outcome and for each intervention group whenever applicable)
  - number of participants randomised
  - number of participants included for the analysis
  - number of participants with events for binary outcomes, mean and standard deviation for continuous outcomes, number of events and the mean follow-up period for count outcomes, and number of participants with events and the mean follow-up period for time-to-event outcomes
  - natural logarithm of hazard ratio and its standard error, if this was reported, rather than the number of participants with events and the mean follow-up period for time-to-event outcomes
  - definition of outcomes or scale used, if appropriate
- Data on potential effect modifiers
  - participant characteristics, such as age, sex, presence of other features of decompensation (hepatorenal syndrome, hepatic encephalopathy, and variceal bleeding), the aetiology for cirrhosis, and the interval between diagnosis of SBP and treatment
  - details of the intervention and control (including dose, frequency, and duration)
  - length of follow-up
  - information related to 'Risk of bias' assessment (please see below)
- Other data
  - year and language of publication
  - country in which the participants were recruited
  - year(s) in which the trial was conducted
  - inclusion and exclusion criteria

We collected outcomes at maximum follow-up, but also at short-term (up to 3 months) and medium-term (from 3 months to 5 years), if applicable.

We attempted to contact the trial authors in the case of unclear or missing information. If there was any doubt as to whether trials shared the same participants, completely or partially (by identifying common authors and centres), we planned to contact the trial authors to clarify whether the trial report was duplicated. We resolved any differences in opinion through discussion.

Assessment of risk of bias in included studies

We followed the guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) to assess the risk of bias in included trials. Specifically, we assessed sources of bias as defined below (Schulz 1995; Moher 1998; Kjaergard 2001; Wood 2008; Savović 2012a; Savović 2012b; Savović 2018).

Allocation sequence generation

- Low risk of bias: the study authors performed sequence generation using computer random number generation or a random number table. Drawing lots, tossing a coin, shuffling cards, and throwing dice are adequate if performed by an independent person not otherwise involved in the study. In general, we classified the risk of bias as low if the method used for allocation concealment suggested that it was extremely likely that the sequence was generated randomly (for example, use of interactive voice response system).
- Unclear risk of bias: the study authors did not specify the method of sequence generation.
- High risk of bias: the sequence generation method was not random. We excluded such quasi-randomised studies.

Allocation concealment

- Low risk of bias: the participant allocations could not have been foreseen in advance of, or during, enrolment. A central and independent randomisation unit controlled allocation. The investigators were unaware of the allocation sequence (e.g. if

the allocation sequence was hidden in sequentially numbered, opaque, and sealed envelopes).
- Unclear risk of bias: the study authors did not describe the method used to conceal the allocation so that the intervention allocations may have been foreseen before, or during, enrolment.
- High risk of bias: it is likely that the investigators who assigned the participants knew the allocation sequence. We excluded such quasi-randomised studies.

Blinding of participants and personnel

- Low risk of bias: blinding of participants and key study personnel was ensured, and it was unlikely that the blinding could have been broken; or there was rarely no blinding or incomplete blinding, but the review authors judged that the outcome was not likely to be influenced by lack of blinding.
- Unclear risk of bias: insufficient information to permit a judgement of 'low risk' or 'high risk'; or the trial did not address this outcome.
- High risk of bias: no blinding or incomplete blinding, and the outcome was likely to be influenced by lack of blinding; or blinding of key study participants and personnel was attempted, but it was likely that the blinding could have been broken, and the outcome was likely to be influenced by lack of blinding.

Blinded outcome assessment

- Low risk of bias: blinding of outcome assessment was ensured, and it was unlikely that the blinding could have been broken; or rarely no blinding of outcome assessment, but the review authors judged that the outcome measurement was not likely to be influenced by lack of blinding.
- Unclear risk of bias: insufficient information to permit a judgement of 'low risk' or 'high risk'; or the trial did not address this outcome.
- High risk of bias: any of the following - no blinding of outcome assessment, and the outcome measurement was likely to be influenced by lack of blinding; or blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement was likely to be influenced by lack of blinding.

Incomplete outcome data

- Low risk of bias: missing data were unlikely to make treatment effects depart from plausible values. The study used sufficient methods, such as multiple imputation, to handle missing data.
- Unclear risk of bias: there was insufficient information to assess whether missing data in combination with the method used to handle missing data were likely to induce bias on the results.
- High risk of bias: the results were likely to be biased due to missing data.

Selective outcome reporting

- Low risk of bias: the trial reported the following predefined outcomes: at least one of the outcomes related to the main reason for treatment of people with SBP, namely, all-cause mortality, resolution of SBP along with adverse events. If the original trial protocol was available, the outcomes should have been those called for in that protocol. If the trial protocol was obtained from a trial registry (e.g. ClinicalTrials.gov), the outcomes sought should have been those enumerated in the original protocol if the trial protocol was registered before or at the time that the trial was begun. If the trial protocol was registered after the trial was begun, those outcomes will not be considered to be reliable.
- Unclear risk of bias: not all predefined, or clinically relevant and reasonably expected, outcomes were reported fully; or it was unclear whether data on these outcomes were recorded or not.
- High risk of bias: one or more predefined or clinically relevant and reasonably expected outcomes were not reported, despite the fact that data on these outcomes should have been available and recorded.

Other bias

- Low risk of bias: the trial appeared to be free of other components that could put it at risk of bias (e.g. inappropriate control or dose or administration of control, baseline differences, early stopping).
- Unclear risk of bias: the trial may or may not have been free of other components that could put it at risk of bias.
- High risk of bias: there were other factors in the trial that could put it at risk of bias (e.g. baseline differences, early stopping).

We considered a trial to be at low risk of bias if we assessed the trial to be at low risk of bias across all listed bias risk domains. Otherwise, we considered trials to be at high risk of bias. At the outcome level, we classified an outcome to be at low risk of bias if the allocation sequence generation, allocation concealment, blinding of participants, healthcare professionals, and outcome assessors, incomplete outcome data, and selective outcome reporting (at the outcome level) were at low risk of bias for objective and subjective outcomes (Savović 2018).

Measures of treatment effect

Relative treatment effects

For dichotomous variables (e.g. proportion of participants with serious adverse events or any adverse events), we calculated the odds ratio (OR) with 95% credible interval (CrI) (or Bayesian confidence interval) (Severini 1993). For continuous variables (e.g. length of hospital stay), we calculated the mean difference (MD) with 95% CrI. We planned to use standardised mean difference (SMD) values with 95% CrI for health-related quality of life if included trials used different scales. We planned to obtain the final scores whenever possible. For count outcomes (e.g. number of serious adverse events or number of any adverse events), we calculated the rate ratio with 95% CrI. This assumes that the events are independent of each other, i.e. if a person has had an event they are not at an increased risk of further outcomes, which is the assumption in Poisson likelihood. For time-to-event data (e.g. all-cause mortality at maximal follow-up), we calculated hazard ratio (HR) with 95% CrI.

Relative ranking

We estimated the ranking probabilities with 95% CrI for all interventions of being at each possible rank for each intervention. We obtained the surface under the cumulative ranking curve (SUCRA) (cumulative probability), rankogram, and relative ranking table with CrI for the ranking probabilities (Salanti 2011; Chaimani 2013).

Unit of analysis issues

The unit of analysis was the participant undergoing treatment for SBP according to the intervention group to which the participant was randomly assigned.

Cluster-randomised clinical trials

If we identified any cluster-randomised clinical trials, we planned to include cluster-randomised clinical trials, provided that the effect estimate adjusted for cluster correlation was available or if there was sufficient information available to calculate the design effect (which would allow us to take clustering into account). We also planned to assess additional domains of risk of bias for cluster-randomised trials according to guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Cross-over randomised clinical trials

If we identified any cross-over randomised clinical trials, we planned to include only the outcomes after the period of first intervention because the included treatments could have residual effects.

Trials with multiple intervention groups

We collected data for all trial intervention groups that met the inclusion criteria. The codes, we used for analysis, accounted for the correlation between the effect sizes from trials with more than two groups.

Dealing with missing data

We performed an intention-to-treat analysis whenever possible (Newell 1992); otherwise, we used the data available to us. When intention-to-treat analysis is not used and the data are not missing at random (for example, treatment was withdrawn due to adverse events or duration of treatment was shortened because of lack of response and such participants were excluded from analysis), this can lead to biased results; therefore, we conducted best-worst case scenario analysis (assuming a good outcome in the intervention group and bad outcome in the control group) and worst-best case scenario analysis (assuming a bad outcome in the intervention group and good outcome in the control group) as sensitivity analyses whenever possible for binary and time-to-event outcomes, where binomial likelihood was used.

For continuous outcomes, we planned to impute the standard deviation from P values, according to guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). If the data were likely to be normally distributed, we planned to use the median for meta-analysis when the mean was not available; otherwise, we planned to simply provide a median and interquartile range of the difference in medians. If it was not possible to calculate the standard deviation from the P value or the confidence intervals, we planned to impute the standard deviation using the largest standard deviation in other trials for that outcome. This form of imputation can decrease the weight of the study for calculation of mean differences and may bias the effect estimate to no effect for calculation of standardised mean differences (Higgins 2011).

Assessment of heterogeneity

We assessed clinical and methodological heterogeneity by carefully examining the characteristics and design of included trials. We also planned to assess the presence of clinical heterogeneity by comparing effect estimates (please see Subgroup analysis and investigation of heterogeneity) in trial reports of different drug dosages, presence of other features of decompensation (hepatorenal syndrome, hepatic encephalopathy, or variceal bleeding), different aetiologies for cirrhosis (for example, alcohol-related liver disease, viral liver diseases, autoimmune liver disease), and based on the cointerventions (for example, both groups receive albumin). Different study designs and risk of bias can contribute to methodological heterogeneity.

We assessed statistical heterogeneity by comparing the results of the fixed-effect model meta-analysis and the random-effects model meta-analysis, between-study variance (Tau^2, and comparing this with values reported in the study of the distribution of between-study heterogeneity) (Turner 2012), and by calculating I^2 (Jackson 2014), using Stata/SE 15.1 (if applicable). If we identified substantial clinical, methodological, or statistical heterogeneity, we planned to explore and address the heterogeneity in subgroup analysis (see 'Subgroup analysis and investigation of heterogeneity').

Assessment of transitivity across treatment comparisons

We assessed the transitivity assumption by comparing the distribution of the potential effect modifiers (clinical: presence of other features of decompensation, i.e. hepatorenal syndrome, hepatic encephalopathy, or variceal bleeding; methodological: risk of bias, year of randomisation, duration of follow-up) across the different pairwise comparisons.

Assessment of reporting biases

For the network meta-analysis, we planned to perform a comparison-adjusted funnel plot. However, to interpret a comparison-adjusted funnel plot, it is necessary to rank the studies in a meaningful way as asymmetry may be due to small sample sizes in newer studies (comparing newer treatments with older treatments) or higher risk of bias in older studies (comparing older treatments with placebo) (Chaimani 2012). As there was no meaningful way in which to rank these studies (i.e. there was no specific change in the risk of bias in the studies, sample size, or the control group used over time), we judged the reporting bias by the completeness of the search (Chaimani 2012).

Data synthesis

Methods for indirect and mixed comparisons

We conducted network meta-analyses to compare multiple interventions simultaneously for each of the primary and secondary outcomes. Network meta-analysis combines direct evidence within trials and indirect evidence across trials (Mills 2012). We obtained a network plot to ensure that the trials were connected by interventions using Stata/SE 15.1 (Chaimani 2013). We excluded any trials that were not connected to the network from the network meta-analysis, and we reported only the direct pairwise meta-analysis for such comparisons. We summarised the population and methodological characteristics of the trials included in the network meta-analysis in a table based on pairwise comparisons. We conducted a Bayesian network meta-analysis using the Markov chain Monte Carlo method in OpenBUGS 3.2.3, according to guidance from the National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) documents (Dias 2016). We modelled the treatment contrast (i.e. log odds

ratio for binary outcomes, mean difference or standardised mean difference for continuous outcomes, log rate ratio for count outcomes, and log hazard ratio for time-to-event outcomes) for any two interventions ('functional parameters') as a function of comparisons between each individual intervention and the reference group ('basic parameters'), using appropriate likelihood functions and links (Lu 2006). We used binomial likelihood and logit link for binary outcomes, Poisson likelihood and log link for count outcomes, binomial likelihood and complementary log-log link (a semiparametric model which excludes censored individuals from the denominator of 'at risk' individuals at the point when they are censored), and normal likelihood and identity link for continuous outcomes. We used 'ceftriaxone' as the reference group as this was the commonest intervention in the trials included in this review. We used a fixed-effect model and a random-effects model for the network meta-analysis. We planned to report both models for comparison with the reference group in a forest plot, when applicable. For each pairwise comparison in a table, we reported the fixed-effect model if the two models reported similar results; otherwise, we planned to report the more conservative model.

We used a hierarchical Bayesian model using three different sets of initial values to start the simulation-based parameter estimation, employing codes provided by NICE DSU (Dias 2016). We used a normal distribution with large variance (10,000) for treatment effect priors (vague or flat priors) centred at no effect. For the random-effects model, we used a prior distributed uniformly (limits: 0 to 5) for the between-trial standard deviation and assumed this variability would be the same across treatment comparisons (Dias 2016). We used a 'burn-in' of 30,000 iterations, checked for convergence (of effect estimates and between-study heterogeneity) visually (i.e. checked whether the values in different chains mix very well by visualisation), and ran the models for another 10,000 simulations to obtain effect estimates. If we did not obtain convergence, we increased the number of simulations for the 'burn-in' and used the 'thin' and 'over relax' functions to decrease the autocorrelation. If we still did not obtain convergence, we planned to use alternate initial values and priors employing methods suggested by van Valkenhoef 2012. We estimated the probability that each intervention ranks at each of the possible positions using the NICE DSU codes (Dias 2016).

Assessment of inconsistency

We assessed inconsistency (statistical evidence of the violation of transitivity assumption) by fitting both an inconsistency model and a consistency model. We used inconsistency models employed in the NICE DSU manual, as we used a common between-study standard deviation (Dias 2014). In addition, we planned to use design-by-treatment full interaction model and inconsistency factor plots to assess inconsistency when applicable (Higgins 2012; Chaimani 2013). We planned to report inconsistency factor plots when possible using Stata/SE 15.1. In the presence of inconsistency, we planned to assess whether the inconsistency was due to clinical or methodological heterogeneity by performing separate analyses for each of the different subgroups mentioned in the 'Subgroup analysis and investigation of heterogeneity' section.

If there was evidence of inconsistency, we planned to identify areas in the network where substantial inconsistency might be present in terms of clinical and methodological diversities between trials and, when appropriate, limit network meta-analysis to a more compatible subset of trials.

Direct comparison

We performed the direct comparisons using the same codes and the same technical details.

Subgroup analysis and investigation of heterogeneity

We planned to assess the differences in the effect estimates between the following subgroups and investigate heterogeneity and inconsistency using meta-regression with the help of the codes provided in the NICE DSU guidance (Dias 2012a), if we included a sufficient number of trials (when there were at least two trials in at least two of the subgroups) and when the interaction term could be calculated. We planned to use the following trial-level covariates for meta-regression.

