

New Medicine Assessment

Co-trimoxazole (Septrin®)

Prophylaxis of Primary and Secondary Spontaneous Bacterial Peritonitis (SBP)

Recommendation: Amber 2

Co-trimoxazole is recommended as:

- a second-line option for primary and secondary SBP prophylaxis
- an alternative first-line option for primary and secondary SBP prophylaxis in place of ciprofloxacin if there is known sensitivity

Summary of supporting evidence:

- American and European Guidelines recommend antibiotic prophylaxis to reduce the incidence of SBP. Both guidelines currently recommend norfloxacin, however this is not currently available as a licensed product in the UK. Co-trimoxazole and ciprofloxacin are also listed as possible alternative options, which are currently available in the UK, but neither are licensed for the prophylaxis of SBP.
- There have been several trials assessing antibiotic prophylaxis in SBP, however they are of low quality and the majority focus on the use of norfloxacin.
- Evidence for co-trimoxazole use consists of three studies with small numbers of patients; one retrospective (n=69) in 2008, comparing co-trimoxazole with norfloxacin, a RCT (n=60) from 1995, comparing co-trimoxazole against no prophylaxis and a randomised non-blinded trial (n=80) in 2014, comparing co-trimoxazole to norfloxacin.
- The 2014 paper showed no statistically significant difference in the incidence of SBP, bacteraemia or overall infection between co-trimoxazole and norfloxacin. The retrospective review conducted by the same authors also showed no statistically significant difference in rates of SBP, spontaneous bacteraemia or extraperitoneal infections between norfloxacin and co-trimoxazole.
- The RCT (1995) found SBP developed in 8 patients (27%) receiving no prophylaxis and in 1 patient (3%) receiving co-trimoxazole (p=0.025). It should be noted that the RCT used a dosing schedule of 960mg for 5 days per week and the proposed use is 960 mg daily. The guidance recommending co-trimoxazole for prophylaxis of SBP is based on this 1995 RCT and a Cochrane review rated the quality of this trial as low.
- The incidence of AEs in the trials were found to be similar between co-trimoxazole and norfloxacin groups. However, it was noted that the number of AEs related to the treatment drug was increased for the co-trimoxazole group compared to norfloxacin group (22.5% vs. 0% p=0.01) and included; gastrointestinal, renal and skin related reactions, which resolved on discontinuation of the drug.
- The 1995 paper which compared co-trimoxazole to no treatment stated that no patients experienced AEs. It was noted that one patient developed diarrhoea, with no *C. difficile* present, which resolved despite continuation of the study drug.
- It should be borne in mind that there is an increased incidence of *C. difficile* infection with co-trimoxazole treatment; OR 1.81 (95% CI 1.34 to 2.43). The conclusion of a review of 3

meta-analyses did state however, that the association is greater with quinolones, clindamycin and cephalosporins.

- Co-trimoxazole includes amongst other undesirable effects blood and lymphatic system disorders, which patients with hepatic failure are more susceptible to.
- The annual cost per patient of co-trimoxazole at 960 mg daily for the prophylaxis of SBP is £86. The alternative, ciprofloxacin 500 mg daily, has an annual per patient cost of £40. The request states the expected use to be 1-2 patients per month, equating to 24 a year. Using co-trimoxazole over ciprofloxacin would equate to an additional £1197 annually.

Details of Review

Name of medicine (generic & brand name): Co-trimoxazole (sulfamethoxazole and trimethoprim)
Strength(s) and form(s): Available as 480 mg and 960 mg tablets (containing 400 or 800 mg sulfamethoxazole and 80 or 160 mg trimethoprim). ¹
Dose and administration: 960 mg once daily orally. ²
BNF therapeutic class / mode of action: Chapter 5.1.8 sulfonamides and trimethoprim ¹
Licensed indication(s): Treatment and prophylaxis (primary and secondary) of <i>Pneumocystis jiroveci</i> (<i>P. Carinii</i>) in adults and children. Treatment and prophylaxis of toxoplasmosis, treatment of nocardiosis. Treatment of urinary tract infections and acute exacerbations of chronic bronchitis, where there is bacterial evidence of sensitivity to co-trimoxazole and good reason to prefer this combination to a single antibiotic. Treatment of acute otitis media where there is good reason to prefer co-trimoxazole to a single antibiotic. ³
Proposed use (if different from, or in addition to, licensed indication above): As a second-line option for primary and secondary SBP prophylaxis. Also, as an alternative first-line option for primary and secondary SBP prophylaxis in place of ciprofloxacin if there is known sensitivity. This is an unlicensed indication.
Course and cost: 960 mg 100 tablets = £23.46. 1 year's use = £86 From Mims online 24/4/15
Current standard of care/comparator therapies: Other first line options include ciprofloxacin 500 mg daily. 500 mg 10 tablets = £1.09. 1 year's use = £40. From Mims online 24/4/15 Another option mentioned in guidance is norfloxacin 400 mg daily. However this is currently unavailable as a licensed product in UK.
Relevant NICE guidance: There is currently no NICE guidance for the management of SBP. However, a clinical guideline is in progress, anticipated June 2016 , for the assessment and management of cirrhosis. The majority of cases of SBP are in patients with cirrhosis, so this guidance, when published, could be of relevance.
Other relevant guidance: American Association for study of liver disease (AASLD) guidelines "Management of adult patients with ascites due to cirrhosis: update 2012." ⁴ 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 2010. ²

