National Institute for Health and Care Excellence

Cirrhosis in over 16s: assessment and management (update)

[B] Evidence review for the use of antibiotics to prevent spontaneous bacterial peritonitis

NICE guideline NG50

Evidence reviews underpinning recommendations 1.3.7 and 1.3.8 and research recommendations in the NICE guideline

May 2023

Draft for consultation

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ISBN: xxx

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1.1 Review question

What is the clinical and cost-effectiveness of antibiotics compared with placebo for the primary prevention of spontaneous bacterial peritonitis (SBP) in people with cirrhosis and ascites?

1.1.1 Introduction

NICE guideline NG50 recommends prophylactic oral fluoroquinolones, specifically ciprofloxacin or norfloxacin, for people with cirrhosis and ascites with an ascitic protein of 15 g/litre or less, until the ascites has resolved, as primary prophylaxis for spontaneous bacterial peritonitis. NICE surveillance identified evidence that might impact this recommendation. Norfloxacin has been withdrawn in the UK and there is an MHRA Drug safety update on fluoroquinolones. As a result, a new review of the evidence has been undertaken to allow a committee to consider any changes that may need to be made to the recommendation.

1.1.2 Summary of the protocol

Table 1: PICOS inclusion criteria

Population	Adults with liver cirrhosis and ascites, who were undergoing prophylactic treatment with antibiotics to prevent spontaneous bacterial peritonitis.
Interventions	Any of the following treatments, either alone or in combination: • Cephalosporins. • Quinolones. • Folic acid synthesis inhibitors. • Rifaximin. • Other classes of antibiotics.
Comparator	• Each other • No active intervention
Outcomes	**Primary** • All-cause mortality at maximal follow-up (time to death). • Health-related quality of life using a validated scale, at maximal follow-up • Serious adverse events (during or within six months after cessation of intervention) **Secondary** • Any adverse events. • Liver transplantation (time to liver transplantation at maximal follow-up). • Time to development of spontaneous bacterial peritonitis • Number of decompensation episodes (maximal follow-up)

Study type	See section 1.1.3

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Scoping searches for this question identified a Cochrane network meta-analysis (NMA). The NMA is a near match for inclusion criteria for this review:

> Komolafe O, Roberts D, Freeman SC, Wilson P, Sutton AJ, Cooper NJ, Pavlov CS, Milne EJ, Hawkins N, Cowlin M, Thorburn D, Davidson BR, Tsochatzis E, Gurusamy KS. Antibiotic prophylaxis to prevent spontaneous bacterial peritonitis in people with liver cirrhosis: a network meta-analysis. Cochrane Database of Systematic Reviews 2020, Issue 1. Art. No.: CD013125. https://doi.org/10.1002/14651858.CD013125.pub2.

The committee agreed that although the NMA covered people with and without ascites, and it also covered people who had previously had SBP, the NMA directly addresses the review question, was up to date and thorough, and that to repeat it would be a duplication of effort. They noted that the searches were run in November 2018, and that it was possible that newer studies that might be eligible for inclusion could have been published since that time. They asked NICE to update the searches to identify any potential new randomised controlled trials (RCTs) that would affect the Komolafe et al (2020) NMA results.

The Komolafe et al (2020) NMA included all the studies from the previous version of this review except for 1 study (Soriano G, Guarner C, Teixido M, Such J, Barrios J, Enriquez J et al. Selective intestinal decontamination prevents spontaneous bacterial peritonitis. Gastroenterology. 1991; 100(2):477-481. https://doi.org/10.1016/0016-5085(92)91514-5). This study did not report data that could be fitted to the NMA and was therefore excluded (see appendix J).

1.1.3.1 Search methods

The searches for the clinical effectiveness evidence were run on 15th February 2023. The following databases were searched from November 2018 to February 2023: Central Register of Controlled Trials (Wiley), Cochrane Database of Systematic Reviews (Wiley), Embase (Ovid), Epistemonikos and MEDLINE (Ovid), MEDLINE-in-Process (Ovid), MEDLINE Epub Ahead-of-Print (Ovid). The searches were a rerun of the searches conducted for a previous Cochrane Review. The searches focused on antibiotic prophylaxis to prevent spontaneous bacterial peritonitis in people with cirrhosis. Full search strategies for each database are provided in appendix B.

The searches for the cost effectiveness evidence were run on 15th February 2023. The economic search had no date limit as this type of evidence was not previously considered and the following databases were searched: EconLit (Ovid), Embase (Ovid), INAHTA and MEDLINE (Ovid), MEDLINE-in-Process (Ovid), MEDLINE Epub Ahead-of-Print (Ovid). A new search strategy based on the previous Cochrane Review search was used for the cost

effectiveness searches. This expanded the Cochrane Review search to include additional terms around cirrhosis and antibiotics. Full search strategies for each database are provided in appendix B.

A NICE information specialist conducted the searches. The MEDLINE strategy was quality assured by a trained NICE information specialist and all translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the 2015 PRESS Guideline Statement.

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

The searches undertaken for the Komolafe et al (2020) NMA in November 2018 were repeated to identify potentially relevant studies that had been published since the original search. This search found 263 references (see appendix B for the literature search strategy).

These 263 references were screened at title and abstract level against the review protocol, with 256 excluded at this level. 10% of references were screened separately by two reviewers with 100% agreement.

The full texts of 7 studies, 1 RCT and 6 SRs were ordered for closer inspection. The data from the RCT had already been included in the Komolafe et al 2020 NMA from a previous conference presentation so this study was excluded. The SRs were checked and no RCTs published since November 2018 had been missed.

The clinical evidence study selection is presented as a PRISMA diagram in appendix C.

See section 1.1.5 for a summary of studies included in the effectiveness evidence, and section 1.1.14 References – included studies for the full reference of the included study.

1.1.4.2 Excluded studies

Details of studies excluded at full text, along with reasons for exclusion are given in appendix J.

1.1.5 Summary of studies included in the effectiveness evidence

Table 2 Summary of studies included in the effectiveness evidence

Study details	Population	Intervention	Comparison	Outcomes	Risk of bias

Komolafe et al 2020
 	
Study type: Network Meta-analysis
 	
N= 23 studies
	Randomised clinical trials with adults with liver cirrhosis, who were undergoing prophylactic treatment to prevent spontaneous bacterial peritonitis.
	
	Exclusion: trials in which participants had previously undergone liver transplantation, or were receiving antibiotics for treatment of spontaneous bacterial peritonitis or other purposes, for example, treatment of hepatic encephalopathy.
		Any of the following different antibiotic interventions either alone or in combination:
		• Cephalosporins
		• Quinolones
		• Folic acid synthesis inhibitors
		• Rifaximin
		• Other classes of antibiotics
			Each other or 'no active intervention' (either placebo or no antibiotic treatment),	**Primary outcomes**
				• All-cause mortality at maximal follow-up (time to death).
				• Health-related quality of life using a validated scale at maximal follow-up.
				• Serious adverse events (during or within six months after cessation of intervention).
				  ○ Proportion of people with one or more serious adverse event.
				  ○ Number of serious adverse events per participant.
				
				Secondary outcomes
				• Any adverse events (during or within six months after cessation of intervention) – as above
				• Time to liver transplantation (maximal follow-up).
				• Time to development of spontaneous bacterial peritonitis (however, defined by study authors at maximal follow-up)
					Risk of bias: **Low**
					
					Directness: **Indirect**

Study details	Population	Intervention	Comparison	Outcomes	Risk of bias
				○ According to definitions used for spontaneous bacterial peritonitis. ○ Symptomatic spontaneous bacterial peritonitis. • Number of 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).	

See appendix D for full evidence tables.

1.1.6 Summary of the effectiveness evidence

These tables (Table 3 and Table 4) are the GRADE summary of findings tables from Komolafe et al (2020) and present a summary of the effectiveness estimates from the NMA. See section 1.1.11 of this document for brief narrative summaries of the evidence (evidence statements).

Table 3: Antibiotic prophylaxis to prevent spontaneous bacterial peritonitis in people with liver cirrhosis

Antibiotic prophylaxis to prevent spontaneous bacterial peritonitis in people with liver cirrhosis					
Patient or population: people with liver cirrhosis **Settings:** secondary or tertiary care **Intervention:** various interventions **Comparison:** no active intervention **Follow-up period:** 1–12 months					
Interventions	**Relative effect (95% CrI)**	**Anticipated absolute effect* (95% CrI)**			**Certainty of evidence**
		No active intervention	**Various interventions**	**Difference**	
All-cause mortality Total studies: 17 Total participants: 2169					
No active intervention	**Reference**	—	—	—	
Rifaximin (3 RCTs, 479 participants)	**HR 0.57** (0.33 to 1.00) **Network estimate**	**184 per 1000**	**105 per 1000** (61 to 184)	**79 fewer per 1000** (123 fewer to 0 fewer)	**Very low**[a,b,c]
Norfloxacin (4 RCTs, 546 participants)	**HR 0.74** (0.49 to 1.09) **Network estimate**	**184 per 1000**	**136 per 1000** (90 to 201)	**48 fewer per 1000** (94 fewer to 17 more)	**Very low**[a,b,c]

Ciprofloxacin (3 RCTs, 255 participants)	**HR 0.61** (0.31 to 1.16) **Network estimate**	**184 per 1000**	**113 per 1000** (57 to 213)	**71 fewer per 1000** (126 fewer to 29 more)	**Very low**[a,b,c]
Sulfamethoxazole +trimethoprim (1 RCT, 60 participants)	**HR 0.47** (0.20 to 1.00) **Network estimate**	**184 per 1000**	**85 per 1000** (38 to 184)	**98 fewer per 1000** (146 fewer to 0 more)	**Very low**[a,b,c]
Norfloxacin +rifaximin (no direct RCT)	**HR 0.40** (0.12 to 1.17) **Network estimate**	**184 per 1000**	**73 per 1000** (22 to 215)	**111 fewer per 1000** (161 fewer to 32 more)	**Very low**[a,b,c]
Rufloxacin (no direct RCT)	**HR 1.45** (0.27 to 8.21) **Network estimate**	**184 per 1000**	**265 per 1000** (50 to 1000)	**82 more per 1000** (133 fewer to 816 more)	**Very low**[a,b,c]
Health-related quality of life					
None of the trials reported this outcome.					
Serious adverse events (proportion of participants with one or more serious adverse event)					
None of the trials with no active intervention as control group reported this outcome.					
Serious adverse events (number of serious events per participant) Total studies: 2 Total participants: 353					
No active intervention	**Reference**	—	—	—	
Rifaximin (2 RCTs, 353 participants)	**Rate ratio 1.66** (0.98 to 2.90) **Direct estimate**	**132 per 1000**	**219 per 1000** (129 to 383)	**87 more per 1000** (3 fewer to 251 more)	**Very low**[a,b,c]

Any adverse events (proportion of participants with one or more adverse event) Total studies: 3 Total participants: 631					
No active intervention	**Reference**	—	—	—	
Rifaximin (1 RCT, 299 participants)	**OR 1.01** (0.00 to 853.21) **Network estimate**	**799 per 1000**	**800 per 1000** (5 to 1000)	**1 more per 1000** (201 fewer to 201 more)	**Very low**[a,b,c]
Norfloxacin (no direct RCT)	**OR 11.85** (0.01 to 263,023.85) **Network estimate**	**799 per 1000**	**979 per 1000** (26 to 1000)	**180 more per 1000** (201 fewer to 201 more)	**Very low**[a,b,c]
Any adverse events (number of events per participant) **(Only direct estimates presented as there was evidence of inconsistency in the network meta-analysis involving the main interventions being compared in this review)**					
No active intervention	**Reference**	—	—	—	
Rifaximin (3 RCTs, 418 participants)	**Rate ratio 1.15** (0.98 to 1.34) **Direct estimate**	**531 per 1000**	**609 per 1000** (522 to 710)	**78 more per 1000** (9 fewer to 169 more)	**Very low**[a,b,c]
Norfloxacin (4 RCTs, 546 participants)	**Rate ratio 0.74** (0.59 to 0.94) **Direct estimate**	**531 per 1000**	**393 per 1000** (312 to 498)	**138 fewer per 1000** (219 fewer to 33 fewer)	**Low**[a,b]
Ciprofloxacin (3 RCT; 255 participants)	**Rate ratio 0.72** (0.49 to 1.05) **Direct estimate**	**531 per 1000**	**384 per 1000** (261 to 555)	**152 fewer per 1000** (270 fewer to 24 more)	**Very low**[a,b,c]