- Trials at low risk of bias compared to trials at high risk of bias
- The presence of other features of decompensation (hepatorenal syndrome, hepatic encephalopathy, or variceal bleeding)
- The aetiology for cirrhosis (for example, alcohol-related liver disease, viral liver diseases, autoimmune liver disease)
- Community acquired or nosocomial SBP
- The interval between the diagnosis of SBP and the start of treatment
- Different types of cointerventions (for example, both groups receive albumin as the cointervention)
- The period of follow-up (short-term: up to 3 months; medium-term: more than 3 months to 5 years; long-term: more than 5 years)
- The definition used by authors for serious adverse events and any adverse events compared to other definitions (ICH-GCP 1997)

We planned to calculate a single common interaction term (which assumes that each relative treatment effect versus a common comparator treatment is impacted in the same way by the covariate in question) when applicable (Dias 2012a). If the 95% CrI of the interaction term did not overlap zero, we would have considered this statistically significant heterogeneity or inconsistency (depending upon the factor being used as covariate).

Sensitivity analysis

If there were post-randomisation dropouts, we reanalysed the results using the best-worst case scenario and worst-best case scenario analyses as sensitivity analyses whenever possible. We also planned to perform a sensitivity analysis excluding the trials in which mean or standard deviation, or both were imputed, and use the median standard deviation in the trials to impute missing standard deviations.

Presentation of results

We followed the PRISMA-NMA statement while reporting the results (Hutton 2015). We presented the effect estimates with 95% CrI for each pairwise comparison calculated from the direct comparisons and the network meta-analysis. We originally planned to present the cumulative probability of the treatment ranks (i.e. the probability that the intervention is within the top two, the probability that the intervention is within the top three, etc.) in graphs (SUCRA) (Salanti 2011). We plotted the probability that each intervention was best, second best, third best, etc. for each of the different outcomes (rankograms), which are generally

considered more informative (Salanti 2011; Dias 2012b), but we did not present these because of the sparse data which can lead to misinterpretation of results due to large uncertainty in the rankings (the CrI was 0 to 1 for all the ranks). We uploaded all the raw data and the codes used for analysis in The European Organization for Nuclear Research open source database (Zenodo) (the link is doi.org/10.5281/zenodo.3256132).

Grading of evidence

We presented 'Summary of findings' tables for all the primary and secondary outcomes (see Primary outcomes; Secondary outcomes). We followed the approach suggested by Yepes-Nunez and colleagues (Yepes-Nunez 2019). First, we calculated the direct and indirect effect estimates (when possible) and 95% CrI using the node-splitting approach (Dias 2010), that is, calculating the direct estimate for each comparison by including only trials in which there was direct comparison of interventions and the indirect estimate for each comparison by excluding the trials in which there was direct comparison of interventions (and ensuring a connected network). Next, we rated the quality of direct and indirect effect estimates using GRADE methodology which takes into account the risk of bias, inconsistency (heterogeneity), directness of evidence (including incoherence, the term used in GRADE methodology for inconsistency in network meta-analysis), imprecision, and publication bias (Guyatt 2011). We then presented the relative and absolute estimates of the meta-analysis with the best certainty of evidence (Yepes-Nunez 2019). We also presented the 'Summary of findings' tables in a second format presenting all the outcomes for selected interventions (Yepes-Nunez 2019): we selected the three interventions (cetriaxone, cefotaxime, and ciprofloxacin) which were compared in most trials.

Recommendations for future research

We provided recommendations for future research regarding the population, intervention, control, outcomes, period of follow-up, and study design, based on the uncertainties that we identified from the existing research.

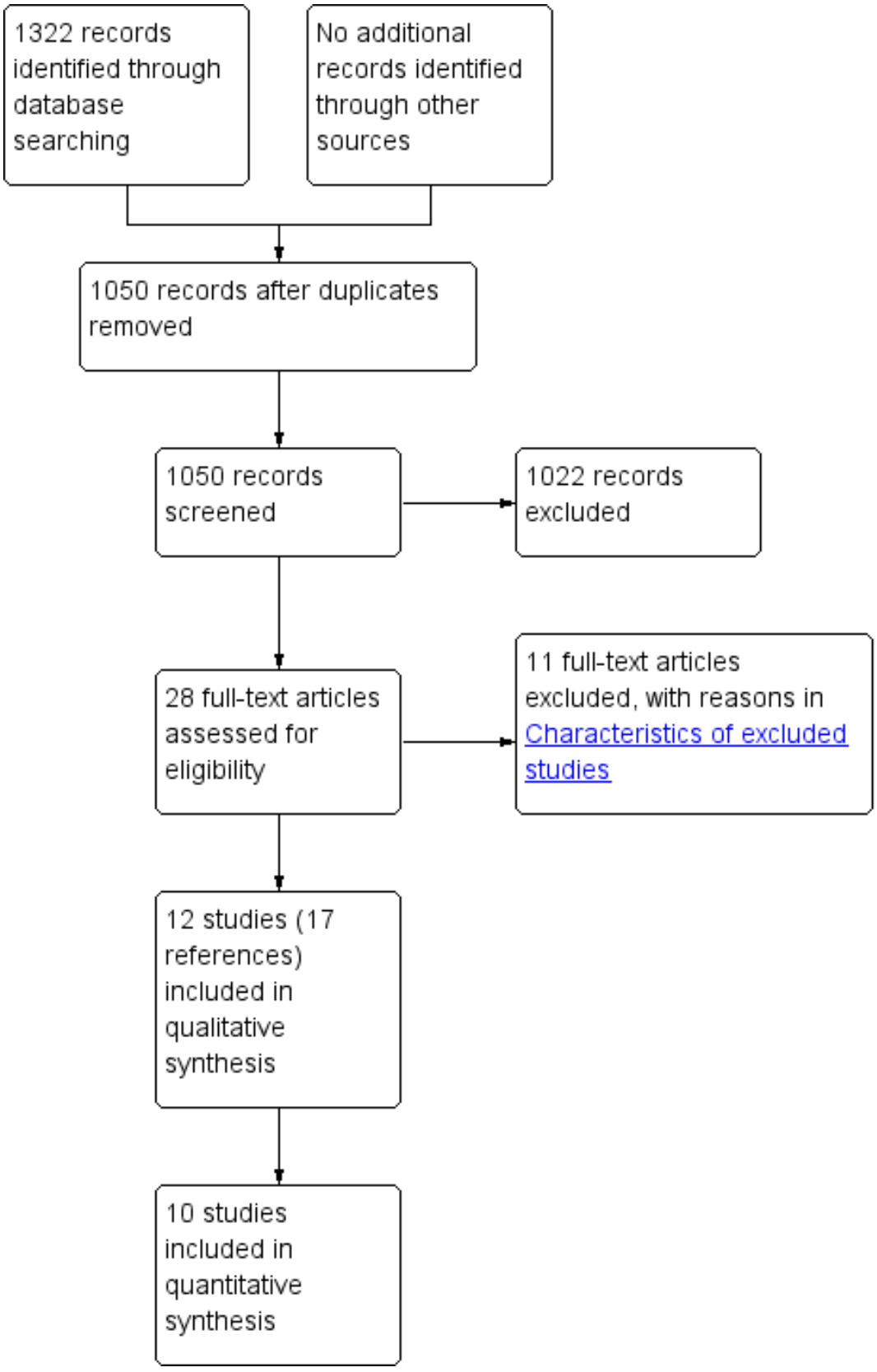
RESULTS

Description of studies

Results of the search

We identified 1322 references through electronic searches of CENTRAL (n = 183), MEDLINE Ovid (n = 501), Embase Ovid (n = 238), Science Citation Index Expanded (n = 316), ClinicalTrials.gov (n = 35) and WHO Trials register (n = 49). After removing duplicate references, there were 1050 references. We excluded 1022 clearly irrelevant references through reading titles and abstracts. We did not identify any additional eligible trial by reference searching or by searching the European Medicines Agency (EMA) or Food and Drug Administration (FDA). We retrieved a total of 28 full-text references for further assessment in detail. We excluded 11 references for the reasons stated in the Characteristics of excluded studies. Thus, we included a total of 12 trials described in 17 references (Characteristics of included studies). The reference flow is shown in Figure 2.

Figure 2. Study flow diagram.



Included studies

We included 12 trials (Gomez-Jimenez 1993; Navasa 1996; Figueiredo 1997; Rastegar 1998; Tuncer 2003; Chen 2005; Angeli 2006; Ahmed Ather Ch 2014; Abd-Elsalam 2016; Jindal 2016; Piano 2016; Yim 2017). A total of 1272 participants were randomised to different interventions. The number of participants ranged from 20 to 261. A total of 893 participants from 10 trials provided data for one or more outcomes (Gomez-Jimenez 1993; Navasa 1996; Figueiredo 1997; Rastegar 1998; Tuncer 2003; Chen 2005; Angeli 2006; Ahmed Ather Ch 2014; Jindal 2016; Piano 2016). The mean or median age in the trials ranged from 42 to 60 years in the trials that reported this information (Gomez-Jimenez 1993; Navasa 1996; Figueiredo 1997; Rastegar 1998; Tuncer 2003; Chen 2005; Angeli 2006; Ahmed Ather Ch 2014; Jindal 2016; Piano 2016). The proportion of females ranged from 18.3% to 42.1% in the trials that reported this information (Gomez-Jimenez 1993; Navasa 1996; Figueiredo 1997; Rastegar 1998; Tuncer 2003; Chen 2005; Angeli 2006; Ahmed Ather Ch 2014; Jindal 2016; Piano 2016). The most common organism isolated was *Eschericia coli* (*E coli*) (18.6% to 56.7%) in the trials that reported the isolated micro-organisms (Gomez-Jimenez 1993; Navasa 1996; Chen 2005; Angeli 2006). The next most common was the *Klebsiella* species (5.0% to 5.7%) and *Streptococcus pneumoniae* (*S pneumoniae*) (1.7% to 9.8%) (Gomez-Jimenez 1993; Navasa 1996); the remaining organisms were less frequent.

All trials had short-term follow-up (Gomez-Jimenez 1993; Navasa 1996; Figueiredo 1997; Rastegar 1998; Tuncer 2003; Chen 2005; Angeli 2006; Ahmed Ather Ch 2014; Abd-Elsalam 2016; Jindal 2016; Piano 2016; Yim 2017), ranging from one week to three months.

A total of 13 interventions were compared in the trials. Ceftriaxone, cefotaxime, and ciprofloxacin were the commonest antibiotics compared in the trials. The important characteristics, antibiotics compared, potential effect modifiers, and follow-up in each trial are reported in Table 1. None of the trials compared antibiotics with no treatment or placebo. Overall, no systematic differences between any of the comparisons seemed to exist.

None of the trials reported the proportion of people with other features of decompensation, such as hepatorenal syndrome and active variceal bleeding. The proportion of participants with alcohol-related cirrhosis ranged between 13.5% to 64.5% in the trials that reported this information (Gomez-Jimenez 1993; Navasa 1996; Chen 2005; Angeli 2006; Jindal 2016; Piano 2016). The proportion of participants with viral-related cirrhosis ranged between 20.6% to 81.1% in the trials that reported this information (Chen 2005; Angeli 2006; Jindal 2016; Piano 2016). None of the trials reported the proportion of people with autoimmune disease-related cirrhosis. The proportion of participants with other causes for cirrhosis ranged between 5.4% to 56.9% in the trials that reported this information (Gomez-Jimenez 1993; Navasa 1996; Chen 2005; Angeli 2006; Jindal 2016; Piano 2016). None of the trials reported the proportion of people treated for ascites, in addition to antibiotics (for example, albumin or diuretics).

Funding: the source of funding for two trials was industrial organisations who would benefit from the results of the study (Navasa 1996; Piano 2016); the source of funding for the remaining 10 trials was unclear (Gomez-Jimenez 1993; Figueiredo 1997; Rastegar 1998; Tuncer 2003; Chen 2005; Angeli 2006; Ahmed Ather Ch 2014; Abd-Elsalam 2016; Jindal 2016; Yim 2017).

Excluded studies

The reasons for exclusion are provided in the 'Characteristics of excluded studies' tables.

Risk of bias in included studies

The risk of bias is summarised in Figure 3, Figure 4, and in Table 2. As none of the trials were at low risk of bias in all domains, we considered all trials to be at high risk of bias.