Sulfamethoxazole + trimethoprim (1 RCT, 60 participants)	**Rate ratio 0.19** (0.02 to 0.81) **Direct estimate**	**531 per 1000**	**102 per 1000** (13 to 431)	**138 fewer per 1000** (219 fewer to 33 fewer)	**Low**[a,b]
Liver transplantation Total studies: 3 Total participants: 260					
No active intervention	**Reference**	—	—	—	
Norfloxacin (1 RCT, 68 participants)	**HR 0.93** (0.31 to 3.44) **Network estimate**	**182 per 1000**	**168 per 1000** (56 to 625)	**14 fewer per 1000** (126 fewer to 443 more)	**Very low**[a,b,c]
Ciprofloxacin (no direct RCT)	**HR 0.62** (0.12 to 3.31) **Network estimate**	**182 per 1000**	**113 per 1000** (22 to 602)	**69 fewer per 1000** (160 fewer to 420 more)	**Very low**[a,b,c]
Sulfamethoxazole + trimethoprim (no direct RCT)	**HR 2.62** (0.62 to 11.91) **Network estimate**	**182 per 1000**	**477 per 1000** (114 to 1000)	**295 more per 1000** (68 fewer to 818 more)	**Very low**[a,b,c]
Spontaneous bacterial peritonitis (as per definition used for spontaneous bacterial peritonitis) Total studies: 15 Total participants: 1504 **(Only direct estimates presented as there was evidence of inconsistency in the network meta-analysis involving the main interventions being compared in this review)**					
No active intervention	**Reference**	—	—	—	

Rifaximin (2 RCTs, 106 participants)	**HR 7.80** (0.13 to 4647.11) **Direct estimate**	**140 per 1000**	**1000 per 1000** (19 to 1000)	**860 more per 1000** (121 fewer to 860 more)	**Very low**[a,b,c]
Norfloxacin (3 RCTs, 255 participants)	**HR 0.16** (0.00 to 1.56) **Direct estimate**	**140 per 1000**	**23 per 1000** (0 to 219)	**117 fewer per 1000** (140 fewer to 79 more)	**Very low**[a,b,c]
Ciprofloxacin (3 RCTs, 255 participants)	**HR 0.56** (0.02 to 60.64) **Direct estimate**	**140 per 1000**	**78 per 1000** (2 to 1000)	**62 fewer per 1000** (138 fewer to 860 more)	**Very low**[a,b,c]
Sulfamethoxazole + trimethoprim (1 RCT, 60 participants)	**HR not estimable** Direct estimate	**140 per 1000**	**Not estimable**	**Not estimable**	**Very low**[a,b,c]
Number of decompensation episodes (per participant) Total studies: 8 Total participants: 1275					
No active intervention	**Reference**	—	—	—	
Norfloxacin + neomycin (1 RCT, 22 participants)	**Rate ratio 0.06** (0.00 to 0.33) **Network estimate**	**459 per 1000**	**25 per 1000** (1 to 152)	**434 fewer per 1000** (458 fewer to 307 fewer)	**Low**[a,b]
Norfloxacin + rifaximin (no direct RCT)	**Rate ratio 0.33** (0.04 to 1.40) **Network estimate**	**459 per 1000**	**151 per 1000** (19 to 643)	**308 fewer per 1000** (440 fewer to 184 more)	**Very low**[a,b,c]

Rifaximin (3 RCTs, 575 participants)	**Rate ratio 0.61** (0.46 to 0.80) **Network estimate**	**459 per 1000**	**280 per 1000** (209 to 365)	**179 fewer per 1000** (250 fewer to 94 fewer)	**Low**[a,b]
Norfloxacin (3 RCTs, 439 participants)	**Rate ratio 0.81** (0.58 to 1.12) **Network estimate**	**459 per 1000**	**372 per 1000** (268 to 515)	**87 fewer per 1000** (192 fewer to 56 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.

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

Table 4: Antibiotic prophylaxis to prevent spontaneous bacterial peritonitis in people with liver cirrhosis – comparison by antibiotic

Antibiotic prophylaxis to prevent spontaneous bacterial peritonitis in people with liver cirrhosis

Patient or population: people with liver cirrhosis

Settings: secondary or tertiary care **Intervention: various interventions** **Comparison: no active intervention** **Follow-up period: 1–12 months**						
Outcomes	**Rifaximin**		**Norfloxacin**		**Ciprofloxacin**	
All-cause mortality						
No active intervention **184 per 1000** **(18.4%)**	**HR 0.57** (0.33 to 1.00) **Network estimate**	**79 fewer per 1000** (123 fewer to 0 fewer)	**HR 0.74** (0.49 to 1.09) **Network estimate**	**48 fewer per 1000** (94 fewer to 17 more)	**HR 0.61** (0.31 to 1.16) **Network estimate**	**71 fewer per 1000** (126 fewer to 29 more)
—	**Very low**[a,b,c]		**Very low**[a,b,c]		**Very low**[a,b,c]	
—	Based on 479 participants (3 RCTs)		Based on 546 participants (4 RCTs)		Based on 255 participants (3 RCTs)	
Serious adverse events (number of events per participant)						
No active intervention **132 per 1000** **(13.2 per 100 participants)**	**Rate ratio 1.66** (0.98 to 2.90) **Direct estimate**	**87 more per 1000** (3 fewer to 253 more)	—		—	
—	**Very low**[a,b,c]		—		—	
—	Based on 353 participants (2 RCTs)		—		—	
Any adverse events (proportion of participants with one or more adverse event)						
No active intervention **799 per 1000** **(79.9%)**	**OR 1.01** (0.00 to 853.21) **Network estimate**	**1 more per 1000** (201 fewer to 201 more)	**OR 11.85** (0.01 to 263023.85) **Network estimate**	**180 more per 1000** (201 fewer to 201 more)	—	
—	**Very low**[a,b,c]		**Very low**[a,b,c]		—	

—	Based on 299 participants (1 RCT)		No direct RCTs		—	
Any adverse events (number of events per participant)						
No active intervention 531 per 1000 (53.1 per 100 participants)	**Rate ratio 1.15** (0.98 to 1.34) **Direct estimate**	**78 more per 1000** (9 fewer to 169 more)	**Rate ratio 0.74** (0.59 to 0.94) **Direct estimate**	**138 fewer per 1000** (219 fewer to 33 fewer)	**Rate ratio 0.72** (0.49 to 1.05) **Direct estimate**	**152 fewer per 1000** (270 fewer to 24 more)
—	**Very low**[a,b,c]		**Low**[a,b]		**Very low**[a,b,c]	
—	Based on 418 participants (3 RCTs)		Based on 546 participants (4 RCTs)		Based on 255 participants (3 RCTs)	
Liver transplantation						
No active intervention 182 per 1000 (18.2%)	—		**HR 0.93** (0.31 to 3.44) **Network estimate**	**14 fewer per 1000** (126 fewer to 443 more)	**HR 0.62** (0.12 to 3.31) **Network estimate**	**69 fewer per 1000** (160 fewer to 420 more)
—	—		**Very low**[a,b,c]		**Very low**[a,b,c]	
—	—		Based on 68 participants (1 RCT)		No direct RCT	
Spontaneous bacterial peritonitis (as per definition used for spontaneous bacterial peritonitis)						
No active intervention 140 per 1000 (14%)	**HR 7.80** (0.13 to 4647.11) **Direct estimate**	**860 more per 1000** (121 fewer to 860 more)	**HR 0.16** (0.00 to 1.56) **Direct estimate**	**117 fewer per 1000** (140 fewer to 79 more)	**HR 0.56** (0.02 to 60.64) **Direct estimate**	**62 fewer per 1000** (138 fewer to 860 more)
—	**Very low**[a,b,c]		**Very low**[a,b,c]		**Very low**[a,b,c]	
—	Based on 106 participants (2 RCTs)		Based on 255 participants (3 RCTs)		Based on 255 participants (3 RCTs)	
Number of decompensation episodes (per participant)						

No active intervention 459 per 1000 (45.9%)	**Rate ratio 0.61** (0.46 to 0.80) **Network estimate**	**179 fewer per 1000** (250 fewer to 94 fewer)	**Rate ratio 0.81** (0.58 to 1.12) **Network estimate**	**87 fewer per 1000** (192 fewer to 56 more)	—	
—	**Low**[a,b]		**Very low**[a,b,c]		—	
—	Based on 575 participants (3 RCTs)		Based on 439 participants (3 RCTs)		—	
Length of hospital stay						
No active intervention 17.6 days	—		—		**MD –8.29 days** (–11.09 to –5.50) **Network estimate**	**8.29 fewer days** (11.09 fewer to 5.5 fewer)
—	—		—		**Low**[a,b]	
—	—		—		Based on 60 participants (1 RCT)	

CrI: credible interval; HR: hazard ratio; MD: mean difference; 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]Downgraded one level because the trial(s) included in the analysis was/were at high risk of bias.
[b]Downgraded one level because the sample size was small.
[c]Downgraded one level because the credible intervals were wide (included clinical benefit and harms).

1

1.1.7 Economic evidence

1.1.7.1 Included economic studies

A search was performed to identify published economic evaluations of relevance to this guideline update. This search retrieved 500 studies. Based on title and abstract screening, all the studies were excluded for this question.

1.1.7.2 Excluded economic studies

No studies were examined at full text.

1.1.8 Summary of included economic evidence

No economic studies were included in this review.

1.1.9 Economic model

We conducted an analysis to evaluate the cost savings that could be generated by giving antibiotics to people with ascites by preventing SBP. To be cost saving, ciprofloxacin has to prevent at least one episode of SBP per 43.32 person years. The clinical evidence shows that prophylactic treatment with ciprofloxacin could reduce incidence of SBP by an average of 62 cases per 1000 (i.e.1 SBP episode in every 16 people), which is within the threshold. We are not able to quantify cost savings for rifaximin and co-trimoxazole due to the lack of robust clinical evidence. The full write up of the methods and results is in Appendix I.

Table 5: Health economic evidence profile: antibiotics vs placebo for preventing spontaneous bacterial peritonitis

Study type	Applicability	Antibiotic	Drug costs per year	Threshold (cases averted to be cost saving)	Risk reduction in SBP	Cost saving
Threshold analysis	Directly applicable	Ciprofloxacin	£47	1 episode averted per 43.32 person years	1 case in every 16 people	Yes
		Rifaximin	£3,379	Prevention with rifaximin costs more than SBP treatment (£2,024)	Risk of developing SBP is higher than no active intervention	Cannot quantify
		Co-trimoxazole	£89	1 episode averted per 22.80 person years	Lack of clinical data	Cannot quantify

1.1.10 Unit costs

The costs of the drugs and the management costs of SBP included in recommendations for this review question are given below, respectively. For further details about how the management costs of SBP were calculated, see Appendix I.

Table 6: Unit costs of antibiotics

Resource	Daily dose	Unit costs	Source
Norfloxacin	400mg	Not available	BNF (accessed March 2023)
Ciprofloxacin	500mg	£1.28 for 10×500mg tablets	
Rifaximin	1100mg	£259.23 for 56×550mg tablets	
Co-trimoxazole	800 mg sulfamethoxazole/ 160 mg trimethoprim	£24.32 for 100×800/160mg tablets	

Table 7: Management costs of SBP

Cost type	Unit costs	Source
7-day hospital stay: GBO3D (elective inpatient-excess bed days)	£1,651.29	Previous guideline, with cost inflation
Tazocin (Piperacillin 4 g/tazobactam 500 mg IV every 8 hours for 5 days)	£227.55	BNF (2023)
Paracentesis	£82.51	Previous guideline, with cost inflation
Ultrasound (RD40Z: outpatient, ultrasound scan with duration of less than 20 minutes, without Contrast)	£62.39	NHS Cost Collection 2019/2020

1.1.11 Evidence statements

Effectiveness evidence: primary outcomes

The outcomes of the NMA were presented as hazard ratio (HR) or odds ratios (OR), and credible intervals (CrI) (CrI are essentially similar to a 95% confidence interval but incorporates problem-specific contextual information from prior distributions as well as the present study data – Yang et al 2022). A HR or OR<1 favours treatment over control, a HR or OR>1 favours control over treatment and a HR or OR=1 demonstrates treatment equivalence. To demonstrate a significant effect the CrI surrounding the HR or OR will not go through the line of effect (HR or OR=1).