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

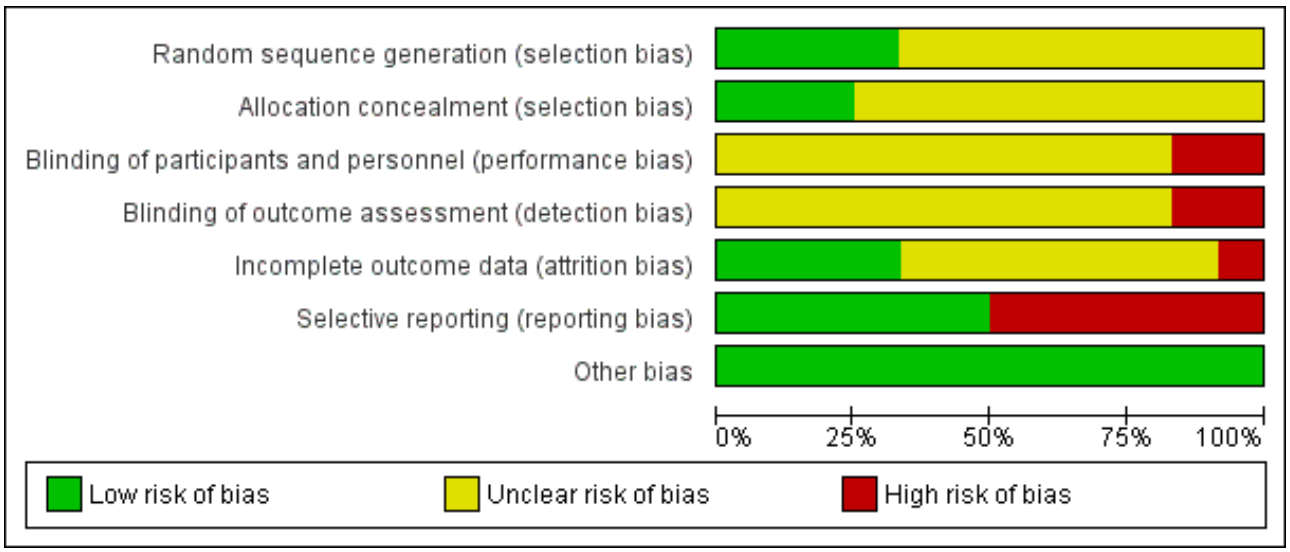
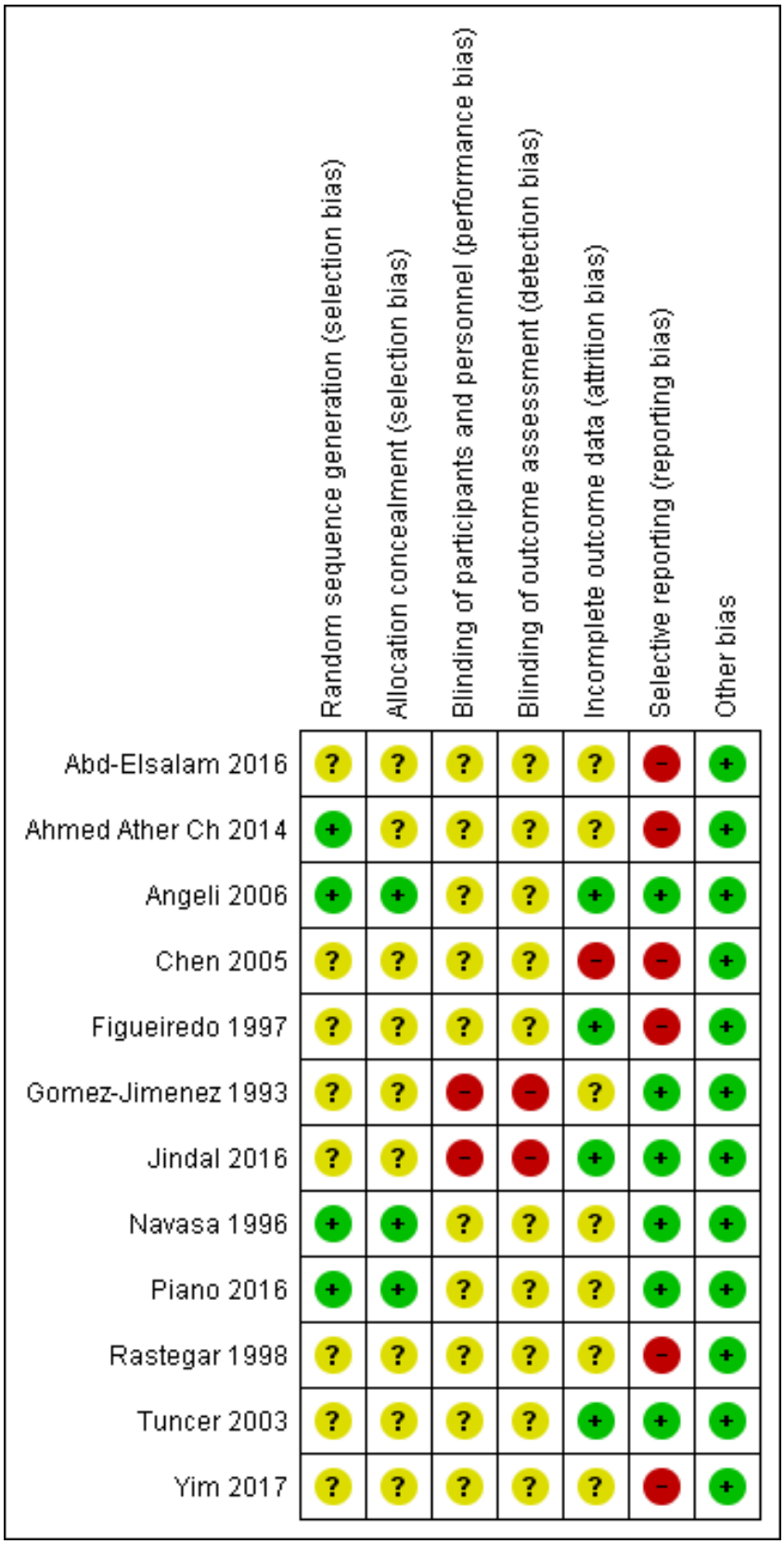


Figure 4. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Four trials were at low risk of sequence generation bias (Navasa 1996; Angeli 2006; Ahmed Ather Ch 2014; Piano 2016); the remaining eight trials, which did not provide sufficient details, were at unclear risk of sequence generation bias (Gomez-Jimenez 1993; Figueiredo 1997; Rastegar 1998; Tuncer 2003; Chen 2005; Abd-Elsalam 2016; Jindal 2016; Yim 2017).

Three trials were at low risk of allocation concealment bias (Navasa 1996; Angeli 2006; Piano 2016); the remaining nine trials, which did not provide sufficient details, were at unclear risk of allocation concealment bias (Gomez-Jimenez 1993; Figueiredo 1997; Rastegar 1998; Tuncer 2003; Chen 2005; Ahmed Ather Ch 2014; Abd-Elsalam 2016; Jindal 2016; Yim 2017).

Blinding

None of the trials were at low risk of blinding of patients and healthcare providers' bias; 10 trials were at unclear risk of blinding of patients and healthcare providers' bias (Navasa 1996; Figueiredo 1997; Rastegar 1998; Tuncer 2003; Chen 2005; Angeli 2006; Ahmed Ather Ch 2014; Abd-Elsalam 2016; Piano 2016; Yim 2017); the remaining two trials were at high risk of blinding of patients and healthcare providers' bias (Gomez-Jimenez 1993; Jindal 2016).

None of the trials were at low risk of blinding of outcome assessors' bias; 10 trials were at unclear risk of blinding of outcome assessors' bias (Navasa 1996; Figueiredo 1997; Rastegar 1998; Tuncer 2003; Chen 2005; Angeli 2006; Ahmed Ather Ch 2014; Abd-Elsalam 2016; Piano 2016; Yim 2017); the remaining two trials were at high risk of blinding of outcome assessors' bias (Gomez-Jimenez 1993; Jindal 2016).

Incomplete outcome data

Four trials were at low risk of missing outcome bias (Figueiredo 1997; Tuncer 2003; Angeli 2006; Jindal 2016); seven trials were at unclear risk of missing outcome bias (Gomez-Jimenez 1993; Navasa 1996; Rastegar 1998; Ahmed Ather Ch 2014; Abd-Elsalam 2016; Piano 2016; Yim 2017), because they either did not state the number of post-randomisation dropouts or we could not assess whether the post-randomisation dropouts were related to the intervention and outcome; the remaining one trial was at high risk of missing outcome bias, because the post-randomisation dropouts were likely to be related to the outcome (Chen 2005).

Selective reporting

Six trials were at low risk of selective outcome reporting bias (Gomez-Jimenez 1993; Navasa 1996; Tuncer 2003; Angeli 2006; Jindal 2016; Piano 2016): although a protocol published prior to recruitment was not available for these trials, these trials reported all-cause mortality or resolution of SBP along with adverse events; the remaining six trials were at high risk of selective outcome reporting bias (Figueiredo 1997; Rastegar 1998; Chen 2005; Ahmed Ather Ch 2014; Abd-Elsalam 2016; Yim 2017): a protocol published prior to recruitment was not available for these trials, and these trials did not report reasonably expected clinical outcomes which would have been measured in a trial of this nature.

Other potential sources of bias

There were no other biases in the trials.

Effects of interventions

See: **Summary of findings for the main comparison**; **Summary of findings 2**

The network plot for all outcomes for which network meta-analysis was performed is shown in Figure 1. If a network meta-analysis was not performed, the reason for not performing the network meta-analysis is reported under the outcome. Only one trial was included for each comparison in all outcomes other than resolution of spontaneous bacterial peritonitis (SBP). Even for resolution of SBP, where one of the comparisons had two trials, the between-study standard deviation was the same as the mean of the prior distribution: the 95% credible intervals (CrIs) of the random-effects model were not representative. Therefore, we used the fixed-effect model for all the network meta-analyses and did not present the forest plots comparing the fixed-effect and random-effects models. In addition, the deviance information criteria statistics showed that model fit was not improved with the random-effects model (Table 3), and the random-effects model did not alter the interpretation on the effectiveness of treatments. These findings support the use of the fixed-effect model.

There was no evidence of inconsistency, as indicated by deviance information criteria. As a consequence of the sparse data (only 1 trial was included for each comparison for most outcomes), we did not consider the results from the design-by-treatment interaction model to assess inconsistency. We were unable to obtain inconsistency factor plots in Stata/SE 15.1. This was either because there was only one closed loop resulting from a single three-arm trial or because heterogeneity could not be calculated due to the presence of a single trial for the comparison.

The 95% CrI of the probability ranks were wide and included 0 and 1 in all the comparisons for all the outcomes. This was probably because of the sparse data from small trials. Therefore, we did not present the ranking probabilities (in a table), rankograms, and SUCRA plots as we considered that presenting this information would be misleading due to large uncertainty in the rankings.

Certainty of evidence was very low for all the comparisons. This was because all the trials were at unclear or high risk of bias for two or more risk of bias domains at the outcome level (downgraded 1 level), the sample size was small (downgraded 1 level), and the wide CrIs overlapping significant clinical effect and no effect (downgraded 1 level). There was no evidence of indirectness or publication bias. We could not assess inconsistency in the GRADE context (i.e. heterogeneity) as there was only one trial for each comparison for most outcomes.

All-cause mortality

Nine trials (653 participants) reported all-cause mortality (Gomez-Jimenez 1993; Navasa 1996; Figueiredo 1997; Rastegar 1998; Tuncer 2003; Chen 2005; Angeli 2006; Jindal 2016; Piano 2016). A total of 13 interventions were compared with each other. There were nine interventions connected to the network (Figure 1), and four unconnected interventions. Only one trial was included in each pairwise comparison. There were no significant differences in the all-cause mortality between any of the interventions included in the network meta-analysis (Table 4). There were also no significant differences in the all-cause mortality between the following comparisons which could not be included in the network meta-analysis because they were not connected.

- Pefloxacin versus ampicillin plus gentamycin: HR 0.80 (95% CrI 0.02 to 30.66).
- Imipenem versus cefepime: HR 0.98 (95% CrI 0.60 to 1.57).

Health-related quality of life

None of the trials reported health-related quality of life.

Serious adverse events

One trial (31 participants) reported the proportion of participants with serious adverse events (Piano 2016). It was not clear whether the authors used the ICH-GCP definition of serious adverse events (ICH-GCP 1997). There was no significant difference in the proportion of people with serious adverse events between meropenem plus daptomycin versus ceftazidime: odds ratio (OR) 1.51 (95% credible interval (CrI) 0.35 to 6.71). None of the trials reported the number of serious adverse events per participant.

Any adverse event

Five trials (297 participants) reported the proportion of participants with any adverse event (Gomez-Jimenez 1993; Tuncer 2003; Chen 2005; Angeli 2006; Piano 2016). It was not clear whether the authors used the ICH-GCP definition of adverse events (ICH-GCP 1997). A total of seven interventions were compared with each other. All the interventions were connected (Figure 1). Only one trial compared each pairwise comparison. The fixed-effect model was used. There were no significant differences in the proportion of people who developed any adverse event between any of the interventions (Table 4).

Two trials (291 participants) reported the number of any adverse events (Angeli 2006; Jindal 2016). It was not clear whether the authors used the ICH-GCP definition of adverse events (ICH-GCP 1997). The two trials compared two different pairs of interventions. Therefore, network meta-analysis was not appropriate. There were no significant differences in the number of adverse events per participant in the following comparisons.

- Ceftazdime versus ciprofloxacin: rate ratio 1.39 (95% CrI 0.79 to 2.48).
- Imipenem versus cefepime: rate ratio 1.00 (95% CrI 0.83 to 1.20).

Liver transplantation

One trial (31 participants) reported the proportion of participants requiring liver transplantation (Piano 2016). There was no significant difference in the proportion of people who underwent liver transplantation between meropenem plus daptomycin versus ceftazidime: hazard ratio (HR) 1.77 (95% CrI 0.26 to 15.21).

Resolution of SBP

None of the trials reported resolution of SBP, defined as symptomatic recovery from SBP. Nine trials (873 participants) reported recovery from SBP, as per definitions used for SBP (Gomez-Jimenez 1993; Navasa 1996; Figueiredo 1997; Tuncer 2003; Chen 2005; Angeli 2006; Ahmed Ather Ch 2014; Jindal 2016; Piano 2016). We compared a total of 11 interventions with each other. There were eight connected interventions (Figure 1), and 3 unconnected interventions. Of these, we excluded one comparison because both interventions in the comparison were unconnected. We excluded one intervention as it was connected to the network solely by one trial in which all participants had resolution of SBP. We included only one trial for each pairwise comparison, except for one pairwise comparison. There were no significant differences in the proportion of people in whom resolution of SBP could be achieved (Table 4).

There was no significant difference in the resolution of SBP between imipenem versus cefepime: HR 0.72 (95% CrI 0.45 to 1.12). We could not obtain convergence for the other comparison involving cefonicid versus ceftriaxone, in which all 30 participants in the ceftriaxone group had resolution of SBP and 28/30 (93.3%) of the cefonicid group had resolution of SBP.

Other features of decompensation

Six trials (535 participants) reported other features of decompensation (Navasa 1996; Tuncer 2003; Chen 2005; Angeli 2006; Jindal 2016; Piano 2016). None of the trials reported the number of people who developed decompensation; only the number of decompensation events in each group was reported. A total of nine interventions were compared with each other. There were seven connected interventions (Figure 1), and two unconnected interventions. Only one trial was included for each pairwise comparison. There were no significant differences in the number of other decompensation events between any of the interventions included in the network meta-analysis (Table 4). There was also no significant difference in the number of other decompensation events between the unconnected interventions (imipenem versus cefepime): rate ratio 0.97 (95% CrI 0.75 to 1.25).

Length of hospital stay

Two trials (160 participants) reported length of hospital stay (Navasa 1996; Chen 2005). A total of three interventions were compared with each other. All the interventions were connected (Figure 1). Only one trial was included in each pairwise comparison. There were no significant differences in the length of hospital stay between any of the interventions (Table 4).

Number of work days lost

None of the trials reported this outcome.

Treatment costs

None of the trials reported total treatment costs. Two trials (91 participants) reported antibiotic costs for the regimen used (Figueiredo 1997; Tuncer 2003). The standard deviation of the costs were not reported and could not be calculated from other data available in either trial.

In one trial, oral cefixime was compared with intravenous ceftriaxone (Figueiredo 1997). The non-inflated costs of antibiotic treatment were BRL 62 for the oral cefixime group compared to BRL 2160 for the intravenous ceftriaxone group (Figueiredo 1997). In the second trial, oral ciprofloxacin was compared with intravenous cefotaxime and intravenous ceftriaxone. The non-inflated costs of antibiotic treatment were USD 6.61 for oral ciprofloxacin, USD 127 for intravenous cefotaxime, and USD 118 for intravenous ceftriaxone groups (Tuncer 2003).

Subgroup analysis

We did not perform any of the planned subgroup analysis because of sparse data in the trials, short follow-up in all trials, and the unclear or high risk of bias for each of the outcomes in all trials.

Sensitivity analysis

The scenario analysis we performed for post-randomisation dropouts for binary outcomes and time-to-event outcomes (where binomial likelihood was used). None of these revealed any alterations in the results. We did not impute the standard deviation for any continuous outcome.

Assessment of reporting biases

We were unable to perform the comparison-adjusted funnel plot because there was no meaningful way in which to rank the studies (i.e. there was no specific change in the risk of bias in the studies, sample size, or the control group used over time).

DISCUSSION

Summary of main results

We performed a systematic review and network meta-analysis of all the antibiotic treatments for spontaneous bacterial peritonitis (SBP) in people with decompensated liver cirrhosis. We included a total of 12 trials, with a total of 1272 participants in this review. In the four trials that reported the isolated organisms, the most common organism isolated was *Eschericia coli* (*E coli*) (18.6% to 56.7%) (Gomez-Jimenez 1993; Navasa 1996; Chen 2005; Angeli 2006). We compared a total of 13 interventions in these trials. A total of 10 trials, including 893 participants were included for one or more outcomes of this review (Gomez-Jimenez 1993; Navasa 1996; Figueiredo 1997; Rastegar 1998; Tuncer 2003; Chen 2005; Angeli 2006; Ahmed Ather Ch 2014; Jindal 2016; Piano 2016). Only one outcome, resolution of SBP, featured more than one trial for the same comparison.