All-cause mortality

Based on network estimates with very low certainty of evidence, 17 studies containing 2,169 participants were unable to demonstrate a difference between no intervention/placebo and

- rifaximin (HR 0.57; 95% CrI 0.33 to 1.00)
- norfloxacin (HR 0.74; 95% CrI 0.49 to 1.09)
- ciprofloxacin (HR 0.61; 95% CrI 0.31 to 1.16)
- sulfamethoxazole + trimethoprim (HR 0.47; 95% CrI 0.20 to 1.00)
- norfloxacin + rifaximin (HR 0.40; 95% CrI 0.12 to 1.17) or
- rufloxacin (HR 1.45; 95% CrI 0.27 to 8.21)

on all-cause mortality.

Health-related quality of life

None of the trials included in the NMA reported this outcome.

Proportion of participants with one or more serious adverse event

None of the trials included in the NMA reported this outcome.

Number of serious adverse events per participant

Based on a direct estimate with very low certainty of evidence, 2 studies containing 353 participants were unable to demonstrate a difference between no intervention/placebo and rifaximin (Rate ratio 1.66; 95% CI 0.98 to 2.90) for the number of serious adverse events per participant.

Effectiveness evidence: secondary outcomes

Proportion of participants with one or more adverse event

Based on network estimates with very low certainty of evidence, 3 studies containing 631 participants were unable to demonstrate a difference between no intervention/placebo and

- rifaximin (OR 1.01; 95% CrI 0.00 to 853.21)
- norfloxacin (OR 11.85; 95% CrI 0.01 to 263,023.85)

for the proportion of participants with one or more adverse event.

Number of adverse events per participant

Based on direct estimates, the number of 'any' adverse events per participant was fewer with

- norfloxacin (rate ratio 0.74; 95% CrI 0.59 to 0.94; 4 trials, 546 participants; low certainty)
- sulfamethoxazole plus trimethoprim (rate ratio 0.19; 95% CrI 0.02 to 0.81; 1 trial, 60 participants; low certainty)

versus no active intervention.

Based on direct estimates, the review was unable to demonstrate a difference between

- rifaximin (rate ratio 1.15; 95% CrI 0.98 to 1.34; 3 trials, 418 participants; very low certainty)
- ciprofloxacin (rate ratio 0.72; 95% CrI 0.49 to 1.05; 3 trials, 255 participants; very low certainty)

versus no active intervention.

Liver transplantation

Based on network estimates with very low certainty of evidence, 3 studies containing 260 participants were unable to demonstrate a difference between no intervention/placebo and

- norfloxacin (HR 0.93; 95% CrI 0.31 to 3.44)
- ciprofloxacin (HR 0.62; 95% CrI 0.12 to 3.31)
- sulfamethoxazole + trimethoprim (HR 2.62; 95% CrI 0.62 to 11.91)

for liver transplantation

Spontaneous bacterial peritonitis

Based on direct estimates with very low certainty evidence, the NMA was unable to demonstrate a difference between no intervention/placebo and

- rifaximin (HR 7.80; 95% CrI 0.13 to 4,647.11; 2 trials, 106 participants)
- norfloxacin (HR 0.16; 95% CrI 0.00 to 1.56; 3 trials, 255 participants)
- ciprofloxacin (HR 0.56; 95% CrI 0.02 to 60.64; 3 trials, 255 participants)
- sulfamethoxazole + trimethoprim (HR not estimable based on 1 trial of 60 participants)

for spontaneous bacterial peritonitis.

Number of decompensation episodes per participant

Based on 8 studies with 1,275 participants there were fewer decompensation events with

- rifaximin (rate ratio 0.61, 65% CrI 0.46 to 0.80; low certainty)
- norfloxacin plus neomycin (rate ratio 0.06, 95% CrI 0.00 to 0.33; low certainty)

versus no active intervention.

Based on direct estimates, the NMA was unable to demonstrate a difference between

- norfloxacin plus rifaximin (rate ratio 0.33; 95% CrI 0.04 to 1.40; no direct RCT; very low certainty)

versus no active intervention

Economic evidence

- Based on the estimates of effect from the effectiveness review, an economic analysis demonstrated that ciprofloxacin may provide cost savings by preventing episodes of SBP. It was not possible to estimate cost savings for co-trimoxazole due to a lack of evidence for this outcome, and very low certainty evidence for rifaximin indicated that it was not more effective than placebo for preventing SBP and therefore would not be associated with cost savings.

1.1.12 The committee's discussion and interpretation of the evidence

1.1.12.1. The outcomes that matter most

The committee agreed that the most important outcomes for this question were mortality, quality of life and adverse events, since these were the key outcomes for people living with cirrhosis and ascites. They also noted that it was important to look at the time to development of spontaneous bacterial peritonitis (SBP), and proxy measures like liver transplantation and other kinds of decompensation. The committee also agreed that it was very important to look at the evidence from a perspective of good antimicrobial stewardship. They commented that they were aware that antimicrobial resistance may be higher among people with cirrhosis and ascites who have had frequent antimicrobial treatment, although that evidence was not formally part of this review..

1.1.12.2 The quality of the evidence

The committee considered the evidence from a Cochrane network meta-analysis (Komolafe et al, 2020). The network meta-analysis (NMA) looked for evidence for all-cause mortality, health-related quality of life, proportion of participants with one or more serious adverse events, number of serious adverse events per participants, proportion of participants with one or more adverse events, number of adverse events per participant, liver transplantation, spontaneous bacterial peritonitis and number of decompensation episodes per participant, There was no evidence for health-related quality of life and proportion of participants with one or more serious adverse event. All of the evidence in this NMA was of low or very low quality. This is because, in spite of including 23 studies, most of the studies were small and poorly

reported. This meant that most of the evidence was downgraded for risk of methodological bias (mostly for selective reporting and for lack of blinding) and for imprecision, because the size of the studies made the 95% credible intervals very wide.

The committee also considered the recommendation from the previous guideline which recommended ciprofloxacin or norfloxacin for preventing SBP.

1.1.12.3 Benefits and harms

The committee discussed the UK context for this question, and agreed that in spite of the NICE guidance, practice in relation to preventing SBP in people with cirrhosis and ascites was very variable, and that it was mostly dependent on individual clinicians whether they prescribed prophylactic antibiotics for people with ascites and a low ascitic protein.

The committee noted that previously, ciprofloxacin or norfloxacin were routinely used for preventing SBP in people at high risk, but norfloxacin has been withdrawn in the UK and ciprofloxacin is subject to an MHRA drug safety update on the fluoroquinolone class of antibiotics. (MHRA drug safety update) because of potentially irreversible adverse reactions meant that they were no longer the drug of choice in this indication.

The evidence from the NMA could not demonstrate a difference between any of the antibiotics and no intervention in terms of mortality (very low certainty) or number of serious adverse events (very low certainty). None of the studies reported health related quality of life. The committee noted that the central effect estimates for many of the antibiotics showed quite substantial effects, and were they correct they would be clinically important, however there was a great deal of uncertainty associated with the effect estimates which is likely to be due to the small study sizes.

The committee discussed this and noted that because the credible intervals were so wide, it was difficult to assess whether there were clinically important effects, and that important differences cannot be ruled out. This lack of certainty meant that they made a weaker recommendation and added a research recommendation (appendix K) to encourage further, better quality studies in this area to allow a more definitive recommendation when it is next updated by NICE.

The committee noted that for some of the secondary outcomes there were statistically significant effects for norfloxacin and sulfamethoxazole plus trimethoprim versus no active intervention for the number of any adverse events per participants; and rifaximin and norfloxacin plus neomycin versus no active intervention for the number of decompensation episodes per participant. As these findings were of low certainty and focused on secondary outcomes the committee did not make any recommendations in these areas.

Based on the committees' expertise and experience in practice, the low-quality evidence and the cautions around the use of fluoroquinolones, the committee agreed that antibiotics might have a role in preventing SBP in some people who were considered to be at particularly high risk of SBP (for example people with a low ascitic protein (<15g/dl) or severe liver disease (Child-Pugh ≥9 or MELD ≥16 with recurrent ascites), or in whom the consequences were likely to be severe, but that

good antimicrobial stewardship was also important. They noted that people with cirrhosis and ascites who frequently had prophylactic antibiotics had higher rates of antibiotic resistant infection than the general population. In light of these discussions the committee agreed to withdraw the previous recommendation to offer prophylactic oral ciprofloxacin or norfloxacin to people at high risk of developing SBP and updated the recommendation to specify that antibiotics should be prescribed to people at high risk according to local microbiological data and funding agreement. On the basis of the discussion above, they broadened the definition of high risk and gave examples of what could be considered high risk. They added a further group to the recommendation because they agreed that prophylactic antibiotics could be justified for people where their care would be severely impacted by an episode of SBP, for example if they were waiting for a transplant or a TIPS procedure.

Overall, the committee agreed that the recommendation made a good balance between antimicrobial stewardship and good patient care by recommending the use of prophylactic antibiotics in people at high risk. They agreed that local infection patterns and microbiological advice were probably the most useful determinants of which antibiotic to prescribe.

1.1.12.4 Cost effectiveness and resource use

No recent and relevant published economic studies were identified.

We conducted an analysis to evaluate any potential cost savings that could be generated by giving antibiotics to people with ascites at high risk of developing SBP. This analysis considers the costs of antibiotics and the management cost of SBP. The annual costs of each antibiotic for preventing SBP are estimated to be £46.72 for ciprofloxacin, £3,379.25 for rifaximin and £88.77 for co-trimoxazole. The committee noted that rifaximin was much more expensive than the rest of antibiotics, and that it is not typically on local prescribing protocols for this indication. The cost of managing SBP-related complications was estimated to be approximately £2,000, taking into account typical resources for managing SBP such as paracentesis, ultrasound, 7-day hospital stay and 5-day course of tazoxin. The committee described how the management of SBP was complicated and varied greatly by patient, and the costs depended upon the further development of their condition.

To be cost saving, prophylactic treatment needs to prevent at least one episode of SBP per 43.32 person years for ciprofloxacin and one episode per 22.80 person years for co-trimoxazole. The clinical evidence from the Cochrane review for people with ascites at high risk of developing SBP shows that ciprofloxacin can reduce incidence of SBP by 62 cases per 1000 people (1 SBP episode in every 16 people). Hence, using ciprofloxacin may be cost saving compared with no active intervention. However, there is a lack of clinical data to quantify the cost savings for co-trimoxazole. Prophylactic treatment with rifaximin is more costly than treating an episode of SBP each year (£3,379 vs £2,024). The poor-quality clinical evidence where the risk difference with rifaximin is 860 more per 1,000 also suggests that people with rifaximin are more likely to develop SBP than no active intervention, and so we are not able to quantify the cost savings for rifaximin.

Ciprofloxacin belongs to the fluroquinolone class, which are no longer considered as the first choice of antibiotics for prophylaxis due to their associated risks to patients.

As a result of very low certainty evidence on adverse effects of fluoroquinolones, it is difficult to weigh up their impact and the risk of developing SBP, and to quantify the economic impact of managing these adverse effects. The committee argued that not everyone will experience side effects of fluoroquinolones and that it is possible to identify those at high risk of SBP and that these people might benefit from antibiotic prophylaxis. The committee lacks strong evidence to recommend the best option for the primary prevention of SBP, and so felt that it was more appropriate to advise centres to refer to local prescribing protocols for these patients.