Approximately 75% of participants with SBP had resolution of SBP, and 25% of participants died from SBP. Overall, there was no evidence of differences for any of the primary or secondary outcomes of this review. However, it should be noted that the data were sparse and most of the comparisons involved a single trial. Therefore, clinically important differences in the outcomes between the interventions are possible.

Future trials can and should be powered on short-term all-cause mortality. Based on the probability ranks, it is not clear which interventions should be compared in future trials. Intravenous ceftriaxone and cefotaxime were the commonest interventions used in the trials. The sample size required in such trials based on a control group proportion of 25% (weighted median control group proportion in ceftriaxone in the trials), a relative risk reduction of all-cause mortality of 20% in the experimental group, type I error of 5%, and type II error of 20% is 2188 participants. In such a trial, health-related quality of life, and adverse events (due to any cause: disease-related, treatment-related, or comorbidity-related) should be assessed as outcomes. A short period of follow-up of 90 days may be sufficient to determine the effectiveness of an intervention.

Overall completeness and applicability of evidence

The trials included a wide variety of patients with SBP. There did not seem to be any restriction based on the aetiology or the presence of other features of decompensation in the trials that provided this information. Therefore, the results of the study are applicable in all people with cirrhosis and SBP. We excluded trials in which participants had undergone liver transplantation. Therefore, the findings of this review are not applicable in people with liver decompensation after liver transplantation.

Certainty of the evidence

The overall certainty of evidence was very low. One of the main reasons for the very low-certainty evidence was the unclear or high risk of bias in many of the trials. It is possible to perform trials at low risk of bias in the field. To perform a trial at low risk of bias, randomisation can be performed using standard methods, for example, web-based central randomisation; blinding can be achieved by using a double placebo design (i.e. a placebo for intervention and a placebo for control); an intention-to-treat analysis can be performed; and a protocol can be published prior to recruitment. None of these have any major ethical considerations; therefore, a low risk of bias trial is very much feasible.

Another major reason for very low-certainty evidence is imprecision: the trials had small sample sizes and the credible intervals (CrIs) overlapped clinically significant benefits and clinically significant harms for all comparisons. Therefore, future trials should be adequately powered with sample sizes, as described in the previous section.

Heterogeneity could not be measured because of the presence of a single trial for most comparisons. We used clinical outcomes; therefore, there is no issue of indirectness due to outcomes. The direct comparisons and network meta-analysis results did not result in altered conclusions and the indirect evidence was applicable only in very few comparisons because of the nature of the network. In the comparisons for which indirect evidence was available, the effect estimates were similar to that of direct comparisons. There was no evidence that the patient selection or methodological differences were systematically different across comparisons (i.e. there was no concern regarding the transitivity assumption). Therefore, there is no concern about indirectness of evidence. There was no meaningful way to rank these studies (i.e. there was no specific change in the risk of bias in the studies, sample size, or the control group used over time); we have completed a thorough search for studies on effectiveness. We found no evidence of publication bias.

Potential biases in the review process

We selected a range of databases to search without using any language restrictions and conducted the network meta-analysis according to NICE DSU guidance (Dias 2016). In addition, we have analysed data using the fixed-effect and random-effects model, although we used the fixed-effect model for all the outcomes for the reasons described above. These are the strengths of the review process.

We have excluded studies that compared variations in duration or dose in the different interventions. Hence, this review does not provide information on whether one variation is better than another. Another major limitation of this review was the paucity of data. Few trials were included for each comparison; in many comparisons, only one trial was included. This makes it difficult to assess whether the effect estimates are reproducible. This paucity of data decreases the confidence in the results.

All of the network meta-analyses included only sparse data from trials at high risk of bias. We were able to compare the direct and indirect estimates for very few comparisons. However, the potential

effect modifiers in the trials that reported them were broadly similar across comparisons. The results of direct comparisons and indirect comparisons were also similar, when applicable. However, one cannot rule out violation of the transitivity assumption because of the sparse data; potential differences in the cointerventions, and potential differences in the definitions used by trial authors for adverse events and serious adverse events.

We included only randomised clinical trials which are known to focus mostly on benefits and do not collect and report harms in a detailed manner. Therefore, it is possible that we missed a large number of non-randomised studies addressing the reporting of harms. A significant effort is required to identify the non-randomised studies and assess the risk of bias in those studies. Since it is possible to conduct future studies powered on mortality, a systematic review on adverse events appears to be unnecessary in a superiority trial (as a treatment that reduces short-term mortality will be used even if it increases the adverse events).

Agreements and disagreements with other studies or reviews

This is the first network meta-analysis on the topic. The only systematic review on this topic compared third-generation cephalosporins with other empirical broad-spectrum antibiotics in patients with nosocomial SBP (Fiore 2018). This study included eight non-randomised studies and concluded that there was higher prevalence of antibiotic resistance to third-generation cephalosporins than empirical broad-spectrum antibiotics in patients with nosocomial SBP (Fiore 2018). Only one of the included studies in this review included solely people with nosocomial SBP (Piano 2016). There was no evidence of a difference in any of the outcomes between the meropenem plus daptomycin versus ceftazidime group in this trial. However, this was a small trial and included only 31 participants, indicating that clinically important benefits or harms are possible in this comparison. Therefore, our conclusions are that there is significant uncertainty about whether broad-spectrum antibiotics (meropenem plus daptomycin) are better than third-generation cephalosporins (ceftazidime) in the treatment of nosocomial SBP.

AUTHORS' CONCLUSIONS

Implications for practice

Short-term mortality after spontaneous bacterial peritonitis (SBP) is high (around 25%). There is significant uncertainty about which antibiotic therapy is better in people with SBP. The majority of the randomised clinical trials used third-generation cephalosporins, such as intravenous ceftriaxone or cefotaxime as one of the interventions.

Implications for research

Further well-designed randomised clinical trials are necessary. Some aspects of the design of the randomised clinical trials should be as follows.

- Study design
  - Placebo-controlled, parallel, randomised clinical trial
- Participants
  - People with cirrhosis and SBP
- Intervention
  - Not identified from this network meta-analysis. This could be one of the newer broad-spectrum antibiotics (or combination of antibiotics) or oral third-generation cephalosporins or oral ciprofloxacin.
- Control
  - Intravenous ceftriaxone or cefotaxime until at least resolution of SBP or availability of culture results.
- Outcomes
  - Primary outcome: short-term mortality (90-day all-cause mortality)
  - Secondary outcomes: health-related quality of life, adverse events, resolution of SBP, and resource utilisation measures including length of hospital stay
  - Minimum length of follow-up: 90 days
- Sample size: please see Discussion.

Trials need to be conducted and reported according to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement (Chan 2013), and CONSORT statement (Schulz 2010).

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Danish State and The Copenhagen Trial Unit disclaimer

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REFERENCES

References to studies included in this review

Abd-Elsalam 2016 *{published data only}*

Abd-Elsalam SM, Soliman HH, Elkhalawany WA, Soliman SM, Awny SA, Khalil HS, et al. Is spontaneous bacterial peritonitis still responding to third generation cephalosporins?. *Hepatology International* 2016;**10**(1 Suppl):s489.

Ahmed Ather Ch 2014 *{published data only}*

Ahmed Ather Ch A, Chaudhary S, Khan IM. Comparison of intravenous ciprofloxacin and ceftriaxone in the management of spontaneous bacterial peritonitis in cirrhosis of liver at Mayo hospital, Lahore. *Pakistan Journal of Medical and Health Sciences* 2014;**8**(1):82-4.

Angeli 2006 *{published data only}*

Angeli P, Guarda S, Fasolato S, Miola E, Craighero R, Del Piccolo F, et al. Switch therapy with ciprofloxacin vs. Intravenous ceftazidime in the treatment of spontaneous bacterial peritonitis in patients with cirrhosis: similar efficacy at lower cost. *Alimentary Pharmacology & Therapeutics* 2006;**23**(1):75-84.

Chen 2005 *{published data only}*

Chen TA, Lo GH, Lai KH, Lin WJ. Single daily amikacin versus cefotaxime in the short-course treatment of spontaneous bacterial peritonitis in cirrhotics. *World Journal of Gastroenterology* 2005;**11**(43):6823-7.

Figueiredo 1997 *{published data only}*

Figueiredo FA, Coelho HS, Alvariz RG, Silva FD, Godinho F, Salgueiro E. Randomized trial comparing intravenous ceftriaxone with oral cefixime for treatment of spontaneous bacterial peritonitis (SBP) in cirrhotic patients: pilot study. United European Gastroenterology Week 1996:4 0103.

* Figueiredo FA, Coelho HS, Soares JA, Salgueiro E, Pinto CA. Oral cephalosporin for the treatment of non-severe spontaneous bacterial peritonitis in liver disease: a prospective study of 38 cases. *Gastrenterologia Endoscopia Digestiva* 1997;**16**(6):231-6.

Gomez-Jimenez 1993 *{published data only}*

Gomez-Jimenez J, Ribera E, Gasser I, Artaza MA, Del Valle O, Pahissa A, et al. Randomized trial comparing ceftriaxone with cefonicid for treatment of spontaneous bacterial peritonitis in cirrhotic patients. *Antimicrobial Agents and Chemotherapy* 1993;**37**(8):1587-92.

Jindal 2016 *{published data only}*

* Jindal A, Kumar M, Bhadoria AS, Maiwall R, Sarin SK. A randomized open label study of 'imipenem vs. cefepime' in spontaneous bacterial peritonitis. *Liver International* 2016;**36**(5):677-87.

Jindal A, Maiwal R, Vashishta C, Kumar M, Kumar Chandan KN, Bhatia V, et al. A randomized, comparative open label study of imipenem versus cefepime in difficult to treat spontaneous bacterial peritonitis. *Indian Journal of Gastroenterology* 2014;**33**(1 Suppl 1):a22.

Navasa 1996 *{published data only}*

* Navasa M, Follo A, Llovet JM, Clemente G, Vargas V, Rimola A, et al. Randomized, comparative study of oral ofloxacin versus intravenous cefotaxime in spontaneous bacterial peritonitis. *Gastroenterology* 1996;**111**(4):1011-7.

Navasa M, Planas R, Clemente G, Vargas V, Guarner C, Follo A, et al. Oral ofloxacin versus intravenous cefotaxime in the treatment of non-complicated spontaneous bacterial peritonitis (SBP) in cirrhosis results of a multicenter, prospective, randomized trial. *Journal of Hepatology* 1994;**21**(Suppl 1):s11.

Piano 2016 *{published data only}*

* Piano S, Fasolato S, Salinas F, Romano A, Tonon M, Morando F, et al. The empirical antibiotic treatment of nosocomial spontaneous bacterial peritonitis: results of a randomized, controlled clinical trial. *Hepatology (Baltimore, Md.)* 2016;**63**(4):1299-309.

Piano S, Salinas F, Morando F, Cavallin M, Romano A, Rosi S, et al. The empirical antibiotic treatment of nosocomial spontaneous bacterial peritonitis in patients with decompensated liver cirrhosis: Results of a randomized controlled clinical trial. *Journal of Hepatology* 2015;**62**:s241.

Piano S, Salinas F, Morando F, Cavallin M, Romano A, Rosi S, et al. The empirical antibiotic treatment of nosocomial spontaneous bacterial peritonitis in patients with decompensated liver cirrhosis: results of a randomized controlled clinical trial. *Hepatology (Baltimore, Md.)* 2014;**60**:479a.

Rastegar 1998 *{published data only}*

Rastegar LA, Omrani G, Dehbashi N, Malec F. Evaluation of the therapeutic effect of pefloxacin in comparison with ampicillin and gentamicin in cirrhotic patients with spontaneous bacterial peritonitis. *Hepato-gastroenterology* 1998;**45**(21):783-5.

Tuncer 2003 *{published data only}*

Tuncer I, Topcu N, Durmus A, Turkdogan MK. Oral ciprofloxacin versus intravenous cefotaxime and ceftriaxone in the treatment of spontaneous bacterial peritonitis. *Hepato-gastroenterology* 2003;**50**(53):1426-30.

Yim 2017 *{published data only}*

Yim HJ, Suh SJ, Jung YK, Kim MY, Baik SK, Kim HS, et al. Comparison of efficacy of cefotaxime, ceftriaxone, and ciprofloxacin for the treatment of spontaneous bacterial peritonitis in patients with liver cirrhosis: a randomized controlled trial. *Journal of Hepatology* 2017;**66**(1):s374-s5.

References to studies excluded from this review

Ariza 1991 *{published data only}*

Ariza J, Xiol X, Esteve M, Fernandez Baneres F, Linares J, Alonso T, et al. Aztreonam vs. cefotaxime in the treatment of gram-negative spontaneous peritonitis in cirrhotic patients. *Hepatology (Baltimore, Md.)* 1991;**14**(1):91-8.

Badawy 2013 *{published data only}*

Badawy AA, Zaher TI, Sharaf SM, Emara MH, Shaheen NE, Aly TF. Effect of alternative antibiotics in treatment of cefotaxime resistant spontaneous bacterial peritonitis. *World Journal of Gastroenterology* 2013;**19**(8):1271-7.

Felisart 1985 *{published data only}*

Felisart J, Rimola A, Arroyo V, Perez-Ayuso RM, Quintero E, Gines P, et al. Cefotaxime is more effective than is ampicillin-tobramycin in cirrhotics with severe infections. *Hepatology (Baltimore, Md.)* 1985;**5**(3):457-62.

Grange 2004 *{published data only}*

Grange JD, Thabut D, Lucidarme D, Adler M, Navasa M, Petit P, et al. Randomized, comparative study of moxifloxacin versus amoxicillin-clavulanate in the treatment of bacterial infections in cirrhotic patients. *Hepatology (Baltimore, Md.)* 2004;**40**(4 Suppl 1):631a.

Lim 2011 *{published data only}*

Lim JK, Tandon P, Garcia-Tsao G. Antibiotic prophylaxis and management of bacterial infections. Chronic Liver Failure: Mechanisms and Management. Ginès P, Kamath PS, Arroyo V, 2011:395-410.

Liu 2000 *{published data only}*

Liu XM, Wu Y. The value of therapeutic paracentesis, peritoneal lavage and abdominal antibiotic administration in cirrhotic patients with spontaneous bacterial peritonitis. *Chinese Journal of Clinical Hepatology* 2000;**16**(3):175-7.

McCue 1981 *{published data only}*

McCue JD. Spontaneous bacterial peritonitis. *Hospital Practice* 1981;**16**(8):117, 20, 22-3 passim.

Piano 2011 *{published data only}*

Piano S, Morando F, Angeli P. Spontaneous bacterial peritonitis in patients with cirrhosis and ascites. link.springer.com/chapter/10.1007/978-3-642-18081-1_51 2011 (accessed 16 August 2019).

Ricart 2000 *{published data only}*

Ricart E, Soriano G, Novella MT, Ortiz J, Sabat M, Kolle L, et al. Amoxicillin-clavulanic acid versus cefotaxime in the therapy of bacterial infections in cirrhotic patients. *Journal of Hepatology* 2000;**32**(4):596-602.

Rimola 1984 *{published data only}*

Rimola A, Felisart J, Terés J, Gatell J, Rodés J. Controlled study of the therapeutic efficacy of two antibiotic regimens in spontaneous bacterial peritonitis in cirrhosis prognostic value of bacteriologic data. *Gastroenterologia y Hepatologia* 1984;**7**(5):235-41.

Taskiran 2004 *{published data only}*

Taskiran B, Colakoglu O, Sozmen B, Unsal B, Aslan SL, Buyrac Z. Comparison of cefotaxime and ofloxacin in treatment of spontaneous bacterial peritonitis. *Turkish Journal of Gastroenterology* 2004;**15**(1):34-8.

References to studies awaiting assessment

Zafar 2018 *{published data only}*

Zafar MH, Asghar A, Ather U. Role of oral verses intravenous antibiotic in patients with spontaneous bacterial peritonitis. *Medical Forum Monthly* 2018;**29**(7):32-4.

Additional references

Adam 2012

Adam R, Karam V, Delvart V, O'Grady J, Mirza D, Klempnauer J, et al. Evolution of indications and results of liver transplantation in Europe. A report from the European Liver Transplant Registry (ELTR). *Journal of Hepatology* 2012;**57**(3):675-88.

Aldred 2014

Aldred KJ, Kerns RJ, Osheroff N. Mechanism of quinolone action and resistance. *Biochemistry* 2014;**53**(10):1565-74.

Bernardi 2010

Bernardi M. Spontaneous bacterial peritonitis: from pathophysiology to prevention. *Internal and Emergency Medicine* 2010;**5**(Suppl 1):S37-44.

Best 2018

Best LM, Freeman S, Sutton AJ, Hawkins N, Tsochatzis E, Gurusamy KS. Treatment for hepatorenal syndrome in people with decompensated liver cirrhosis: a network meta-analysis. *Cochrane Database of Systematic Reviews* 2018, Issue 9. [DOI: 10.1002/14651858.CD013103]

Cadranel 2013

Cadranel JF, Nousbaum JB, Bessaguet C, Nahon P, Nguyen-Khac E, Moreau R, et al. Low incidence of spontaneous bacterial peritonitis in asymptomatic cirrhotic outpatients. *World Journal of Hepatology* 2013;**5**(3):104-8.

Castellote 2008

Castellote J, Girbau A, Maisterra S, Charhi N, Ballester R, Xiol X. Spontaneous bacterial peritonitis and bacterascites prevalence in asymptomatic cirrhotic outpatients undergoing large-volume paracentesis. *Journal of Gastroenterology and Hepatology* 2008;**23**(2):256-9.

Chaimani 2012

Chaimani A, Salanti G. Using network meta-analysis to evaluate the existence of small-study effects in a network of interventions. *Research Synthesis Methods* 2012;**3**(2):161-76.

Chaimani 2013

Chaimani A, Higgins JP, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in STATA. *PloS One* 2013;**8**(10):e76654.

Chan 2013

Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gotzsche PC, Krleza-Jeric K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Annals of Internal Medicine* 2013;**158**(3):200-7.

Chavez-Tapia 2009

Chavez-Tapia NC, Soares-Weiser K, Brezis M, Leibovici L. Antibiotics for spontaneous bacterial peritonitis in cirrhotic patients. *Cochrane Database of Systematic Reviews* 2009, Issue 1. [DOI: 10.1002/14651858.CD002232.pub2]

D'Amico 2006

D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. *Journal of Hepatology* 2006;**44**(1):217-31.

D'Amico 2014

D'Amico G, Pasta L, Morabito A, D'Amico M, Caltagirone M, Malizia G, et al. Competing risks and prognostic stages of cirrhosis: a 25-year inception cohort study of 494 patients. *Alimentary Pharmacology & Therapeutics* 2014;**39**(10):1180-93.

de Franchis 2015

de Franchis R, Baveno VIF. Expanding consensus in portal hypertension: report of the Baveno VI consensus workshop: stratifying risk and individualizing care for portal hypertension. *Journal of Hepatology* 2015;**63**(3):743-52.

Devani 2017

Devani K, Charilaou P, Jaiswal P, Patil N, Radadiya D, Patel P, et al. Trends in hospitalization, acute kidney injury, and mortality in patients with spontaneous bacterial peritonitis. Journal of Clinical Gastroenterology 2019; Vol. 53, issue 2:e68-e74. [DOI: 10.1097/MCG.0000000000000973]

Dias 2010

Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. *Statistics in Medicine* 2010;**29**(7-8):932-44.

Dias 2012a

Dias S, Sutton AJ, Welton NJ, Ades AE. NICE DSU technical support document 3: heterogeneity: subgroups, meta-regression, bias and bias-adjustment, September 2011 (last updated April 2012). nicedsu.org.uk/wp-content/uploads/2016/03/TSD3-Heterogeneity.final-report.08.05.12.pdf 2012 (accessed 17 July 2018).

Dias 2012b

Dias S, Welton NJ, Sutton AJ, Ades AE. NICE DSU technical support document 1: introduction to evidence synthesis for decision making, April 2011 (last updated April 2012). scharr.dept.shef.ac.uk/nicedsu/wp-content/uploads/sites/7/2016/03/TSD1-Introduction.final_.08.05.12.pdf 2012 (accessed 17 July 2018).

Dias 2014

Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE. NICE DSU technical support document 4: inconsistency in networks of evidence based on randomised controlled trials, May 2011 (last updated April 2014). nicedsu.org.uk/wp-content/uploads/2016/03/TSD4-Inconsistency.final_.15April2014.pdf 2014 (accessed 17 July 2018).

Dias 2016

Dias S, Welton NJ, Sutton AJ, Ades AE. NICE DSU technical support document 2: a generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials, August 2011 (last updated September 2016). www.ncbi.nlm.nih.gov/pubmedhealth/PMH0088912/pdf/PubMedHealth_PMH0088912.pdf 2016 (accessed 17 July 2018).

EASL 2010

European Association for the Study of the Liver. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. *Journal of Hepatology* 2010;**53**(3):397-417.

EASL 2018

European Association for the Study of the Liver. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. Journal of Hepatology 2018; Vol. 69, issue 2:406-60. [DOI: 10.1016/j.jhep.2018.03.024]

EuroQol 2018

EuroQol. EQ-5D Instruments | About EQ-5D, 2018. euroqol.org/eq-5d-instruments/ (accessed 17 July 2018).

Fiore 2018

Fiore M, Gentile I, Maraolo AE, Leone S, Simeon V, Chiodini P, et al. Are third-generation cephalosporins still the empirical antibiotic treatment of community-acquired spontaneous bacterial peritonitis? A systematic review and meta-analysis. *European Journal of Gastroenterology & Hepatology* 2018;**30**(3):329-36.

Fleming 2008

Fleming KM, Aithal GP, Solaymani-Dodaran M, Card TR, West J. Incidence and prevalence of cirrhosis in the United Kingdom, 1992-2001: a general population-based study. *Journal of Hepatology* 2008;**49**(5):732-8.

Gurusamy 2019

Gurusamy K, Walmsley M, Davidson BR, Frier C, Fuller B, Madden A, et al. Top research priorities in liver and gallbladder disorders in the UK. *BMJ Open* 2019;**9**(3):e025045.

Guyatt 2011

Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *Journal of Clinical Epidemiology* 2011;**64**(4):383-94.

Higgins 2011

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

Higgins 2012

Higgins JP, Jackson D, Barrett JK, Lu G, Ades AE, White IR. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. *Research Synthesis Methods* 2012;**3**(2):98-110.

Hutton 2015

Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Annals of Internal Medicine* 2015;**162**(11):777-84.

ICH-GCP 1997

International Conference on Harmonisation Expert Working Group. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline. Guideline for Good Clinical Practice CFR & ICH Guidelines. Vol. **1**, Philadelphia (PA): Barnett International/PAREXEL, 1997.

Jackson 2014

Jackson D, Barrett JK, Rice S, White IR, Higgins JP. A design-by-treatment interaction model for network meta-analysis with random inconsistency effects. *Statistics in Medicine* 2014;**33**(21):3639-54.

Khan 2009

Khan J, Pikkarainen P, Karvonen AL, Makela T, Peraaho M, Pehkonen E, et al. Ascites: aetiology, mortality and the prevalence of spontaneous bacterial peritonitis. *Scandinavian Journal of Gastroenterology* 2009;**44**(8):970-4.

Kjaergard 2001

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

Lu 2006

Lu G, Ades AE. Assessing evidence inconsistency in mixed treatment comparisons. *Journal of the American Statistical Association* 2006;**101**(474):447-59.

McPherson 2016

McPherson S, Lucey MR, Moriarty KJ. Decompensated alcohol related liver disease: acute management. *BMJ (Clinical Research Ed.)* 2016;**352**:i124.

Merion 2010

Merion RM. Current status and future of liver transplantation. *Seminars in Liver Disease* 2010;**30**(4):411-21.

Mills 2012

Mills EJ, Ioannidis JP, Thorlund K, Schunemann HJ, Puhan MA, Guyatt GH. How to use an article reporting a multiple treatment comparison meta-analysis. *JAMA* 2012;**308**(12):1246-53.

Moher 1998

Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses?. *Lancet* 1998;**352**(9128):609-13.

Mokdad 2014

Mokdad AA, Lopez AD, Shahraz S, Lozano R, Mokdad AH, Stanaway J, et al. Liver cirrhosis mortality in 187 countries between 1980 and 2010: a systematic analysis. *BMC Medicine* 2014;**12**:145.

NCBI 2018a

NCBI. Liver cirrhosis. www.ncbi.nlm.nih.gov/mesh/68008103 (accessed 17 July 2018).

NCBI 2018b

National Center for Biotechnology Information. Ascites. www.ncbi.nlm.nih.gov/mesh/68001201 (accessed 17 July 2018).

Newell 1992

Newell DJ. Intention-to-treat analysis: implications for quantitative and qualitative research. *International Journal of Epidemiology* 1992;**21**(5):837-41.

Nousbaum 2007

Nousbaum JB, Cadranel JF, Nahon P, Khac EN, Moreau R, Thevenot T, et al. Diagnostic accuracy of the multistix 8 sg reagent strip in diagnosis of spontaneous bacterial peritonitis. *Hepatology (Baltimore, Md.)* 2007;**45**(5):1275-81.

Optum 2018

Optum. Patient-reported Outcomes | What We Do | SF Health Surveys | SF-36v2 Health Survey, 2018. campaign.optum.com/optum-outcomes/what-we-do/health-surveys/sf-36v2-health-survey.html (accessed 14 April 2018).

Puhan 2014

Puhan MA, Schünemann HJ, Murad MH, Li T, Brignardello-Petersen R, Singh JA, et al. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. *BMJ (Clinical Research Ed.)* 2014;**349**:g5630.

Ratib 2015

Ratib S, Fleming KM, Crooks CJ, Walker AJ, West J. Causes of death in people with liver cirrhosis in England compared with the general population: a population-based cohort study. *American Journal of Gastroenterology* 2015;**110**(8):1149-58.

Read 1972

Read AE. Clinical physiology of the liver. *British Journal of Anaesthesia* 1972;**44**(9):910-7.

Rimola 2000

Rimola A, Garcia-Tsao G, Navasa M, Piddock LJ, Planas R, Bernard B, et al. Diagnosis, treatment and prophylaxis of spontaneous bacterial peritonitis: a consensus document. International Ascites Club. *Journal of Hepatology* 2000;**32**(1):142-53.

Royle 2003

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

Runyon 2013

Runyon BA, Committee APG. Management of adult patients with ascites due to cirrhosis: an update. *Hepatology (Baltimore, Md.)* 2013;**57**(4):1651-3.

Saab 2009

Saab S, Hernandez JC, Chi AC, Tong MJ. Oral antibiotic prophylaxis reduces spontaneous bacterial peritonitis occurrence and improves short-term survival in cirrhosis: a meta-analysis. *American Journal of Gastroenterology* 2009;**104**(4):993-1001.

Salanti 2011

Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *Journal of Clinical Epidemiology* 2011;**64**(2):163-71.

Salanti 2012

Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. *Research Synthesis Methods* 2012;**3**(2):80-97.

Savović 2012a

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

Savović 2012b

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

Savović 2018

Savović J, Turner RM, Mawdsley D, Jones HE, Beynon R, Higgins JP, et al. Association between risk-of-bias assessments and results of randomized trials in Cochrane Reviews: The ROBES Meta-Epidemiologic Study. *American Journal of Epidemiology* 2018;**187**(5):1113-22.

Scaglione 2015

Scaglione S, Kliethermes S, Cao G, Shoham D, Durazo R, Luke A, et al. The epidemiology of cirrhosis in the united states: a population-based study. *Journal of Clinical Gastroenterology* 2015;**49**(8):690-6.

Schulz 1995

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

Schulz 2010

Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ (Clinical Research Ed.)* 2010;**340**:c332.

Setiawan 2016

Setiawan VW, Stram DO, Porcel J, Lu SC, Le Marchand L, Noureddin M. Prevalence of chronic liver disease and cirrhosis by underlying cause in understudied ethnic groups: the multiethnic cohort. *Hepatology (Baltimore, Md.)* 2016;**64**(6):1969-77.

Severini 1993

Severini Thomas A. Bayesian interval estimates which are also confidence intervals. *Journal of the Royal Statistical Society. Series B (Methodological)* 1993;**55**(2):533-40.

Stata/SE 15.1 [Computer program]

StataCorp. Stata. Version 15. College Station, TX, USA: StataCorp, 2017.

Tandon 2011

Tandon P, Garcia-Tsao G. Renal dysfunction is the most important independent predictor of mortality in cirrhotic patients with spontaneous bacterial peritonitis. *Clinical Gastroenterology and Hepatology* 2011;**9**(3):260-5.

Tsochatzis 2014

Tsochatzis EA, Bosch J, Burroughs AK. Liver cirrhosis. *Lancet* 2014;**383**(9930):1749-61.

Tsochatzis 2017

Tsochatzis EA, Gerbes AL. Diagnosis and treatment of ascites. *Journal of Hepatology* 2017;**67**(1):184-5.

Turner 2012

Turner RM, Davey J, Clarke MJ, Thompson SG, Higgins JP. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. *International Journal of Epidemiology* 2012;**41**(3):818-27.

van Valkenhoef 2012

van Valkenhoef G, Lu G, de Brock B, Hillege H, Ades AE, Welton NJ. Automating network meta-analysis. *Research Synthesis Methods* 2012;**3**(4):285-99.

Williams 2014

Williams R, Aspinall R, Bellis M, Camps-Walsh G, Cramp M, Dhawan A, et al. Addressing liver disease in the UK: a blueprint for attaining excellence in health care and reducing premature mortality from lifestyle issues of excess consumption of alcohol, obesity, and viral hepatitis. *Lancet* 2014;**384**(9958):1953-97.

Wood 2008

Wood L, Egger M, Gluud LL, Schulz KF, Juni P, Altman DG, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. *BMJ (Clinical Research Ed.)* 2008;**336**(7644):601-5.