The committee advised that people with the G6PD deficiency, an inherited condition which results in an inadequate number of enzymes for healthy, functioning red blood cells, are advised to avoid using fluoroquinolones and co-trimoxazole. It is more common in men than women and in people with Asian, African or Mediterranean heritage. Testing for this condition is not part of routine practice and only done if there is a clinical suspicion, such as suspected haemolytic anaemia or a family history of the condition. If a person who has G6PD deficiency is prescribed certain drugs, they may be at a higher risk of developing adverse events such as haemolytic anaemia, jaundice, dizziness, headache. Treating people with G6PD deficiency with inappropriate antibiotics may have resource implications because of the treatment of adverse events. However, the cost of a test for G6PD is minimal compared to the cost of managing SBP and the associated adverse effects of giving fluoroquinolones to those with G6PD deficiency. Overall, this is unlikely to impact upon the cost effectiveness results since this will likely affect only a very small number of people within the cirrhotic population.

1.1.12.5 Other factors the committee took into account

The committee discussed the potential equalities issues relating to medicines compliance and support, antibiotic contraindication and fluoroquinolone use. The committee agreed that the new recommendation was unlikely to increase inequalities in any particular group of people, and that the new recommendation would remove the risk of the potentially negative impact of prescribing fluoroquinolones for this indication.

1.1.13 Recommendations supported by this evidence review

This evidence review supports recommendation 1.3.7 and 1.3.8 and the research recommendation on antibiotic prophylaxis to prevent spontaneous bacterial peritonitis.

1.1.14 References – included studies

1.1.14.1 Effectiveness

Komolafe O, Roberts D, Freeman SC, Wilson P, Sutton AJ, Cooper NJ, Pavlov CS, Milne EJ, Hawkins N, Cowlin M, Thorburn D, Davidson BR, Tsochatzis E, Gurusamy KS. Antibiotic prophylaxis to prevent spontaneous bacterial peritonitis in people with liver cirrhosis: a network meta-analysis. Cochrane Database of Systematic Reviews

2020, Issue 1. Art. No.: CD013125.
https://doi.org/10.1002/14651858.CD013125.pub2.

1.1.14.2 Economic

None

1.1.14.3 Other references

Aithal, G. P., Palaniyappan, N., China, L., Härmälä, S., Macken, L., Ryan, J. M., Wilkes, E. A., Moore, K., Leithead, J. A., Hayes, P. C., O'Brien, A. J., & Verma, S. (2021). Guidelines on the management of ascites in cirrhosis. Gut, 70(1), 9–29. https://doi.org/10.1136/gutjnl-2020-321790

British National Formulary (2023). Accessed at: https://bnf.nice.org.uk/

National Schedule of NHS Costs 2019/20. Accessed at: https://www.england.nhs.uk/publication/2019-20-national-cost-collection-data-publication/

Unit Costs of Health and Social Care (PSSRU) 2020. Accessed at: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2020/

Appendices

Appendix A – Review protocols

This review reports a network meta-analysis undertaken by Komolafe et al (2020) for Cochrane. Please see that paper for details of the protocol.

Appendix B – Literature search strategies

Background and development

Search design and peer review

A NICE information specialist conducted the literature searches for the evidence review. The searches were run on 15th February 2023. This search report is compliant with the requirements of the PRISMA Statement for Reporting Literature Searches in Systematic Reviews (for further details see: Rethlefsen M et al. PRISMA-S. *Systematic Reviews*, 10(1), 39).

The MEDLINE strategies below were quality assured (QA) by a trained NICE information specialist. All translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the Peer Review of Electronic Search Strategies Guideline Statement (for further details see: McGowan J et al. PRESS 2015 Guideline Statement. *Journal of Clinical Epidemiology*, 75, 40-46).

The principal search strategies were developed in MEDLINE (Ovid interface) and adapted, as appropriate, for use in the other sources listed in the protocol, taking into account their size, search functionality and subject coverage.

Review management

The search results were managed in EPPI-Reviewer v5. Duplicates were removed in EPPI-R5 using a two-step process. First, automated deduplication is performed using a high-value algorithm. Second, manual deduplication is used to assess 'low-probability' matches. All decisions made for the review can be accessed via the deduplication history.

Prior work

The clinical search is a direct rerun of the search conducted for the following Cochrane review; the search strategy matches the search strategy used in this review:

Komolafe O, Roberts D, Freeman SC et al. (2020) Antibiotic prophylaxis to prevent spontaneous bacterial peritonitis in people with liver cirrhosis: a network meta-analysis. Cochrane Database of Systematic Reviews issue 1: CD013125

The economic search expanded the search strategy originally used in the Cochrane review to include additional search terms around cirrhosis, antibiotic prophylaxis, and specific antibiotics. This is because economic evidence was not considered as part of the original Cochrane review and with the potentially smaller evidence base additional search terms were considered useful in identify relevant evidence.

Limits and restrictions

English language limits were applied in adherence to standard NICE practice.

The clinical search was limited from November 2018 to February 2023. The economic search had no date limit as this type of evidence was not previously considered as part of the Cochrane review.

The limit to remove animal studies in the searches was the standard NICE practice, which has been adapted from: Dickersin K, Scherer R & Lefebvre C. (1994) Systematic Reviews: Identifying relevant studies for systematic reviews. *BMJ*, 309(6964), 1286.

Search filters and classifiers

Clinical searches

- RCT filters:
    - McMaster Therapy – Medline - "best balance of sensitivity and specificity" version.
      Haynes RB et al. (2005) Optimal search strategies for retrieving scientifically strong studies of treatment from Medline: analytical survey. *BMJ*, 330, 1179-1183.

    - McMaster Therapy – Embase "best balance of sensitivity and specificity" version.
      Wong SSL et al. (2006) Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. Journal of the Medical Library Association, 94(1), 41-47.

- Systematic reviews filters:
      Lee, E. et al. (2012) An optimal search filter for retrieving systematic reviews and meta-analyses. *BMC Medical Research Methodology,* 12(1), 51.

In MEDLINE, the standard NICE modifications were used: pubmed.tw added; systematic review.pt added from MeSH update 2019.

In Embase, the standard NICE modifications were used: pubmed.tw added to line medline.tw.

Cost effectiveness searches

The following search filters were applied to the search strategies in MEDLINE and Embase to identify cost-effectiveness studies:

- Glanville J et al. (2009) Development and Testing of Search Filters to Identify Economic Evaluations in MEDLINE and EMBASE. Alberta: Canadian Agency for Drugs and Technologies in Health (CADTH)
- Hubbard W, Walsh N, Hudson T et al. (2022) Development and validation of paired MEDLINE and Embase search filters for cost-utility studies. BMC Medical Research Methodology 22(1), 310

Key decisions

The clinical search strategy was a direct copy of that run in the original Cochrane review, this was following the decision to use this review as the basis for any recommendations made within the guideline. The search was rerun to identify any relevant evidence published since November 2018 when the Cochrane review search was last run.

The economic search expanded the search strategy originally used in the Cochrane review to include additional search terms around cirrhosis, antibiotic prophylaxis, and specific antibiotics that were identified in the published Cochrane review. The economic search was not a rerun of the Cochrane review as this evidence was not considered as part of that review but a new search as part of this guideline. Given the potentially smaller evidence base additional search terms were considered useful in identify any relevant evidence.

In January 2023 there was a data processing error in Ovid Embase. This error was fixed on 22nd February 2023. Additional results missed during the data processing error in Embase were added to the total search results on 22nd February 2023.

Clinical searches

Main search – Databases

Database	Date searched	Database Platform	Database segment or version	No. of results downloaded
Cochrane Central Register of Controlled Trials (CENTRAL)	15/02/2023	Wiley	Cochrane Central Register of Controlled Trials Issue 2 of 12, February 2023	49
Cochrane Database of Systematic Reviews (CDSR)	15/02/2023	Wiley	Cochrane Database of Systematic Reviews Issue 2 of 12, February 2023	5
Embase	15/02/2023	Ovid	Embase 1974 to 2023 February 13	97 + 7
Epistemonikos	15/02/2023	Epistemonikos	-	155
MEDLINE	15/02/2023	Ovid	Ovid MEDLINE(R) 1946 to February 14, 2023	50
MEDLINE-in-Process	15/02/2023	Ovid	Ovid MEDLINE(R) In-Process & In-Data-Review Citations 1946 to February 14, 2023	0
MEDLINE Epub Ahead-of-Print	15/02/2023	Ovid	Ovid MEDLINE(R) Epub Ahead of Print February 14, 2023	1

Search strategy history

Database name: MEDLINE

1 exp antibiotic prophylaxis/ (15353)
2 antibiotic*.tw. (344105)
3 (antibacteri* adj prophyl*).tw. (354)
4 or/1-3 (350969)
5 exp Liver Cirrhosis/ (100587)
6 ((hepatic* or liver*) and (fibrosis* or cirrhosis* or cirrhotic*)).tw. (108665)
7 5 or 6 (147174)
8 4 and 7 (1600)
9 Animals/ not Humans/ (5059178)
10 8 not 9 (1531)
11 limit 10 to english language (1247)
12 limit 11 to ed=20181101-20230215 (320)
13 randomized controlled trial.pt. (586427)
14 randomi?ed.mp. (950211)
15 placebo.mp. (222459)
16 or/13-15 (1007086)
17 (MEDLINE or pubmed).tw. (250196)
18 systematic review.tw. (202919)
19 systematic review.pt. (213313)
20 meta-analysis.pt. (175576)
21 intervention$.ti. (162963)
22 or/17-21 (545518)
23 16 or 22 (1403419)
24 12 and 23 (50)

Database name: MEDLINE-in-Process

1 exp antibiotic prophylaxis/ (0)
2 antibiotic*.tw. (157)
3 (antibacteri* adj prophyl*).tw. (0)
4 or/1-3 (157)
5 exp Liver Cirrhosis/ (0)
6 ((hepatic* or liver*) and (fibrosis* or cirrhosis* or cirrhotic*)).tw. (51)
7 5 or 6 (51)
8 4 and 7 (0)
9 Animals/ not Humans/ (0)
10 8 not 9 (0)
11 limit 10 to english language (0)
12 limit 11 to dt=20181101-20230215 (0)
13 randomized controlled trial.pt. (0)
14 randomi?ed.mp. (441)
15 placebo.mp. (63)

16 or/13-15 (456)
17 (MEDLINE or pubmed).tw. (335)
18 systematic review.tw. (321)
19 systematic review.pt. (12)
20 meta-analysis.pt. (0)
21 intervention$.ti. (154)
22 or/17-21 (588)
23 16 or 22 (914)
24 12 and 23 (0)

Database name: MEDLINE Epub Ahead-of-Print

1 exp antibiotic prophylaxis/ (0)
2 antibiotic*.tw. (4133)
3 (antibacteri* adj prophyl*).tw. (6)
4 or/1-3 (4137)
5 exp Liver Cirrhosis/ (0)
6 ((hepatic* or liver*) and (fibrosis* or cirrhosis* or cirrhotic*)).tw. (1222)
7 5 or 6 (1222)
8 4 and 7 (20)
9 Animals/ not Humans/ (0)
10 8 not 9 (20)
11 limit 10 to english language (19)
12 limit 11 to dt=20181101-20230214 (13)
13 randomized controlled trial.pt. (1)
14 randomi?ed.mp. (11917)
15 placebo.mp. (2405)
16 or/13-15 (12687)
17 (MEDLINE or pubmed).tw. (8516)
18 systematic review.tw. (8653)
19 systematic review.pt. (195)
20 meta-analysis.pt. (84)
21 intervention$.ti. (3497)
22 or/17-21 (15119)
23 16 or 22 (24353)
24 12 and 23 (1)

Database name: Embase

1 antibiotic prophylaxis/ (37441)
2 antibiotic*.tw. (527398)
3 (antibacteri* adj prophyl*).tw. (649)
4 or/1-3 (546839)
5 exp liver cirrhosis/ (185337)
6 ((hepatic* or liver*) and (fibrosis* or cirrhosis* or cirrhotic*)).tw. (201316)
7 5 or 6 (272357)
8 4 and 7 (5197)

9 nonhuman/ not human/ (5203284)
10 8 not 9 (5069)
11 limit 10 to english language (4621)
12 limit 11 to (conference abstract or conference paper or "conference review") (2285)
13 11 not 12 (2336)
14 limit 13 to dc=20181101-20230215 (735)
15 random:.tw. (1906565)
16 placebo:.mp. (513305)
17 double-blind:.tw. (240349)
18 or/15-17 (2179979)
19 (MEDLINE or pubmed).tw. (386450)
20 exp systematic review/ or systematic review.tw. (481667)
21 meta-analysis/ (277367)
22 intervention$.ti. (254963)
23 or/19-22 (923784)
24 18 or 23 (2817531)
25 14 and 24 (97)

Database name: Cochrane library

#1 MeSH descriptor: [Antibiotic Prophylaxis] explode all trees1571
#2 (antibiotic*):ti,ab,kw 35678
#3 ((antibacteri* NEAR/1 prophyl*)):ti,ab,kw 93
#4 {or #1-#3} 35718
#5 MeSH descriptor: [Liver Cirrhosis] explode all trees3474
#6 ((hepatic* or liver*) AND (fibrosis* or cirrhosis* or cirrhotic*)):ti,ab,kw 12150
#7 #5 OR #6 12150
#8 #4 AND #7 447
#9 "conference":pt or (clinicaltrials or trialsearch):so 659511
#10 #8 not #9 with Cochrane Library publication date Between Nov 2018 and Feb 2023 55

Database name: Epistemonikos

(title:((title:((title:(antibiotic*) OR abstract:(antibiotic*))) OR abstract:((title:(antibiotic*) OR abstract:(antibiotic*)))) OR (title:((title:(antibacteri*) OR abstract:(antibacteri*)) AND (title:(prophyl*) OR abstract:(prophyl*))) OR abstract:((title:(antibacteri*) OR abstract:(antibacteri*)) AND (title:(prophyl*) OR abstract:(prophyl*))))) OR abstract:((title:((title:(antibiotic*) OR abstract:(antibiotic*))) OR abstract:((title:(antibiotic*) OR abstract:(antibiotic*)))) OR (title:((title:(antibacteri*) OR abstract:(antibacteri*)) AND (title:(prophyl*) OR abstract:(prophyl*))) OR abstract:((title:(antibacteri*) OR abstract:(antibacteri*)) AND (title:(prophyl*) OR abstract:(prophyl*)))))) AND (title:((title:(hepatic* OR liver*) OR abstract:(hepatic* OR liver*)) AND (title:(fibrosis* OR cirrhosis* OR cirrhotic*) OR abstract:(fibrosis* OR cirrhosis* OR cirrhotic*))) OR abstract:((title:(hepatic* OR liver*) OR abstract:(hepatic* OR liver*)) AND (title:(fibrosis* OR cirrhosis* OR cirrhotic*) OR abstract:(fibrosis* OR cirrhosis* OR cirrhotic*))))

Cost-effectiveness searches

Main search – Databases

Database	Date searched	Database Platform	Database segment or version	No. of results downloaded
EconLit	15/02/2023	OVID	Econlit 1886 to February 09, 2023	0
Embase	15/02/2023	Ovid	Embase 1974 to 2023 February 13	490 + 10
INAHTA	15/02/2023	INAHTA	-	1
MEDLINE	15/02/2023	Ovid	Ovid MEDLINE(R) 1946 to February 14, 2023	132
MEDLINE-in-Process	15/02/2023	Ovid	Ovid MEDLINE(R) In-Process & In-Data-Review Citations 1946 to February 14, 2023	0
MEDLINE Epub Ahead-of-Print	15/02/2023	Ovid	Ovid MEDLINE(R) Epub Ahead of Print February 14, 2023	3

Search strategy history

Database name: MEDLINE

1 exp Liver Cirrhosis/ (100566)
2 Fibrosis/ and Liver/ (2191)
3 cirrho*.tw. (99800)
4 ((liver* or hepat* or alcohol* or biliar*) adj4 (fibro* or myxofibro* or cholang* or angiocholit*)).tw. (47040)
5 or/1-4 (159754)
6 Antibiotic Prophylaxis/ (15353)
7 (antibiotic* or anti-biotic*).tw. (344087)
8 ((antibacter* or anti-bacter* or bacteriocid* or antimycobacter* or anti-mycobacter* or antimicrob* or anti-microb*) adj4 (prophyla* or premed* or pre-med* or prevent*)).tw. (5409)
9 Pre-Exposure Prophylaxis/ or Post-Exposure Prophylaxis/ (5946)
10 exp Anti-Bacterial Agents/ (805991)
11 9 and 10 (169)
12 or/6-8,11 (353832)
13 exp Ciprofloxacin/ (14996)
14 (cipro* or ciprinol* or cetraxal* or ciloxan*).tw. (27459)
15 exp Neomycin/ (8181)
16 (neom?cin* or neofradin* or neo-fradin*).tw. (9250)
17 Norfloxacin/ (2717)

18 (norfloxacin* or noroxin*).tw. (4926)
19 Rifaximin/ (924)
20 (rifaximin* or redactiv* or xifaxan* or targaxan* or normix*).tw. (1212)
21 (rufloxacin* or sparfloxacin*).tw. (1278)
22 exp Sulfamethoxazole/ (11849)
23 (sulfamethoxazole* or sulfamethylisoxazole* or sulfisomezole* or gantanol* or co-trimoxazole* or cotrimoxazole*).tw. (18788)
24 or/13-23 (67481)
25 12 or 24 (396311)
26 5 and 25 (2372)
27 Animals/ not Humans/ (5058539)
28 26 not 27 (2266)
29 limit 28 to english language (1863)
30 Economics/ (27491)
31 exp "Costs and Cost Analysis"/ (262649)
32 Economics, Dental/ (1920)
33 exp Economics, Hospital/ (25676)
34 exp Economics, Medical/ (14383)
35 Economics, Nursing/ (4013)
36 Economics, Pharmaceutical/ (3094)
37 Budgets/ (11676)
38 exp Models, Economic/ (16181)
39 Markov Chains/ (15900)
40 Monte Carlo Method/ (31918)
41 Decision Trees/ (12049)
42 econom$.tw. (309764)
43 cba.tw. (10451)
44 cea.tw. (23347)
45 cua.tw. (1140)
46 markov$.tw. (22551)
47 (monte adj carlo).tw. (35651)
48 (decision adj3 (tree$ or analys$)).tw. (20254)
49 (cost or costs or costing$ or costly or costed).tw. (571118)
50 (price$ or pricing$).tw. (41256)
51 budget$.tw. (27972)
52 expenditure$.tw. (58953)
53 (value adj3 (money or monetary)).tw. (2649)
54 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (3856)
55 or/30-54 (1126939)
56 "Quality of Life"/ (259224)
57 quality of life.tw. (300212)
58 "Value of Life"/ (5800)
59 Quality-Adjusted Life Years/ (15415)
60 quality adjusted life.tw. (14504)
61 (qaly$ or qald$ or qale$ or qtime$).tw. (11901)
62 disability adjusted life.tw. (4162)

63 daly$.tw. (3696)
64 Health Status Indicators/ (24077)
65 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (26437)
66 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (1567)
67 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (6361)
68 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (33)
69 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (412)
70 (euroqol or euro qol or eq5d or eq 5d).tw. (13308)
71 (qol or hql or hqol or hrqol).tw. (59038)
72 (hye or hyes).tw. (63)
73 health$ year$ equivalent$.tw. (38)
74 utilit$.tw. (215467)
75 (hui or hui1 or hui2 or hui3).tw. (1589)
76 disutili$.tw. (511)
77 rosser.tw. (100)
78 quality of wellbeing.tw. (27)
79 quality of well-being.tw. (431)
80 qwb.tw. (201)
81 willingness to pay.tw. (6662)
82 standard gamble$.tw. (832)
83 time trade off.tw. (1202)
84 time tradeoff.tw. (249)
85 tto.tw. (1122)
86 or/56-85 (617720)
87 Cost-Benefit Analysis/ (91679)
88 Quality-Adjusted Life Years/ (15415)
89 Markov Chains/ (15900)
90 exp Models, Economic/ (16181)
91 cost*.ti. (122023)
92 (cost* adj2 utilit*).tw. (6239)
93 (cost* adj2 (effective* or assess* or evaluat* or analys* or model* or benefit* or threshold* or quality or expens* or saving* or reduc*)).tw. (216170)
94 (economic* adj2 (evaluat* or assess* or analys* or model* or outcome* or benefit* or threshold* or expens* or saving* or reduc*)).tw. (37204)
95 (qualit* adj2 adjust* adj2 life*).tw. (14810)
96 QALY*.tw. (11773)
97 (incremental* adj2 cost*).tw. (14373)
98 ICER.tw. (4716)
99 utilities.tw. (7444)
100 markov*.tw. (22551)

101 (dollar* or USD or cents or pound or pounds or GBP or sterling* or pence or euro or euros or yen or JPY).tw. (45398)
102 ((utility or effective*) adj2 analys*).tw. (20227)
103 (willing* adj2 pay*).tw. (7607)
104 (EQ5D* or EQ-5D*).tw. (10479)
105 ((euroqol or euro-qol or euroquol or euro-quol or eurocol or euro-col) adj3 ("5" or five)).tw. (2826)
106 (european* adj2 quality adj3 ("5" or five)).tw. (534)
107 or/87-106 (402616)
108 55 or 86 or 107 (1686615)
109 29 and 108 (132)

Database name: MEDLINE-in-Process

1 Cirrhosis.kw. (4)
2 (Fibrosis and Liver).kw. (1)
3 cirrho*.tw. (25)
4 ((liver* or hepat* or alcohol* or biliar*) adj4 (fibro* or myxofibro* or cholang* or angiocholit*)).tw. (38)
5 or/1-4 (58)
6 Antibiotic Prophylaxis.kw. (2)
7 (antibiotic* or anti-biotic*).tw. (157)
8 ((antibacter* or anti-bacter* or bacteriocid* or antimycobacter* or anti-mycobacter* or antimicrob* or anti-microb*) adj4 (prophyla* or premed* or pre-med* or prevent*)).tw. (5)
9 (Pre-Exposure Prophylaxis or Post-Exposure Prophylaxis).kw. (2)
10 Anti-Bacterial Agents.kw. (0)
11 9 and 10 (0)
12 or/6-8,11 (160)
13 Ciprofloxacin.kw. (1)
14 (cipro* or ciprinol* or cetraxal* or ciloxan*).tw. (20)
15 Neomycin.kw. (0)
16 (neom?cin* or neofradin* or neo-fradin*).tw. (1)
17 Norfloxacin.kw. (0)
18 (norfloxacin* or noroxin*).tw. (3)
19 Rifaximin.kw. (0)
20 (rifaximin* or redactiv* or xifaxan* or targaxan* or normix*).tw. (1)
21 (rufloxacin* or sparfloxacin*).tw. (0)
22 Sulfamethoxazole.kw. (0)
23 (sulfamethoxazole* or sulfamethylisoxazole* or sulfisomezole* or gantanol* or co-trimoxazole* or cotrimoxazole*).tw. (2)
24 or/13-23 (26)
25 12 or 24 (166)
26 5 and 25 (1)
27 Animals/ not Humans/ (0)
28 26 not 27 (1)
29 limit 28 to english language (0)
30 Economics/ (0)