Yepes-Nunez 2019

Yepes-Nunez JJ, Li SA, Guyatt G, Jack SM, Brozek JL, Beyene J, et al. Development of the summary of findings table for network meta-analysis. Journal of Clinical Epidemiology 2019; Vol. 115:1-13. [DOI: 10.1016/j.jclinepi.2019.04.018]

Yocum 1980

Yocum RR, Rasmussen JR, Strominger JL. The mechanism of action of penicillin. Penicillin acylates the active site of *Bacillus stearothermophilus* d-alanine carboxypeptidase. *Journal of Biological Chemistry* 1980;**255**(9):3977-86.

Yotsuji 1988

Yotsuji A, Mitsuyama J, Hori R, Yasuda T, Saikawa I, Inoue M, et al. Mechanism of action of cephalosporins and resistance caused by decreased affinity for penicillin-binding proteins in *Bacteroides fragilis*. *Antimicrobial Agents and Chemotherapy* 1988;**32**(12):1848-53.

CHARACTERISTICS OF STUDIES

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

Abd-Elsalam 2016

Methods	Randomised clinical trial
Participants	Country: Egypt Number randomised: not stated Post-randomisation dropouts: not stated Revised sample size: not stated Average age: not stated Females: not stated Presence of other features of decompensation (hepatorenal syndrome, hepatic encephalopathy, or variceal bleeding): not stated Alcohol-related cirrhosis: not stated Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis (e.g. PSC, PBC, AIH): not stated Other causes for cirrhosis: not stated Treated for ascites in addition to antibiotics (e.g. albumin or diuretics): not stated Follow-up in months: 0.25 Years of recruitment: 2014 Inclusion criteria • First episode of SBP
Interventions	Participants were randomly assigned to two groups Group 1: cefotaxime (n = not stated) Further details: cefotaxime 2 gm twice/day (route and duration not stated clearly, but appears to be 5 days or 1 week) Group 2: ceftriaxone (n = not stated) Further details: ceftriaxone 2 gm once/day (route duration not stated clearly, but appears to be 5 days or 1 week) Total number of participants and number of participants in each group was not reported

References to other published versions of this review

Gurusamy 2018

Gurusamy KS, Wilson P, Tsochatzis E. Antibiotic treatment for spontaneous bacterial peritonitis in people with decompensated liver cirrhosis: a network meta-analysis. *Cochrane Database of Systematic Reviews* 2018, Issue 9. [DOI: 10.1002/14651858.CD013120]

* Indicates the major publication for the study

Abd-Elsalam 2016 *(Continued)*

Outcomes	None of the outcomes of interest were reported.
Notes	Attempts were made to contact the authors in December 2018; there were no replies.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available.
Selective reporting (reporting bias)	High risk	Comment: a prepublished protocol was not available, but the authors do not report routinely measured clinical outcomes adequately.
Other bias	Low risk	Comment: no other bias was noted.

Ahmed Ather Ch 2014

Methods	Randomised clinical trial
Participants	Country: Pakistan Number randomised: 240 Post-randomisation dropouts: not stated Revised sample size: 240 Average age: 44 years Females: 67 (27.9%). Presence of other features of decompensation (hepatorenal syndrome, hepatic encephalopathy, or variceal bleeding): not stated Alcohol-related cirrhosis: not stated Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis (e.g. PSC, PBC, AIH): not stated Other causes for cirrhosis: not stated

Ahmed Ather Ch 2014 *(Continued)*

	Treated for ascites in addition to antibiotics (e.g. albumin or diuretics): not stated Follow-up in months: 0.25 Years of recruitment: 2011 Exclusion criteria • Patients with haemorrhagic or malignant ascites • Secondary peritonitis • Tuberculosis peritonitis • Hepatocellular carcinoma • Diabetes mellitus
Interventions	Participants were randomly assigned to two groups Group 1: ciprofloxacin (n = 120) Further details: ciprofloxacin 200 mg IV twice/day for 5 days Group 2: ceftriaxone (n = 120) Further details: ceftriaxone 1 gm IV twice/day for 5 days
Outcomes	Outcomes reported • Proportion with recovery from SBP
Notes	Attempts were made to contact the authors in December 2018; there were no replies.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly allocated in two groups using random number table".
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available.
Selective reporting (reporting bias)	High risk	Comment: a prepublished protocol was not available, but the authors do not report routinely measured clinical outcomes adequately.
Other bias	Low risk	Comment: no other bias was noted.

Angeli 2006

Methods	Randomised clinical trial
Participants	Country: Italy Number randomised: 116 Post-randomisation dropouts: 0 Revised sample size: 116 Average age: 60 years Females: 48 (41.4%) Presence of other features of decompensation (hepatorenal syndrome, hepatic encephalopathy, or variceal bleeding): not stated Alcohol-related cirrhosis: both Viral-related cirrhosis: both Autoimmune disease-related cirrhosis (e.g. PSC, PBC, AIH): not stated Other causes for cirrhosis: both Treated for ascites in addition to antibiotics (e.g. albumin or diuretics): both Follow-up in months: 3 Years of recruitment: not stated Exclusion criteria • Antibiotic treatment including prophylactic treatment with quinolones within 1 month of inclusion • History of hypersensitivity to quinolones or beta-lactam antibiotics • Age < 18 years and > 75 years • Evidence of other bacterial or fungal infections • Evidence of organic nephropathy • Presence of shock • Gastrointestinal bleeding • Dehydration • Hepatocellular carcinoma • Cardiac failure • Extrahepatic neoplasia
Interventions	Participants were randomly assigned to two groups. Group 1: ceftazidime (n = 55) Further details: ceftazidime 1 g to 2 g once/day or twice/day depending on creatinine levels for 8 days Group 2: ciprofloxacin (n = 61) Further details: ciprofloxacin 200 mg IV once/day or twice/day depending on serum creatinine converted to oral ciprofloxacin 250 mg twice/day to 500 mg twice/day depending on serum creatinine when possible for a total of 8 days
Outcomes	Outcomes reported • Mortality • Any adverse events (number of people) • Proportion with recovery from SBP • Other features of decompensation

Angeli 2006 *(Continued)*

Notes	Attempts were made to contact the authors in December 2018; there were no replies.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was performed with sealed envelopes containing treatment options prepared with random numbers generated by the STATISTICA 6.1 software."
Allocation concealment (selection bias)	Low risk	Quote: "Randomisation was performed with sealed envelopes containing treatment options prepared with random numbers generated by the STATISTICA 6.1 software."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: a prepublished protocol was not available but the authors report routinely measured clinical outcomes adequately.
Other bias	Low risk	Comment: no other bias was noted.

Chen 2005

Methods	Randomised clinical trial
Participants	Country: China Number randomised: 45 Post-randomisation dropouts: 8 Revised sample size: 37 Average age: 56 years Females: 9 (24.3%) Presence of other features of decompensation (hepatorenal syndrome, hepatic encephalopathy, or variceal bleeding): not stated Alcohol-related cirrhosis: both Viral-related cirrhosis: both Autoimmune disease-related cirrhosis (e.g. PSC, PBC, AIH): not stated Other causes for cirrhosis: both

Chen 2005 *(Continued)*

	Treated for ascites in addition to antibiotics (e.g. albumin or diuretics): not stated Follow-up in months: 1 Years of recruitment: 2000-2002 Exclusion criteria • Allergy to penicillins, cephalosporins or aminoglycoside • Expected life expectancy of less than one month • Secondary peritonitis or tumour rupture • Renal impairment • Antibiotic treatment during previous 2 weeks
Interventions	Participants were randomly assigned to two groups. Group 1: cefotaxime (n = 19) Further details: cefotaxime 1 g IV three times/day for minimum 5 day Group 2: amikacin (n = 18) Further details: amikacin with plasma level maintained at <= 30 mg/dL after a loading dose of 500 mg or 8 mg/Kg depending on weight for a total duration of minimum 5 days
Outcomes	Outcomes reported • Mortality • Any adverse event (number of people) • Proportion with recovery from SBP • Other features of decompensation • Length of hospital stay
Notes	Attempts were made to contact the authors in December 2018; there were no replies. Reason for post-randomisation dropouts: other causes of peritonitis, death, discharged against medical advice before starting treatment

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts which were related to the outcomes.

Chen 2005 *(Continued)*

Selective reporting (reporting bias)	High risk	Comment: a prepublished protocol was not available but the authors do not report routinely measured clinical outcomes adequately
Other bias	Low risk	Comment: no other bias was noted.

Figueiredo 1997

Methods	Randomised clinical trial
Participants	Country: Brazil Number randomised: 38 Post-randomisation dropouts: 0 Revised sample size: 38 Average age: 54 years Females: 16 (42.1%) Presence of other features of decompensation (hepatorenal syndrome, hepatic encephalopathy, or variceal bleeding): not stated Alcohol-related cirrhosis: not stated Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis (e.g. PSC, PBC, AIH): not stated Other causes for cirrhosis: not stated Treated for ascites in addition to antibiotics (e.g. albumin or diuretics): yes Follow-up in months: 0.25 Years of recruitment: not stated Exclusion criteria • Hypersensitivity to cephalosporins • Secondary bacterial peritonitis • Severe shock • Renal failure • Grade III and IV encephalopathy • Hypotension
Interventions	Participants were randomly assigned to two groups. Group 1: cefixime (n = 20) Further details: cefixime 400 mg/day oral until 2 days after resolution of signs/symptoms/polymorphonuclear count < 250/mm^3 Group 2: ceftriaxone (n = 18) Further details: ceftriaxone 1g IV twice/day until 2 days after resolution of signs/symptoms/polymorphonuclear count < 250/mm^3
Outcomes	Outcomes reported • Mortality • Proportion with recovery from SBP

Figueiredo 1997 *(Continued)*

- Treatment costs

Notes	We were unable to locate the current contact details of the author.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Quote: "Sealed envelope method" Comment: further details were not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: prepublished protocol was not available but the authors do not report routinely measured clinical outcomes adequately.
Other bias	Low risk	Comment: no other bias was noted.

Gomez-Jimenez 1993

Methods	Open randomised clinical trial
Participants	Country: Spain Number randomised: 60 Post-randomisation dropouts: not stated Revised sample size: 60 Average age: 59 years Females: 13 (21.7%) Presence of other features of decompensation (hepatorenal syndrome, hepatic encephalopathy, or variceal bleeding): not stated Alcohol-related cirrhosis: both Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis (e.g. PSC, PBC, AIH): not stated Other causes for cirrhosis: both

Gomez-Jimenez 1993 *(Continued)*

	Treated for ascites in addition to antibiotics (for example albumin or diuretics): not stated Follow-up in months: 0.5 Years of recruitment: 1987-1990 Exclusion criteria • History of allergy to beta-lactam antibiotics • Haemorrhage into ascites • Pancreatitis • Tuberculous peritonitis • Peritoneal carcinomatosis
Interventions	Participants were randomly assigned to two groups. Group 1: cefonicid (n = 30) Further details: cefonicid 2g IV twice/day for 10 or 4 days after becoming afebrile, whichever was shortest. Group 2: ceftriaxone (n = 30) Further details: ceftriaxone 2g IV once/day for 10 or 4 days after becoming afebrile, whichever was shortest.
Outcomes	Outcomes reported • Mortality • Any adverse event (number of people) • Proportion with recovery from SBP
Notes	We were unable to locate the current contact details of the author.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: open clinical trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: open clinical trial
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available.
Selective reporting (reporting bias)	Low risk	Comment: a prepublished protocol was not available but the authors report routinely measured clinical outcomes adequately.
Other bias	Low risk	Comment: no other bias was noted.

Jindal 2016

Methods	Open randomised clinical trial
Participants	Country: India Number randomised: 175 Post-randomisation dropouts: 0 Revised sample size: 175 Average age: 49 years Females: 32 (18.3%) Presence of other features of decompensation (hepatorenal syndrome, hepatic encephalopathy, or variceal bleeding): both Alcohol-related cirrhosis: both Viral-related cirrhosis: both Autoimmune disease-related cirrhosis (e.g. PSC, PBC, AIH): not stated Other causes for cirrhosis: both Treated for ascites in addition to antibiotics (e.g. albumin or diuretics): not stated Follow-up in months: 3 Years of recruitment: 2012-2014 Inclusion criteria (if at least one of the following conditions is met) • No response at 48 hours on 3rd generation cephalosporins • Current or recent (within 3 months) infection with 3rd generation cephalosporin-resistant bacteria • New onset SBP detected after 48 hours of hospitalisation Exclusion criteria • Pregnant females • Secondary peritonitis • Tubercular or fungal peritonitis • Advanced hepatocellular carcinoma • Human immunodeficiency virus infection • Patients on immunosuppressive therapy • Patients who had undergone liver transplantation
Interventions	Participants were randomly assigned to two groups. Group 1: cefepime (n = 88) Further details: cefepime 2 g IV twice/day for 5 days Group 2: imipenem (n = 87) Further details: imipenem 1 g IV three times/day for 5 days
Outcomes	Outcomes reported • Mortality • Any adverse events (number of events) • Proportion with recovery from SBP • Other features of decompensation

Jindal 2016 *(Continued)*

Notes	Attempts were made to contact the authors in December 2018; there were no replies.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: open clinical trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: open clinical trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: a prepublished protocol was not available but the authors report routinely measured clinical outcomes adequately.
Other bias	Low risk	Comment: no other bias was noted.

Navasa 1996

Methods	Randomised clinical trial
Participants	Country: Spain Number randomised: 132 Post-randomisation dropouts: 9 Revised sample size: 123 Average age: 59 years Females: 44 (35.8%) Presence of other features of decompensation (hepatorenal syndrome, hepatic encephalopathy, or variceal bleeding): both Alcohol-related cirrhosis: both Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis (e.g. PSC, PBC, AIH): not stated Other causes for cirrhosis: both Treated for ascites in addition to antibiotics (e.g. albumin or diuretics): not stated

Navasa 1996 *(Continued)*

	Follow-up in months: 0.5 Years of recruitment: 1992-1994 Exclusion criteria • Absence of severe complications at infection diagnosis, i.e. shock, gastrointestinal haemorrhage, renal impairment or grade II-IV hepatic encephalopathy • Antibiotic treatment within 2 weeks before inclusion • History of hypersensitivity to quinolones or beta-lactam antibiotics
Interventions	Participants were randomly assigned to two groups. Group 1: ofloxacin (n = 64) Further details: ofloxacin 100 mg/day to 800 mg/day depending upon creatinine levels (4 days to 2 weeks) Group 2: cefotaxime (n = 59) Further details: cefotaxime 1 g/day to 8 g/day depending upon creatinine levels (4 days to 2 weeks)
Outcomes	Outcomes reported • Mortality • Proportion with recovery from SBP • Other features of decompensation • Length of hospital stay
Notes	We were unable to locate the current contact details of the author. Reason for post-randomisation dropouts: secondary peritonitis, voluntary dropout

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed with sealed envelopes containing the treatment options prepared with random numbers generated by the SAS statistical package (SAS Institute Inc., Cary, NC)".
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was performed with sealed envelopes containing the treatment options prepared with random numbers generated by the SAS statistical package (SAS Institute Inc., Cary, NC)".
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there were post-randomisation dropouts; it is not clear whether this was related to treatment and/or outcomes.
Selective reporting (reporting bias)	Low risk	Comment: a prepublished protocol was not available but the authors report routinely measured clinical outcomes adequately.
Other bias	Low risk	Comment: no other bias was noted.