31 exp "Costs and Cost Analysis"/ (0)
32 Economics, Dental/ (0)
33 exp Economics, Hospital/ (0)
34 exp Economics, Medical/ (0)
35 Economics, Nursing/ (0)
36 Economics, Pharmaceutical/ (0)
37 Budgets/ (0)
38 exp Models, Economic/ (0)
39 Markov Chains/ (0)
40 Monte Carlo Method/ (0)
41 Decision Trees/ (0)
42 econom$.tw. (346)
43 cba.tw. (0)
44 cea.tw. (11)
45 cua.tw. (0)
46 markov$.tw. (11)
47 (monte adj carlo).tw. (17)
48 (decision adj3 (tree$ or analys$)).tw. (28)
49 (cost or costs or costing$ or costly or costed).tw. (382)
50 (price$ or pricing$).tw. (35)
51 budget$.tw. (15)
52 expenditure$.tw. (46)
53 (value adj3 (money or monetary)).tw. (4)
54 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (1)
55 or/30-54 (771)
56 "Quality of Life"/ (0)
57 quality of life.tw. (272)
58 "Value of Life"/ (0)
59 Quality-Adjusted Life Years/ (0)
60 quality adjusted life.tw. (4)
61 (qaly$ or qald$ or qale$ or qtime$).tw. (3)
62 disability adjusted life.tw. (3)
63 daly$.tw. (3)
64 Health Status Indicators/ (0)
65 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (14)
66 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (1)
67 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (7)
68 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (0)
69 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (1)
70 (euroqol or euro qol or eq5d or eq 5d).tw. (12)
71 (qol or hql or hqol or hrqol).tw. (51)

72 (hye or hyes).tw. (0)
73 health$ year$ equivalent$.tw. (0)
74 utilit$.tw. (114)
75 (hui or hui1 or hui2 or hui3).tw. (1)
76 disutili$.tw. (0)
77 rosser.tw. (0)
78 quality of wellbeing.tw. (0)
79 quality of well-being.tw. (0)
80 qwb.tw. (0)
81 willingness to pay.tw. (9)
82 standard gamble$.tw. (0)
83 time trade off.tw. (0)
84 time tradeoff.tw. (0)
85 tto.tw. (0)
86 or/56-85 (404)
87 Cost-Benefit Analysis/ (0)
88 Quality-Adjusted Life Years/ (0)
89 Markov Chains/ (0)
90 exp Models, Economic/ (0)
91 cost*.ti. (42)
92 (cost* adj2 utilit*).tw. (2)
93 (cost* adj2 (effective* or assess* or evaluat* or analys* or model* or benefit* or threshold* or quality or expens* or saving* or reduc*)).tw. (147)
94 (economic* adj2 (evaluat* or assess* or analys* or model* or outcome* or benefit* or threshold* or expens* or saving* or reduc*)).tw. (37)
95 (qualit* adj2 adjust* adj2 life*).tw. (4)
96 QALY*.tw. (3)
97 (incremental* adj2 cost*).tw. (5)
98 ICER.tw. (1)
99 utilities.tw. (4)
100 markov*.tw. (11)
101 (dollar* or USD or cents or pound or pounds or GBP or sterling* or pence or euro or euros or yen or JPY).tw. (21)
102 ((utility or effective*) adj2 analys*).tw. (10)
103 (willing* adj2 pay*).tw. (11)
104 (EQ5D* or EQ-5D*).tw. (9)
105 ((euroqol or euro-qol or euroquol or euro-quol or eurocol or euro-col) adj3 ("5" or five)).tw. (2)
106 (european* adj2 quality adj3 ("5" or five)).tw. (1)
107 or/87-106 (236)
108 55 or 86 or 107 (1154)
109 29 and 108 (0)

Database name: MEDLINE Epub Ahead-of-Print

1 Cirrhosis.kw. (116)
2 (Fibrosis and Liver).kw. (5)

3 cirrho*.tw. (902)
4 ((liver* or hepat* or alcohol* or biliar*) adj4 (fibro* or myxofibro* or cholang* or angiocholit*)).tw. (678)
5 or/1-4 (1465)
6 Antibiotic Prophylaxis.kw. (26)
7 (antibiotic* or anti-biotic*).tw. (4133)
8 ((antibacter* or anti-bacter* or bacteriocid* or antimycobacter* or anti-mycobacter* or antimicrob* or anti-microb*) adj4 (prophyla* or premed* or pre-med* or prevent*)).tw. (84)
9 (Pre-Exposure Prophylaxis or Post-Exposure Prophylaxis).kw. (51)
10 Anti-Bacterial Agents.kw. (17)
11 9 and 10 (0)
12 or/6-8,11 (4185)
13 Ciprofloxacin.kw. (24)
14 (cipro* or ciprinol* or cetraxal* or ciloxan*).tw. (232)
15 Neomycin.kw. (2)
16 (neom?cin* or neofradin* or neo-fradin*).tw. (37)
17 Norfloxacin.kw. (11)
18 (norfloxacin* or noroxin*).tw. (36)
19 Rifaximin.kw. (4)
20 (rifaximin* or redactiv* or xifaxan* or targaxan* or normix*).tw. (17)
21 (rufloxacin* or sparfloxacin*).tw. (5)
22 Sulfamethoxazole.kw. (11)
23 (sulfamethoxazole* or sulfamethylisoxazole* or sulfisomezole* or gantanol* or co-trimoxazole* or cotrimoxazole*).tw. (170)
24 or/13-23 (461)
25 12 or 24 (4427)
26 5 and 25 (31)
27 Animals/ not Humans/ (0)
28 26 not 27 (31)
29 limit 28 to english language (30)
30 Economics/ (0)
31 exp "Costs and Cost Analysis"/ (0)
32 Economics, Dental/ (0)
33 exp Economics, Hospital/ (0)
34 exp Economics, Medical/ (0)
35 Economics, Nursing/ (0)
36 Economics, Pharmaceutical/ (0)
37 Budgets/ (0)
38 exp Models, Economic/ (0)
39 Markov Chains/ (0)
40 Monte Carlo Method/ (0)
41 Decision Trees/ (0)
42 econom$.tw. (7370)
43 cba.tw. (56)
44 cea.tw. (236)
45 cua.tw. (18)

46 markov$.tw. (557)
47 (monte adj carlo).tw. (896)
48 (decision adj3 (tree$ or analys$)).tw. (657)
49 (cost or costs or costing$ or costly or costed).tw. (12497)
50 (price$ or pricing$).tw. (1048)
51 budget$.tw. (527)
52 expenditure$.tw. (1031)
53 (value adj3 (money or monetary)).tw. (76)
54 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (43)
55 or/30-54 (21349)
56 "Quality of Life"/ (0)
57 quality of life.tw. (7222)
58 "Value of Life"/ (0)
59 Quality-Adjusted Life Years/ (0)
60 quality adjusted life.tw. (405)
61 (qaly$ or qald$ or qale$ or qtime$).tw. (341)
62 disability adjusted life.tw. (116)
63 daly$.tw. (103)
64 Health Status Indicators/ (0)
65 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (362)
66 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (41)
67 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (133)
68 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (0)
69 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (5)
70 (euroqol or euro qol or eq5d or eq 5d).tw. (451)
71 (qol or hql or hqol or hrqol).tw. (1447)
72 (hye or hyes).tw. (1)
73 health$ year$ equivalent$.tw. (0)
74 utilit$.tw. (4192)
75 (hui or hui1 or hui2 or hui3).tw. (30)
76 disutili$.tw. (17)
77 rosser.tw. (0)
78 quality of wellbeing.tw. (2)
79 quality of well-being.tw. (5)
80 qwb.tw. (2)
81 willingness to pay.tw. (212)
82 standard gamble$.tw. (7)
83 time trade off.tw. (27)
84 time tradeoff.tw. (0)
85 tto.tw. (29)
86 or/56-85 (11721)

87 Cost-Benefit Analysis/ (0)
88 Quality-Adjusted Life Years/ (0)
89 Markov Chains/ (0)
90 exp Models, Economic/ (0)
91 cost*.ti. (1687)
92 (cost* adj2 utilit*).tw. (228)
93 (cost* adj2 (effective* or assess* or evaluat* or analys* or model* or benefit* or threshold* or quality or expens* or saving* or reduc*)).tw. (4978)
94 (economic* adj2 (evaluat* or assess* or analys* or model* or outcome* or benefit* or threshold* or expens* or saving* or reduc*)).tw. (1006)
95 (qualit* adj2 adjust* adj2 life*).tw. (409)
96 QALY*.tw. (340)
97 (incremental* adj2 cost*).tw. (354)
98 ICER.tw. (150)
99 utilities.tw. (150)
100 markov*.tw. (557)
101 (dollar* or USD or cents or pound or pounds or GBP or sterling* or pence or euro or euros or yen or JPY).tw. (802)
102 ((utility or effective*) adj2 analys*).tw. (535)
103 (willing* adj2 pay*).tw. (232)
104 (EQ5D* or EQ-5D*).tw. (382)
105 ((euroqol or euro-qol or euroquol or euro-quol or eurocol or euro-col) adj3 ("5" or five)).tw. (102)
106 (european* adj2 quality adj3 ("5" or five)).tw. (24)
107 or/87-106 (7783)
108 55 or 86 or 107 (31624)
109 29 and 108 (3)

Database name: Embase

1 exp liver cirrhosis/ (185321)
2 fibrosis/ and liver/ (10796)
3 cirrho*.tw. (175270)
4 ((liver* or hepat* or alcohol* or biliar*) adj4 (fibro* or myxofibro* or cholang* or angiocholit*)).tw. (88580)
5 or/1-4 (285085)
6 antibiotic prophylaxis/ (37437)
7 (antibiotic* or anti-biotic*).tw. (527426)
8 ((antibacter* or anti-bacter* or bacteriocid* or antimycobacter* or anti-mycobacter* or antimicrob* or anti-microb*) adj4 (prophyla* or premed* or pre-med* or prevent*)).tw. (8892)
9 prophylaxis/ or post exposure prophylaxis/ or pre-exposure prophylaxis/ (144273)
10 antiinfective agent/ or antibiotic agent/ (561357)
11 9 and 10 (8411)
12 or/6-8,11 (553916)
13 ciprofloxacin/ (117034)
14 (cipro* or ciprinol* or cetraxal* or ciloxan*).tw. (46147)

15 neomycin/ (22082)
16 (neom?cin* or neofradin* or neo-fradin*).tw. (10132)
17 norfloxacin/ (18676)
18 (norfloxacin* or noroxin*).tw. (7294)
19 rifaximin/ (5999)
20 (rifaximin* or redactiv* or xifaxan* or targaxan* or normix*).tw. (3191)
21 (rufloxacin* or sparfloxacin*).tw. (1918)
22 sulfamethoxazole/ (20864)
23 (sulfamethoxazole* or sulfamethylisoxazole* or sulfisomezole* or gantanol* or co-trimoxazole* or cotrimoxazole*).tw. (28402)
24 or/13-23 (189399)
25 12 or 24 (671058)
26 5 and 25 (8189)
27 nonhuman/ not human/ (5202149)
28 26 not 27 (8009)
29 limit 28 to english language (7255)
30 limit 29 to (conference abstract or conference paper or "conference review") (2966)
31 29 not 30 (4289)
32 exp Health Economics/ (997805)
33 exp "Health Care Cost"/ (328824)
34 exp Pharmacoeconomics/ (225449)
35 Monte Carlo Method/ (48771)
36 Decision Tree/ (20018)
37 econom$.tw. (473546)
38 cba.tw. (13934)
39 cea.tw. (40363)
40 cua.tw. (1804)
41 markov$.tw. (38167)
42 (monte adj carlo).tw. (59133)
43 (decision adj3 (tree$ or analys$)).tw. (35056)
44 (cost or costs or costing$ or costly or costed).tw. (956590)
45 (price$ or pricing$).tw. (70336)
46 budget$.tw. (45801)
47 expenditure$.tw. (88327)
48 (value adj3 (money or monetary)).tw. (4159)
49 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (9527)
50 or/32-49 (2162956)
51 "Quality of Life"/ (593303)
52 Quality Adjusted Life Year/ (34081)
53 Quality of Life Index/ (3109)
54 Short Form 36/ (37612)
55 Health Status/ (147112)
56 quality of life.tw. (564085)
57 quality adjusted life.tw. (25622)
58 (qaly$ or qald$ or qale$ or qtime$).tw. (25995)
59 disability adjusted life.tw. (5937)

60 daly$.tw. (5695)
61 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (48670)
62 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (2859)
63 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (11807)
64 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (70)
65 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (507)
66 (euroqol or euro qol or eq5d or eq 5d).tw. (28695)
67 (qol or hql or hqol or hrqol).tw. (125434)
68 (hye or hyes).tw. (161)
69 health$ year$ equivalent$.tw. (41)
70 utilit$.tw. (362967)
71 (hui or hui1 or hui2 or hui3).tw. (2965)
72 disutili$.tw. (1209)
73 rosser.tw. (139)
74 quality of wellbeing.tw. (71)
75 quality of well-being.tw. (555)
76 qwb.tw. (266)
77 willingness to pay.tw. (12318)
78 standard gamble$.tw. (1183)
79 time trade off.tw. (2004)
80 time tradeoff.tw. (316)
81 tto.tw. (2121)
82 or/51-81 (1239896)
83 cost utility analysis/ (11868)
84 quality adjusted life year/ (34081)
85 cost*.ti. (189067)
86 (cost* adj2 utilit*).tw. (12234)
87 (cost* adj2 (effective* or assess* or evaluat* or analys* or model* or benefit* or threshold* or quality or expens* or saving* or reduc*)).tw. (367638)
88 (economic* adj2 (evaluat* or assess* or analys* or model* or outcome* or benefit* or threshold* or expens* or saving* or reduc*)).tw. (63181)
89 (qualit* adj2 adjust* adj2 life*).tw. (26234)
90 QALY*.tw. (25734)
91 (incremental* adj2 cost*).tw. (27522)
92 ICER.tw. (12392)
93 utilities.tw. (14521)
94 markov*.tw. (38167)
95 (dollar* or USD or cents or pound or pounds or GBP or sterling* or pence or euro or euros or yen or JPY).tw. (69237)
96 ((utility or effective*) adj2 analys*).tw. (36070)
97 (willing* adj2 pay*).tw. (13893)

98 (EQ5D* or EQ-5D*).tw. (24281)
99 ((euroqol or euro-qol or euroquol or euro-quol or eurocol or euro-col) adj3 ("5" or five)).tw. (4817)
100 (european* adj2 quality adj3 ("5" or five)).tw. (900)
101 or/83-100 (605806)
102 50 or 82 or 101 (3247919)
103 31 and 102 (490)

Database name: Econlit

1 cirrho*.tw. (33)
2 ((liver* or hepat* or alcohol* or biliar*) adj4 (fibro* or myxofibro* or cholang* or angiocholit*)).tw. (3)
3 1 or 2 (35)
4 (antibiotic* or anti-biotic*).tw. (328)
5 ((antibacter* or anti-bacter* or bacteriocid* or antimycobacter* or anti-mycobacter* or antimicrob* or anti-microb*) adj4 (prophyla* or premed* or pre-med* or prevent*)).tw. (5)
6 4 or 5 (332)
7 (cipro* or ciprinol* or cetraxal* or ciloxan*).tw. (12)
8 (neom?cin* or neofradin* or neo-fradin*).tw. (0)
9 (norfloxacin* or noroxin*).tw. (0)
10 (rifaximin* or redactiv* or xifaxan* or targaxan* or normix*).tw. (0)
11 (rufloxacin* or sparfloxacin*).tw. (0)
12 (sulfamethoxazole* or sulfamethylisoxazole* or sulfisomezole* or gantanol* or co-trimoxazole* or cotrimoxazole*).tw. (1)
13 or/7-12 (13)
14 6 or 13 (342)
15 3 and 14 (0)

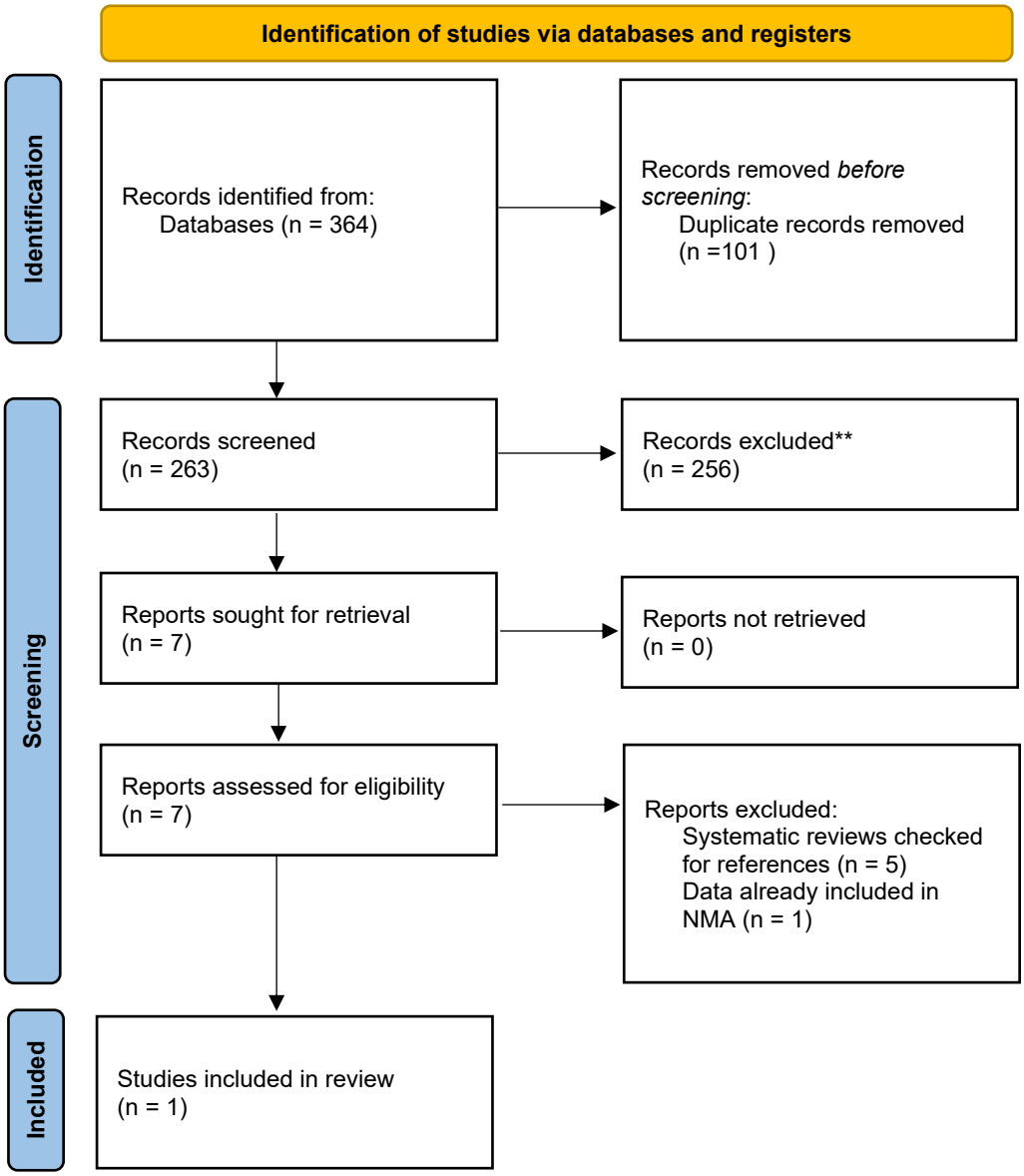
Database name: INAHTA

17	#16 AND #4	1
16	#15 OR #8	276
15	#14 OR #13 OR #12 OR #11 OR #10 OR #9	14
14	("Sulfamethoxazole[mhe]") OR (sulfamethoxazole* or sulfamethylisoxazole* or sulfisomezole* or gantanol* or co-trimoxazole* or cotrimoxazole*)	7
13	(rufloxacin* or sparfloxacin*)	0

12	("Rifaximin[mh]") OR (rifaximin* or redactiv* or xifaxan* or targaxan* or normix*)	3
11	("Norfloxacin[mh]") OR (norfloxacin* or noroxin*)	2
10	("Neomycin[mhe]") OR (neomycin* or neomicin* or neofradin* or neo-fradin*)	0
9	("Ciprofloxacin[mhe]") OR (cipro* or ciprinol* or cetraxal* or ciloxan*)	4
8	#7 OR #6 OR #5	270
7	("Pre-Exposure Prophylaxis[mh]" or "Post-Exposure Prophylaxis[mh]") AND ("Anti-Bacterial Agents[mhe]")	0
6	(antibacter* or anti-bacter* or bacteriocid* or antimycobacter* or anti-mycobacter* or antimicrob* or anti-microb*) AND (prophyla* or premed* or pre-med* or prevent*)	34
5	("Antibiotic Prophylaxis[mh]") OR (antibiotic* or anti-biotic*)	249
4	#3 OR #2 OR #1	115
3	(liver* or hepat* or alcohol* or biliar*) AND (fibro* or myxofibro* or cholang* or angiocholit*)	70
2	("Fibrosis"[MH]) AND ("Liver"[MH])	4
1	("Liver Cirrhosis[mhe]") OR (cirrho*)	64

Appendix C – Effectiveness evidence study selection

Figure 1: PRISMA flow diagram



Appendix D – Effectiveness evidence

Komolafe, 2020

Bibliographic Reference	Komolafe, Oluyemi; Roberts, Danielle; Freeman, Suzanne C; Wilson, Peter; Sutton, Alex J; Cooper, Nicola J; Pavlov, Chavdar S; Milne, Elisabeth Jane; Hawkins, Neil; Cowlin, Maxine; Thorburn, Douglas; Davidson, Brian R; Tsochatzis, Emmanuel; Gurusamy, Kurinchi Selvan; Antibiotic prophylaxis to prevent spontaneous bacterial peritonitis in people with liver cirrhosis: a network meta-analysis.; The Cochrane database of systematic reviews; 2020; vol. 1; cd013125

Study Characteristics

Study type	Network Meta-Analysis
Study details	Searches conducted November 2018

Study Inclusion criteria	• Randomised controlled trial (RCT)
	• RCTs including cluster-randomised trial and cross-over randomised trial.
	• Studies that compare treatment of interest with placebo or to each other
	• Studies comparing the following antibiotic interventions against each other and no active intervention or placebo, either alone or in combination.
	  ○ Cephalosporins.
	  ○ Quinolones.
	  ○ Folic acid synthesis inhibitors.
	  ○ Rifaximin.
	  ○ Other classes of antibiotics.

Study Exclusion Criteria	Not stated
Participant inclusion criteria	• Liver cirrhosis • Undergoing prophylaxis for SBP
Participant exclusion criteria	• Previous liver transplant • People receiving antibiotics for the treatment of SBP or other reasons, eg hepatic encephalopathy.
Number of included studies	29 studies reported in 50 references.
Interventions	• Rifaximin • Norfloxacin • Ciprofloxacin

	• Sulfamethoxazole + trimethoprim • Norfloxacin + rifaximin • Rufloxacin • No active intervention/placebo

Critical appraisal - GDT Crit App - modified PRISMA for NMA

Section	Question	Answer
Overall quality and applicability	Overall quality	High *(Only partial discussion of limitations, otherwise NMA fully follows PRISMA-NMA reporting standards.)*
Overall quality and applicability	Applicability as a source of data	Partially applicable *(Includes secondary prophylaxis and also includes people without ascites)*

Critical appraisal - GDT Crit App - ROBIS checklist for systematic review

Section	Question	Answer
Overall study ratings	Overall risk of bias	Low
Overall study ratings	Applicability as a source of data	Partially applicable *(Not all of the included population had ascites and some studies reported secondary prophylaxis.)*

Appendix E – Forest plots

No forest plots were produced for this review because no meta-analysis was undertaken.

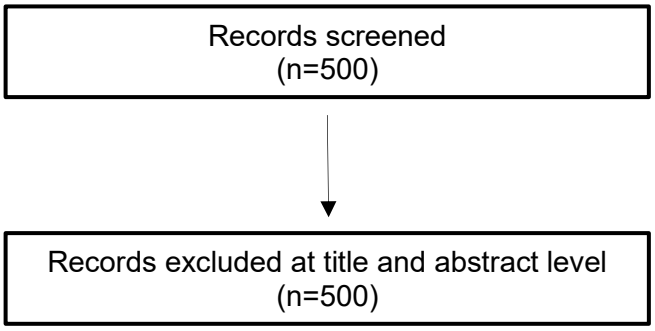
The included NMA presents network diagrams for the comparators it includes – see figure 1 in Komolafe et al (2020).