Piano 2016

Methods	Randomised clinical trial
Participants	Country: Italy Number randomised: 32 Post-randomisation dropouts: 1 Revised sample size: 31 Average age: 60 years Females: 12 (38.7%) Presence of other features of decompensation (hepatorenal syndrome, hepatic encephalopathy, or variceal bleeding): not stated Alcohol-related cirrhosis: both Viral-related cirrhosis: both Autoimmune disease-related cirrhosis (e.g. PSC, PBC, AIH): not stated Other causes for cirrhosis: both Treated for ascites in addition to antibiotics (e.g. albumin or diuretics): not stated Follow-up in months: 3 Years of recruitment: 2011-2014 Inclusion criteria • Nosocomial SBP Exclusion criteria • Secondary peritonitis • Onset of infection ≤ 72 hours from hospitalisation • Abdominal surgery in the previous 4 weeks • Hepatocellular carcinoma beyond the Milan Criteria • Congestive heart failure and/or respiratory failure • Treatment with third-generation cephalosporins, carbapenems or daptomycin at the time of diagnosis of SBP • Isolation of bacteria resistant to third-generation cephalosporins, carbapenems and/or daptomycin in cultures performed in the previous 7 days • Allergy to ceftazidime, meropenem and/or daptomycin
Interventions	Participants were randomly assigned to two groups. Group 1: ceftazidime (n = 16) Further details: ceftazidime 2 g/day to 6 g/day depending on glomerular filtration rate for at least 7 days Group 2: meropenem + daptomycin (n = 15) Further details: meropenem 0.5 g to 3 g/day plus daptomycin 3 mg/Kg/day to 6 mg/Kg/day depending on glomerular filtration rate for at least 7 days
Outcomes	Outcomes reported • Mortality • Serious adverse events (number of people)

Piano 2016 *(Continued)*

- Any adverse events (number of people)
- Liver transplantation
- Proportion with recovery from SBP
- Other features of decompensation

Notes	Attempts were made to contact the authors in December 2018; there were no replies. Reason for post-randomisation dropout: secondary peritonitis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed using consecutively numbered, computer-generated, sealed, opaque envelopes containing the treatment assigned."
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was performed using consecutively numbered, computer-generated, sealed, opaque envelopes containing the treatment assigned."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Independent laboratory examiners, blinded to assigned treatment, manually assessed the ascitic fluid PMN count". Comment: it is not clear whether patients and healthcare providers were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Independent laboratory examiners, blinded to assigned treatment, manually assessed the ascitic fluid PMN count". Comment: it is not clear whether patients and healthcare providers were blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there were post-randomisation dropouts; it is not clear whether this was related to treatment and/or outcomes.
Selective reporting (reporting bias)	Low risk	Comment: a prepublished protocol was not available but the authors report routinely measured clinical outcomes adequately.
Other bias	Low risk	Comment: no other bias was noted.

Rastegar 1998

Methods	Randomised clinical trial
Participants	Country: Iran Number randomised: 20 Post-randomisation dropouts: not stated Revised sample size: 20 Average age: 42 years Females: 5 (25%)

Rastegar 1998 *(Continued)*

	Presence of other features of decompensation (hepatorenal syndrome, hepatic encephalopathy, or variceal bleeding): not stated Alcohol-related cirrhosis: not stated Viral-related cirrhosis: both Autoimmune disease-related cirrhosis (e.g. PSC, PBC, AIH): not stated Other causes for cirrhosis: both Treated for ascites in addition to antibiotics (e.g. albumin or diuretics): not stated Follow-up in months: 0.25 Years of recruitment: not stated Inclusion and exclusion criteria: not stated
Interventions	Participants were randomly assigned to two groups. Group 1: ampicillin + gentamycin (n = 9) Further details: ampicillin IV 4 g/day plus gentamycin 40 to 60 mg IV three times/day for 10 to 14 days Group 2: pefloxacin (n = 11) Further details: pefloxacin 400 mg/36 hours for 7 to 10 days
Outcomes	Outcomes reported • Mortality
Notes	We were unable to locate the current contact details of the author. Follow-up information was not available, but the follow-up was probably until the end of hospitalisation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available.
Selective reporting (reporting bias)	High risk	Comment: a prepublished protocol was not available but the authors do not report routinely measured clinical outcomes adequately.
Other bias	Low risk	Comment: no other bias was noted.

Tuncer 2003

Methods	Randomised clinical trial
Participants	Country: Turkey Number randomised: 53 Post-randomisation dropouts: 0 Revised sample size: 53 Average age: 46 years Females: 19 (35.8%) Presence of other features of decompensation (hepatorenal syndrome, hepatic encephalopathy, or variceal bleeding): both Alcohol-related cirrhosis: not stated Viral-related cirrhosis: both Autoimmune disease-related cirrhosis (e.g. PSC, PBC, AIH): not stated Other causes for cirrhosis: both Treated for ascites in addition to antibiotics (e.g. albumin or diuretics): not stated Follow-up in months: 0.25 Years of recruitment: not stated Exclusion criteria • Hypersensitivity to quinolones or cephalosporins • Recent antibiotic use • Systemic infections • Secondary peritonitis
Interventions	Participants were randomly assigned to three groups. Group 1: cirpofloxacin (n = 16) Further details: ciprofloxacin 500 mg oral twice/day for 5 days Group 2: cefotaxime (n = 18) Further details: cefotaxime 2 g IV three times/day for 5 days Group 3: ceftriaxone (n = 19) Further details: ceftriaxone 2 g/day IV for 5 days
Outcomes	Outcome reported • Mortality • Any adverse events (number of people) • Proportion with recovery from SBP • Other features of decompensation • Treatment costs
Notes	Attempts were made to contact the authors in December 2018; there were no replies.

Tuncer 2003 *(Continued)*

	Follow-up information was not available but the follow-up was probably until the end of hospitalisation. Although the authors excluded 3 patients from the analysis, these have been included for all outcomes other than complications and decompensated cirrhosis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all patients were included in the analysis of mortality and SBP resolution. There were post-randomisation dropouts related to the treatment and outcome for remaining outcomes; therefore risk of bias is high for these outcomes.
Selective reporting (reporting bias)	Low risk	Comment: a prepublished protocol was not available but the authors report routinely measured clinical outcomes adequately.
Other bias	Low risk	Comment: no other bias was noted.

Yim 2017

Methods	Randomised clinical trial
Participants	Country: South Korea Number randomised: 261 Post-randomisation dropouts: not stated Revised sample size: 261 Average age: not stated Females: not stated Presence of other features of decompensation (hepatorenal syndrome, hepatic encephalopathy, or variceal bleeding): not stated Alcohol-related cirrhosis: not stated Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis (e.g. PSC, PBC, AIH): not stated Other causes for cirrhosis: not stated

Yim 2017 *(Continued)*

	Treated for ascites in addition to antibiotics (e.g. albumin or diuretics): not stated Follow-up in months: 0.25 Years of recruitment: 2007-2016 Exclusion criteria • Allergic to third-generation cephalosporins or quinolones • Antibiotics within 2 weeks • Open abdominal surgery within 4 weeks • Evidence of secondary peritonitis, intra-abdominal haemorrhage, pancreatitis, tuberculous peritonitis or peritoneal carcinomatosis • Hepatocellular carcinoma with portal vein thrombosis • Pregnant women • HIV positivity
Interventions	Participants were randomly assigned to three groups. Group 1: ciprofloxacin (n = not stated) Further details: (route and duration not stated) Group 2: cefotaxime (n = not stated) Further details: (route and duration not stated) Group 3: ceftriaxone (n = not stated) Further details: (route and duration not stated) Number of participants in each group not stated
Outcomes	None of the outcomes of interest were reported.
Notes	Attempts were made to contact the authors in December 2018; there were no replies.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available.
Selective reporting (reporting bias)	High risk	Comment: a prepublished protocol was not available but the authors do not report routinely measured clinical outcomes adequately.

Yim 2017 *(Continued)*

Other bias	Low risk	Comment: no other bias was noted.

AIH: autoimmune hepatitis
IV: intravenous
PBC: primary biliary cholangitis
PSC: primary sclerosing cholangitis
SBP: spontaneous bacterial peritonitis

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

Study	Reason for exclusion
Ariza 1991	Only one group was allowed to receive other antibiotics in addition to the randomised treatment.
Badawy 2013	Randomisation was performed after matching to similar patients; the allocation of the second person can be predicted with 100% accuracy.
Felisart 1985	It includes infections other than SBP and no separate data are available.
Grange 2004	It includes infections other than SBP and no separate data are available.
Lim 2011	This is a review.
Liu 2000	This is not a randomised clinical trial.
McCue 1981	This is a review.
Piano 2011	This is a review.
Ricart 2000	It includes infections other than SBP and no separate data are available.
Rimola 1984	This is not a randomised clinical trial.
Taskiran 2004	This is not a randomised clinical trial.

SBP: spontaneous bacterial peritonitis

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

Zafar 2018

Methods	Randomised clinical trial
Participants	People with cirrhosis and spontaneous bacterial peritonitis
Interventions	Oral antibiotics versus intravenous antibiotics
Outcomes	Mortality
Notes	It was not clear whether a single oral antibiotic was compared with intravenous antibiotic or a group of oral antibiotics was compared with a group of intravenous antibiotics or whether the same antibiotic was compared by oral and intravenous antibiotics. We made attempts to clarify this information from the authors in December 2018, but we did not receive any replies.

ADDITIONAL TABLES

Table 1. Characteristics and potential effect modifiers of included studies ordered by comparison

Study name	Intervention 1	Intervention 2	Intervention 1: number of participants	Intervention 2: number of participants	Presence of other features of decompensation (hepatorenal syndrome, hepatic encephalopathy, or variceal bleeding)	Alcohol-related cirrhosis	Viral-related cirrhosis	Other causes for cirrhosis	Treated for ascites in addition to antibiotics (e.g. albumin or diuretics)	Follow-up in months	Year of recruitment
Abd-El-salam 2016	Cefotaxime	Ceftriaxone	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	0.25	2014
Tuncer 2003	Cefotaxime	Ceftriaxone	18	19	Includes people with and without other features of decompensation	Not stated	Includes people with and without viral-related cirrhosis	Includes people with and without other causes of cirrhosis	Not stated	0.25	Not stated
Yim 2017	Cefotaxime	Ceftriaxone	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	0.25	2007-2016
Ahmed Ather Ch 2014	Ciprofloxacin	Ceftriaxone	120	120	Not stated	Not stated	Not stated	Not stated	Not stated	0.25	2011
Tuncer 2003	Ciprofloxacin	Ceftriaxone	16	19	Includes people with and without other features of decompensation	Not stated	Includes people with and without viral-related cirrhosis	Includes people with and without other causes of cirrhosis	Not stated	0.25	Not stated
Yim 2017	Ciprofloxacin	Ceftriaxone	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	0.25	2007-2016
Figueiredo 1997	Cefixime	Ceftriaxone	20	18	Includes people with and	Includes people with	Not stated	Not stated	Not stated	0.25	Not stated

Table 1. Characteristics and potential effect modifiers of included studies ordered by comparison *(Continued)*

					without other features of decompensation	and without alcohol-related cirrhosis					
Gomez-Jimenez 1993	Cefonicid	Ceftriaxone	30	30	Not stated	Includes people with and without alcohol-related cirrhosis	Not stated	Includes people with and without other causes of cirrhosis	Not stated	0.5	1987-1990
Tuncer 2003	Ciprofloxacin	Cefotaxime	16	18	Includes people with and without other features of decompensation	Not stated	Includes people with and without viral-related cirrhosis	Includes people with and without other causes of cirrhosis	Not stated	0.25	Not stated
Yim 2017	Ciprofloxacin	Cefotaxime	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	0.25	2007-2016
Chen 2005	Amikacin	Cefotaxime	18	19	Not stated	Includes people with and without alcohol-related cirrhosis	Includes people with and without viral-related cirrhosis	Includes people with and without other causes of cirrhosis	Not stated	1	2000-2002
Navasa 1996	Ofloxacin	Cefotaxime	64	59	Includes people with and without other features of decompensation	Includes people with and without alcohol-related cirrhosis	Not stated	Includes people with and without other causes of cirrhosis	Not stated	0.5	1992-1994
Angeli 2006	Ceftazidime	Ciprofloxacin	55	61	Not stated	Includes people with and without alcohol-related cirrhosis	Includes people with and without viral-related cirrhosis	Includes people with and without other causes of cirrhosis	Includes people receiving and not receiving other treatments	3	Not stated

Table 1. Characteristics and potential effect modifiers of included studies ordered by comparison *(Continued)*

									for ascites		
Piano 2016	Meropenem plus daptomycin	Ceftazidime	15	16	Not stated	Includes people with and without alcohol-related cirrhosis	Includes people with and without viral-related cirrhosis	Includes people with and without other causes of cirrhosis	Not stated	3	2011 to 2014
Rastegar 1998	Pefloxacin	Ampicillin plus gentamycin	11	9	Not stated	Not stated	Includes people with and without viral-related cirrhosis	Includes people with and without other causes of cirrhosis	Not stated	0.25	Not stated
Jindal 2016	Imipenem	Cefepime	87	88	Includes people with and without other features of decompensation	Includes people with and without alcohol-related cirrhosis	Includes people with and without viral-related cirrhosis	Includes people with and without other causes of cirrhosis	Not stated	3	2012-2014

Table 2. Risk of bias ordered by comparison

Study name	Intervention 1	Intervention 2	Sequence generation	Allocation concealment	Blinding of patients and healthcare providers	Blinding of outcome assessors	Missing outcome bias	Selective outcome reporting	Source of funding
Abd-Elsalam 2016	Cefotaxime	Ceftriaxone	Unclear	Unclear	Unclear	Unclear	Unclear	High	Unclear
Tuncer 2003	Cefotaxime	Ceftriaxone	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear
Yim 2017	Cefotaxime	Ceftriaxone	Unclear	Unclear	Unclear	Unclear	Unclear	High	Unclear
Ahmed Ather Ch 2014	Ciprofloxacin	Ceftriaxone	Low	Unclear	Unclear	Unclear	Unclear	High	Unclear
Tuncer 2003	Ciprofloxacin	Ceftriaxone	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear
Yim 2017	Ciprofloxacin	Ceftriaxone	Unclear	Unclear	Unclear	Unclear	Unclear	High	Unclear