Some additional plots were not included in the NMA due to concerns about consistency in the network. They can be accessed via https://zenodo.org/record/3457887#.ZBmGPXbP2Um.

Appendix F – GRADE tables

No GRADE tables were produced for this review. The outcomes reported in Komolafe et al (2020) and reproduced in tables 3 and 4 in this review give the summary GRADE assessment made by Komolafe et al 2020.

Appendix G – Economic evidence study selection



Appendix H – Economic evidence tables

No economic studies were included in this review.

Appendix I – Health economic model

Model overview

The objective of this analysis is to evaluate whether antibiotics could be cost saving for the primary prevention of spontaneous bacterial peritonitis (SBP) in people with cirrhosis and ascites.

Population

Adults with liver cirrhosis, who were undergoing prophylactic treatment with antibiotics to prevent spontaneous bacterial peritonitis.

Comparators

Rifaximin, norfloxacin, co-trimoxazole, ciprofloxacin, no treatment

Model structure

We conducted a threshold analysis to assess which antibiotic is cost saving for the primary prevention of SBP. The threshold represents the number of cases of SBP needs to prevent to be cost saving. If the risk reduction of developing SBP is below the threshold, then the antibiotic would be cost saving.

$$Threshold = \frac{Management\ cost\ of\ SBP}{Annual\ cost\ of\ antibiotics}$$

Model inputs

We obtained inputs on cost and resource utilisation from NHS Cost Collection and from the economic analysis that was undertaken for the previous guideline update. All costs have been inflated to 2019/20 price level using the NHS cost inflation index.

This analysis includes the following costs:

- The annual cost of each antibiotic,
- The cost of managing an episode of SBP.

The annual cost of antibiotics

We obtain the costs of individual antibiotics from the BNF and the daily dosages from published clinical guidelines or clinical review. The annual costs are estimated to be £46.72 for ciprofloxacin, £3,379.25 for rifaximin and £88.77 for co-trimoxazole.

Table I1: Costs of antibiotics

Antibiotics	Daily dosage	Unit price per tablet	BNF (package size/drug tariff)	Annual cost
Norfloxacin	400mg×1	Not available	Not available	Not available
Ciprofloxacin	500mg×1	£0.13	500mg×10, £1.28	£46.72
Rifaximin	550mg×2	£4.63	550mg×56, £259.23	£3,379.25
Co-trimoxazole	800 mg sulfamethoxazole/ 160 mg trimethoprim×1	£0.24	800/160mg×100, £24.32	£88.77

The cost of managing an episode of SBP

The analysis conducted for the previous guideline update (2017) outlined a management strategy for SBP, which took into account a 7-day hospital stay, a course of treatment with tazocin, paracentesis and an ultrasound. Where possible, we updated these costs using information from the latest published resources for each item, and where these costs are no longer available (e.g. due to changes in how HRG codes are recorded and reported), we uprated the unit costs to the 2019/20 price level. In total, the cost of managing an episode of SBP was estimated to be £2,023.74.

Table I2: Management costs of SBP

Cost type	Unit costs	Source
7-day hospital stay: GBO3D (elective inpatient-excess bed days)	£1,651.29	Previous guideline, with cost inflation
Tazocin (Piperacillin 4 g/tazobactam 500 mg IV every 8 hours for 5 days)	£227.55	BNF (2023)
Paracentesis	£82.51	Previous guideline, with cost inflation
Ultrasound (RD40Z: outpatient, ultrasound scan with duration of less than 20 minutes, without Contrast)	£62.39	NHS Cost Collection 2019/2020

Treatment effect

We obtained the risk difference of antibiotics versus no active intervention from the Cochrane review (Komolafe, 2020). The clinical data are summarised in the table below.

Table I3: Risk difference with NSBBs

Antibiotic	Risk difference vs no active intervention (95% CI)
Rifaximin	860 more per 1000 (121 fewer to 860 more)
Norfloxacin	117 fewer per 1000 (140 fewer to 79 more)
Ciprofloxacin	62 fewer per 1000 (138 fewer to 860 more)
Co-trimoxazole	Not available

Results

The prophylactic treatment with antibiotics would be cost saving if ciprofloxacin prevents at least one episode per 43.32 person years and for co-trimoxazole one episode per 22.80 person years.

The clinical evidence suggests that ciprofloxacin could reduce incidence of SBP by an average of 62 cases per 1000 (1 SBP episode in every 16 people), and thus using ciprofloxacin is more likely to be cost saving than do nothing. However, there is a lack of clinical data available to model these outcomes for co-trimoxazole, this means we cannot determine whether co-trimoxazole cost saving.

The prophylactic treatment with rifaximin costs more than treating an episode of SBP each year (£3,379.25 vs £2,023.74). Poor-quality clinical data of rifaximin also indicated that people with rifaximin are more likely to develop SBP than no active intervention. Therefore, we cannot quantify the cost savings for rifaximin.

Table I4: Summary of economic results

	Ciprofloxacin	Rifaximin	Co-trimoxazole
Drug cost:	Inexpensive (£47 per year)	Comparatively expensive, costs about £3,379 a year	Inexpensive (£89 per year)
Threshold:	Needs to prevent at least one episode per 43.32 person years in order to be cost saving	Costs more to provide rifaximin than treating an episode of SBP each year	Needs to prevent at least one episode per 22.80 person years in order to be cost saving
Evidence:	Prophylactic treatment could reduce incidence of SBP by an average of 62 cases per 1000 (i.e. 1 SBP episode in every 16 people).	Clinical data is poor quality and implausible: suggests that people with rifaximin are more likely to develop SBP than no active intervention	Lack of clinical data to make a judgement
Conclusion:	Cost saving	Cannot formally quantify whether cost saving	Cannot formally quantify whether cost saving

Discussion

Principal findings

The current analysis is not compelling enough to recommend the routine use of prophylactic treatment with antibiotics for people with ascites. Based on the best available evidence, ciprofloxacin appears more likely to be cost saving than no active intervention. However, there are safety concerns around fluroquinolone class drugs which ciprofloxacin belongs to. The evidence for adverse effects for ciprofloxacin is of very low quality and was not reported in a granular way in the Cochrane report, and it is therefore challenging to quantify their economic impact and weigh up their impact and the risk of developing SBP.

Strengths of the analysis

The strength of this analysis is that it is based on up-to-date cost and resource use assumptions. The clinical evidence was identified from a recent Cochrane review which has been evaluated by the NICE development team.

Weakness of the analysis

One of the weaknesses is that this analysis only takes into account the costs of antibiotics and management costs of SBP. Although clinical experts have validated the resource included for the management of SBP, the management strategy is complicated and, on a case by-case basis, it is challenging to accurately accrue the relevant costs. Also, we have not included the improvements in quality of life from averted SBP and outcomes related to antimicrobial stewardship.

Furthermore, there are lots of uncertainties around the treatment effect. There is a lack of robust evidence for co-trimoxazole and rifaximin. The Cochrane review cannot estimate the hazard ratio of risk difference for co-trimoxazole due to the zero cases of SBP in the co-trimoxazole arm. Poor quality clinical data for rifaximin suggest that prophylactic treatment with rifaximin would increase the risk of developing SBP than no active intervention. As a result, we are not able to quantify potential cost savings for these antibiotics.

Conclusions

Prophylactic treatment with ciprofloxacin might be cost saving. Owing to the poor-quality clinical data for rifaximin and co-trimoxazole, unfortunately, we cannot formally estimate whether they are cost saving or not. Further generation of high-quality data would allow us to predict the benefits of prophylactic treatment with antibiotics with more certainty.

Appendix J – Excluded studies

Effectiveness evidence

Study	Reason for exclusion
Facciorusso, A., Papagiouvanni, I., Cela, M. et al. (2019) Comparative Efficacy of Long-term Antibiotic Treatments in the Primary Prophylaxis of Spontaneous Bacterial Peritonitis. Liver international : official journal of the International Association for the Study of the Liver	- Systematic review used as source of primary studies
Mucke, Marcus M, Mucke, Victoria T, Graf, Christiana et al. (2020) Efficacy of Norfloxacin Prophylaxis to Prevent Spontaneous Bacterial Peritonitis: A Systematic Review and Meta-Analysis. Clinical and translational gastroenterology 11(8): e00223	- Systematic review used as source of primary studies
Pimentel, R; Gregorio, C; Figueiredo, P (2021) Antibiotic prophylaxis for prevention of spontaneous bacterial peritonitis in liver cirrhosis: systematic review. Acta gastro-enterologica Belgica 84(2): 333-342	- Systematic review used as source of primary studies
Praharaj, D.L., Premkumar, M., Roy, A. et al. (2022) Rifaximin Vs. Norfloxacin for Spontaneous Bacterial Peritonitis Prophylaxis: A Randomized Controlled Trial. Journal of Clinical and Experimental Hepatology 12(2): 336-342	- Duplicate reference *This is the final publication of data that was already included in the Komolafe NMA from a conference abstract (Praharaj 2017 in the Komolafe NMA).*
Soriano G, Guarner C, Teixido M, Such J, Barrios J, Enriquez J et al. Selective intestinal decontamination prevents spontaneous bacterial peritonitis. Gastroenterology. 1991; 100(2):477-481.	This study did not report data that could be fitted to the NMA and was therefore excluded
Soni, Hariom, Kumar-M, Praveen, Sharma, Vishal et al. (2020) Antibiotics for prophylaxis of spontaneous bacterial peritonitis: systematic review & Bayesian network meta-analysis. Hepatology international 14(3): 399-413	- Systematic review used as source of primary studies
Wang, J., Liu, C., Song, P. et al. (2019) Norfloxacin, ciprofloxacin, trimethoprim-sulfamethoxazole, and rifaximin for the	- Systematic review used as source of primary studies

Study	Reason for exclusion
prevention of spontaneous bacterial peritonitis: A network meta-analysis. European Journal of Gastroenterology and Hepatology 31(8): 905-910	

Economic evidence

None screened at full text

Appendix K– Research recommendations – full details

K1.1 Research recommendation

What is the clinical and cost-effectiveness of antibiotic prophylaxis to prevent spontaneous bacterial peritonitis in people with cirrhosis and ascites?

K1.1.1 Why this is important

Current evidence is based on methodologically poor studies with small sample sizes and this means that the committee did not find the evidence useful for decision making. Better quality evidence from larger trials will enable a future committee to make a stronger recommendation about the potential use of antibiotics to prevent spontaneous bacterial peritonitis (SBP)

K1.1.2 Rationale for research recommendation

Importance to 'patients' or the population	Practice around the country is variable for the use of antibiotics to prevent SBP and the balance between their usefulness for this indication and good antimicrobial stewardship is not well understood. New evidence will mean that people will not be unnecessarily taking antibiotics that are not helping them. This is turn will mean that fewer resistant strains of bacteria will occur.
Relevance to NICE guidance	This guideline makes specific recommendations about antibiotic use to prevent SBP.
Relevance to the NHS	The outcome would affect the types of prophylaxis provided by the NHS, will make practice more uniform, is cost saving and will reduce antibiotic resistance and unnecessary use of ineffective antibiotic treatment.
National priorities	Moderate
Current evidence base	Methodologically poor RCTs with small sample sizes.
Equality considerations	None known

K1.1.3 Modified PICO table

Population	Adults with liver cirrhosis and ascites
Intervention	Any of the following treatments, either alone or in combination: • Cephalosporins.

	• Quinolones. • Folic acid synthesis inhibitors. • Rifaximin. • Other classes of antibiotics. • No active intervention.
Comparator	Each other
Outcome	**Primary** • All-cause mortality at maximal follow-up (time to death). • Health-related quality of life using a validated scale, at maximal follow-up • Serious adverse events (during or within six months after cessation of intervention) **Secondary** • Any adverse events. • Liver transplantation (time to liver transplantation at maximal follow-up). • Time to development of spontaneous bacterial peritonitis • Number of decompensation episodes (maximal follow-up)
Study design	Large well designed RCT, or SR & NMA of RCTs
Timeframe	Medium term
Additional information	None