Table 2. Risk of bias ordered by comparison *(Continued)*

Figueiredo 1997	Cefixime	Ceftriaxone	Unclear	Unclear	Unclear	Unclear	Low	High	Unclear
Gomez-Jimenez 1993	Cefonicid	Ceftriaxone	Unclear	Unclear	High	High	Unclear	Low	Unclear
Tuncer 2003	Ciprofloxacin	Cefotaxime	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear
Yim 2017	Ciprofloxacin	Cefotaxime	Unclear	Unclear	Unclear	Unclear	Unclear	High	Unclear
Chen 2005	Amikacin	Cefotaxime	Unclear	Unclear	Unclear	Unclear	High	High	Unclear
Navasa 1996	Ofloxacin	Cefotaxime	Low	Low	Unclear	Unclear	Unclear	Low	High
Angeli 2006	Ceftazidime	Ciprofloxacin	Low	Low	Unclear	Unclear	Low	Low	Unclear
Piano 2016	Meropenem plus daptomycin	Ceftazidime	Low	Low	Unclear	Unclear	Unclear	Low	High
Rastegar 1998	Pefloxacin	Ampicillin plus gentamycin	Unclear	Unclear	Unclear	Unclear	Unclear	High	Unclear
Jindal 2016	Imipenem	Cefepime	Unclear	Unclear	High	High	Low	Low	Unclear

Table 3. Model fit

All-cause mortality at maximal follow-up	Fixed-effect model	Random-effects model	Inconsistency model
Dbar	65.76	65.69	65.73
DIC	80.48	80.35	80.43
pD	14.72	14.66	14.7
Adverse events proportion	**Fixed-effect model**	**Random-effects model**	**Inconsistency model**
Dbar	45.75	45.77	45.73
DIC	56.81	56.86	56.79
pD	11.06	11.09	11.06
SBP resolution	**Fixed-effect model**	**Random-effects model**	**Inconsistency model**
Dbar	61.72	62.34	62.42
DIC	75.77	77.07	77.24
pD	14.05	14.73	14.82
Other decompensation	**Fixed-effect model**	**Random-effects model**	**Inconsistency model**
Dbar	56.05	56.01	56.05
DIC	66.88	66.78	66.87
pD	10.83	10.77	10.83

Length of hospital stay	Fixed-effect model	Random-effects model	Inconsistency model
Dbar	14.39	14.38	14.39
DIC	18.39	18.36	18.39
pD	3.999	3.986	3.999

Abbreviations
Dbar: posterior mean of deviance; pD: effective number of parameters or leverage; DIC: deviance information criteria

Table 4. Effect estimates (network meta-analysis)

All-cause mortality	Ceftriaxone	Cefotaxime	Ciprofloxacin	Ceftazidime	Amikacin	Cefixime	Cefonicid	Meropenem + daptomycin	Ofloxacin
Ceftriaxone	-	0.58[0.11,2.54]	0.63[0.12,2.88]	-	-	1.26[0.27,7.01]	1.29[0.53,3.23]		-
Cefotaxime	0.56[0.11,2.28]	-	1.13[0.20,6.67]	-	1.40[0.36,5.85]		-	-	1.01[0.44,2.36]
Ciprofloxacin	0.65[0.12,2.72]	1.16[0.20,6.90]	-	1.76[0.72,4.66]	-	-	-	-	-
Ceftazidime	1.15[0.17,6.37]	2.08[0.28,15.24]	1.77[0.73,4.58]	-	-	-	-	0.56[0.10,2.47]	
Amikacin	0.76[0.09,5.90]	1.39[0.35,6.00]	1.20[0.13,11.68]	0.67[0.06,7.62]	-	-	-	-	-
Cefixime	1.26[0.26,6.90]	2.32[0.27,23.93]	1.99[0.23,21.07]	1.11[0.11,13.68]	1.66[0.12,25.20]		-	-	-
Cefonicid	1.30[0.52,3.24]	2.34[0.43,15.52]	2.02[0.36,13.61]	1.14[0.16,9.30]	1.68[0.18,17.44]	1.02[0.15,6.39]		-	-
Meropenem + daptomycin	0.64[0.05,6.13]	1.16[0.09,13.48]	1.00[0.15,5.60]	0.57[0.11,2.41]	0.83[0.04,13.94]	0.50[0.03,7.76]	0.49[0.03,5.81]		-
Ofloxacin	0.56[0.09,2.93]	1.01[0.44,2.35]	0.87[0.12,6.19]	0.49[0.06,4.25]	0.73[0.14,3.63]	0.43[0.04,4.34]	0.43[0.05,2.87]	0.87[0.06,12.52]	

Proportion of people with any adverse event	Ceftriaxone	Cefotaxime	Ciprofloxacin	Ceftazidime	Amikacin	Cefonicid	Meropenem + daptomycin	-
Ceftriaxone	-	0.65[0.14,2.69]	1.03[0.25,4.33]	-	-	1.00[0.10,10.23]		
Cefotaxime	0.64[0.15,2.62]	-	1.60[0.36,7.38]	-	1.07[0.10,11.19]		-	
Ciprofloxacin	1.02[0.24,4.16]	1.59[0.36,7.46]	-	1.95[0.86,4.49]	-	-	-	
Ceftazidime	1.97[0.38,10.18]	3.06[0.56,17.74]	1.93[0.87,4.47]	-	-	-	0.61[0.10,3.56]	
Amikacin	0.69[0.04,10.94]	1.07[0.10,11.31]	0.66[0.04,10.95]	0.34[0.02,6.58]	-	-	-	
Cefonicid	1.00[0.10,10.16]	1.58[0.10,24.34]	0.98[0.06,14.86]	0.51[0.03,8.72]	1.47[0.04,54.82]		-	
Meropenem + daptomycin	1.20[0.10,13.53]	1.88[0.15,22.83]	1.17[0.16,8.47]	0.61[0.09,3.62]	1.72[0.06,52.67]	1.18[0.04,34.61]		

Table 4. Effect estimates (network meta-analysis) *(Continued)*

Resolution of SBP	**Ceftriaxone**	**Cefotaxime**	**Ciprofloxacin**	**Ceftazidime**	**Amikacin**	**Cefixime**	**Meropenem + daptomycin**	**Ofloxacin**
Ceftriaxone	-	0.95[0.41,2.15]	0.93[0.69,1.25]	-	-	0.78[0.32,1.88]	-	-
Cefotaxime	0.90[0.42,1.86]	-	1.08[0.45,2.53]	-	0.59[0.25,1.34]	-	-	1.23[0.75,2.06]
Ciprofloxacin	0.93[0.69,1.25]	1.03[0.50,2.24]	-	1.05[0.64,1.72]	-	-	-	-
Ceftazidime	0.97[0.55,1.72]	1.08[0.44,2.71]	1.05[0.64,1.72]	-	-	-	1.32[0.51,3.46]	-
Amikacin	0.54[0.17,1.62]	0.60[0.25,1.38]	0.58[0.18,1.78]	0.55[0.16,1.86]	-	-	-	-
Cefixime	0.78[0.32,1.90]	0.87[0.28,2.76]	0.85[0.33,2.14]	0.80[0.28,2.31]	1.47[0.35,6.11]	-	-	-
Meropenem + daptomycin	1.29[0.43,3.92]	1.43[0.39,5.38]	1.38[0.48,4.08]	1.32[0.52,3.51]	2.40[0.51,11.53]	1.64[0.40,6.83]	-	-
Ofloxacin	1.12[0.45,2.70]	1.24[0.76,2.06]	1.21[0.48,2.92]	1.15[0.41,3.23]	2.08[0.79,5.66]	1.43[0.40,5.03]	0.87[0.21,3.53]	-

Other decompensation	**Ceftriaxone**	**Cefotaxime**	**Ciprofloxacin**	**Ceftazidime**	**Amikacin**	**Meropenem + daptomycin**	**Ofloxacin**
Ceftriaxone	-	1.21[0.43,3.48]	1.01[0.31,3.13]	-	-	-	-
Cefotaxime	1.22[0.43,3.53]	-	0.82[0.26,2.40]	-	1.05[0.11,10.05]	-	0.92[0.43,1.95]
Ciprofloxacin	1.01[0.32,3.16]	0.83[0.27,2.46]	-	1.40[0.78,2.51]	-	-	-
Ceftazidime	1.43[0.40,5.19]	1.18[0.33,3.97]	1.42[0.81,2.50]	-	-	1.52[0.72,3.32]	-
Amikacin	1.28[0.11,15.66]	1.05[0.11,10.27]	1.27[0.10,15.24]	0.89[0.07,11.72]	-	-	-
Meropenem + daptomycin	2.19[0.49,9.49]	1.81[0.41,7.57]	2.17[0.85,5.64]	1.53[0.73,3.31]	1.72[0.12,24.31]	-	-
Ofloxacin	1.12[0.31,4.09]	0.92[0.43,1.96]	1.10[0.30,4.24]	0.78[0.19,3.35]	0.88[0.08,9.51]	0.51[0.10,2.63]	-

Length of hospital stay	**Cefotaxime**	**Amikacin**	**Ofloxacin**	-

Table 4. Effect estimates (network meta-analysis) *(Continued)*

Cefotaxime	-	1.01[-4.47,6.41]	-0.99[-4.07,2.09]
Amikacin	1.01[-4.43,6.47]	-	-
Ofloxacin	-0.99[-4.02,2.02]	-2.03[-8.30,4.25]	-

Abbreviations: SBP: spontaneous bacterial peritonitis

The table provides the effect estimates (proportion of people with any adverse events; hazard ratio for all-cause mortality and spontaneous resolution for SBP; rate ratio for other decompensation; and mean difference in days for length of hospital stay) of each pairwise comparison for the different outcomes. The top half of the table indicates the effect estimates from the direct comparisons. The bottom half of the table indicates the effect estimates from the network meta-analysis. For network meta-analysis, to identify the effect estimate of a comparison, say A versus B, look at the cell that occupies the row corresponding to intervention A and the column corresponding to intervention B for the direct effect estimate. If that cell is empty (indicated by a '-'), look at the row corresponding to intervention B and the column corresponding to intervention A. Take the inverse of this number (i.e. 1/number) to arrive at the treatment effect of A versus B. For direct comparisons, this is exactly the opposite; look at the cell that occupies the column corresponding to intervention A and the row corresponding to intervention B for the direct effect estimate. If that cell is empty, look at the column corresponding to intervention B and the row corresponding to intervention A. Take the inverse of this number to arrive at the treatment effect of A versus B. If the cell corresponding to B versus A is also missing in direct comparisons, this means that there was no direct comparison.

There were no significant differences in the effect estimates for any of the comparisons in any of the outcomes for which network meta-analysis could be performed.

APPENDICES

Appendix 1. Search strategies

Database	Time span	Search strategy
Central Register of Controlled Trials (CENTRAL) in the Cochrane Library	Issue 11, 2018	#1 (spontaneous near/3 bacterial near/3 peritonitis) #2 MeSH descriptor: [Liver Cirrhosis] explode all trees #3 ((hepatic or liver) and (fibrosis or cirrhosis or cirrhotic)) #4 #2 or #3 #5 #1 and #4
MEDLINE Ovid	January 1947 to November 2018	1. (spontaneous adj3 bacterial adj3 peritonitis).ti,ab. 2. exp Liver Cirrhosis/ 3. ((hepatic or liver) and (fibrosis or cirrhosis or cirrhotic)).ti,ab. 4. 2 or 3 5. 1 and 4 6. randomized controlled trial.pt. 7. controlled clinical trial.pt. 8. randomized.ab. 9. placebo.ab. 10. drug therapy.fs. 11. randomly.ab. 12. trial.ab. 13. groups.ab. 14. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 15. exp animals/ not humans.sh. 16. 14 not 15 17. 5 and 16
Embase Ovid	January 1974 to November 2018	1. exp bacterial peritonitis/ 2. (spontaneous adj3 bacterial adj3 peritonitis).ti,ab. 3. 1 or 2 4. exp liver cirrhosis/ 5. ((hepatic or liver) and (fibrosis or cirrhosis or cirrhotic)).ti,ab. 6. 4 or 5 7. 3 and 6

(Continued)

		8. exp crossover-procedure/ or exp double-blind procedure/ or exp randomized controlled trial/ or single-blind procedure/ 9. (((((random* or factorial* or crossover* or cross over* or cross-over* or placebo* or double*) adj blind*) or single*) adj blind*) or assign* or allocat* or volunteer*).af. 10. 8 or 9 11. 7 and 10
Science Citation Index Expanded (Web of Science)	January 1945 to November 2018	#1 TS=(spontaneous near/3 bacterial near/3 peritonitis) #2 TS=((hepatic or liver) and (fibrosis or cirrhosis or cirrhotic)) #3 TS=(random* OR rct* OR crossover OR masked OR blind* OR placebo* OR meta-analysis OR systematic review* OR meta-analys*) #4 #1 AND #2 AND #3
World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch/Default.aspx)	November 2018	spontaneous bacterial peritonitis
ClinicalTrials.gov	November 2018	cirrhosis | Interventional Studies | Spontaneous Bacterial Peritonitis | Phase 2, 3, 4
European Medical Agency (www.ema.europa.eu/ema/) and US Food and Drug Administration (www.fda.gov)	November 2018	spontaneous bacterial peritonitis

CONTRIBUTIONS OF AUTHORS

Protocol

Conceiving the protocol: KG
Designing the protocol: KG
Co-ordinating the protocol: KG
Designing search strategies: KG
Writing the protocol: KG
Providing general advice on the protocol: ET, PW
Securing funding for the protocol: KG
Performing previous work that was the foundation of the current study: not applicable

Review

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Study selection: KG, LP, AB, MP, DR
Data extraction: KG, LP
Writing the review: KG with contribution of LP for characteristics and 'Risk of bias' tables
Providing advice on the review: EJM, PW, AJS, NJC, NH, SF, DT, CSP, BRD, ET
Securing funding for the review: KG

DECLARATIONS OF INTEREST

None known for any of the authors.

SOURCES OF SUPPORT

Internal sources

- University College London, UK.

  Writing equipment, software, etc.

External sources

- National Institute for Health Research, UK.

  Payment for writing reviews, writing equipment, software

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. We did not perform Trial Sequential Analysis (TSA), as the risk of false positive results with Bayesian meta-analysis is probably less or at least equivalent to TSA.
2. We used the latest guidance from the GRADE Working group (Yepes-Nunez 2019), rather than the previous guidance (Puhan 2014), for presenting the 'Summary of findings' table.
3. The trials did not report the proportion of people with other episodes of decompensation but reported the number of episodes of decompensation. Therefore, we treated this as a count outcome and used the Poisson likelihood to calculate the rate ratio.
4. We used ceftriaxone rather than cefotaxime as the control group, since ceftriaxone was the commonest control group in the trials.
5. In the absence of a protocol published prior to the start of the study, we have classified the risk of bias as low for selective reporting bias only when mortality, adverse events, and spontaneous bacterial peritonitis (SBP) were reported, as we anticipated these outcomes to be routinely measured in clinical trials of this nature.
6. We used 30,000 iterations as a minimum for burn-in.
7. We did not present some information because of the concern about the misinterpretation of the results. We have highlighted this clearly within the text of the review along with the reasons for not presenting them.

NOTES

The methods section of this protocol is based on a standard Cochrane Hepato-Biliary Group template incorporating advice by the Complex Reviews Support Unit for a network meta-analysis protocol (Best 2018).

INDEX TERMS

Medical Subject Headings (MeSH)

*Quality of Life; Anti-Bacterial Agents [*therapeutic use]; Bayes Theorem; Liver Cirrhosis [*complications] [therapy]; Liver Transplantation; Network Meta-Analysis; Peritonitis [*drug therapy] [etiology]; Randomized Controlled Trials as Topic

MeSH check words

Humans