Background and context

SBP is a serious and life-threatening infection causing inflammation of the peritoneum and is a frequent complication in patients with cirrhosis.² SBP is the infection of pre-existing ascites. Diagnosis is made on a positive ascitic fluid bacterial culture and the polymorphonuclear (PMN) count in ascitic fluid being > 250 cells/mm³, but the absence of an intra-abdominal, surgically treatable, source of infection.⁴ Signs and symptoms are frequently absent in patients with SBP, therefore a diagnostic paracentesis should be performed in all patients with ascites admitted to hospital, regardless of whether there is a clinical suspicion of SBP.⁵ It has a high prevalence, affecting 10-30% of inpatients with cirrhosis and ascities.⁶ The in-hospital mortality rate for the first episode of SBP ranges from 10-50%, dependent on risk factors.⁵ The prevalence of SBP in outpatients was reported in 2012 as 2 - 3%.⁵ SBP has a high recurrence rate of up to 70% in the first year and a poor long-term prognosis with the probability of survival at one year being only 30-50%, falling to 25-30% for two year survival.^{2,6} Due to this, patients recovering from SBP should be considered potential candidates for liver transplantation.²

Because of the poor prognosis and high recurrence rate for patients who acquire SBP, preventing it developing is imperative.⁶ However, due to the threat of antibiotic resistance and the impact that has on society as a whole, only patients at high risk of SBP should receive prophylactic treatment,² which includes both primary and secondary prophylaxis. Primary prophylaxis patients are those who have no prior history of SBP, but are at high risk of developing it as they have liver cirrhosis and a low ascitic fluid total protein of <10 g/L.² Secondary prophylaxis patients have a previous history of SBP infection and without prophylaxis would have a 70% chance of recurrence within the first 12 months.⁶

“The European Association for the Study of the Liver Clinical Practice Guidelines” and “The American Association for the Study of Liver Diseases Practice Guidelines” both recommend oral antibiotic prophylaxis for high risk patients. This recommendation is based on a number of studies demonstrating a reduced incidence of SBP and improvement in short-term survival.^{2,4} A meta-analysis of eight studies ($n = 647$) found that patients with cirrhosis and ascites who received prophylactic antibiotics, (which included norfloxacin, ciprofloxacin and co-trimoxazole) had an ARR of 9% in mortality compared with placebo with an NNT of 12 (RR 0.65; $p=0.006$; 95% CI 0.48-0.88).⁷ The incidence of mortality at 3 months gave an ARR of 16.1% for patients treated with prophylactic antibiotics (RR 0.28; $p=0.005$; 95% CI 0.12 - 0.68).⁷ The same meta-analysis stated that groups treated with prophylactic antibiotics showed a RR reduction of the overall incidence of SBP by 51% when compared with groups not given this intervention (RR 0.49; $p<0.0001$; 95% CI 0.35-0.69).⁷ The overall incidence of SBP during follow up was 12.7% in groups treated with prophylactic antibiotics compared with 25% in groups who weren't.⁷ A Cochrane review noted that trials conducted to support antibiotic prophylaxis have not been to a high standard, it advocated that trials of better design, well reported and of longer follow-up are required before antibiotic prophylaxis can be confidently recommended.⁸

Both the American and European guidelines currently recommend norfloxacin 400 mg daily is used as prophylactic therapy;^{2,4} however this is no longer available as a licensed product in the UK.⁹ The guidelines also list trimethoprim/sulfamethoxazole (co-trimoxazole) and ciprofloxacin as prophylactic options but do state that the evidence supporting these is not strong.^{2,4} The evidence upon which co-trimoxazole is recommended is based on a paper published in the annals of internal medicine in April 1995¹⁰; a Cochrane review in 2009 stated the overall quality of the trial in this paper was rated as low.⁸

There are concerns regarding antibiotic resistance as well as known sensitivities, the guidelines recommended to have more than one prophylactic option available, ideally from different classes of antibiotics.

Co-trimoxazole is an antibiotic comprising a combination of sulfamethoxazole and trimethoprim in the proportions 5 parts to 1 part.^{1,3} The request is for the prophylaxis of SBP, which is an unlicensed indication, as a second-line option, at a dose of 960 mg daily. The currently used first line prophylactic is ciprofloxacin. There is also a request to use co-trimoxazole a first line option, if the sensitivity is known. This review will look at what evidence there is to support the use of co-trimoxazole for the prophylaxis for SBP.

Summary of evidence

Summary of efficacy data in proposed use:

Several trials have taken place for the use of long term oral antibiotic prophylaxis of SBP, however, they have often been of low quality⁸ and the majority assess the efficacy of norfloxacin. One randomised trial compared co-trimoxazole against no prophylaxis in 1995.¹⁰ It is upon this trial that recommendations concerning co-trimoxazole in both the American and European guidelines are based.^{2,4} Since 1995, there have been 3 studies; one of these is a retrospective study the others randomised comparator trials, assessing the efficacy of co-trimoxazole with norfloxacin for the prophylaxis of SBP.^{11,12,13}

The most recent of these comparison trials, which was published in 2014,¹¹ included 80 cirrhotic patients who were either inpatients or outpatients with ascites at high risk for SBP. Baseline characteristics of the two groups were well matched both in terms of their personal and their liver disease characteristics.¹¹ The exclusion criteria can be found in appendix 1. SBP was defined for this study as an ascitic fluid neutrophil count of $\geq 0.25 \times 10^9/L$, with or without a positive ascitic culture, after other abdominal infection causes, such as intestinal abscess or perforation, were excluded. Although the study was randomised, it was not blinded either to investigators or patients. 40 patients were randomly assigned to receive norfloxacin 400 mg orally daily, with the remaining 40 assigned to receive trimethoprim/sulfamethoxazole 160/800 mg (co-trimoxazole) orally daily. Patients were followed up for 12 months, or earlier if an end-point of bacterial infection, liver transplantation or death was reached. Patients were considered non-compliant if they had not taken the study drug for 5 or more consecutive days or for more than 10% of the whole study period. The primary end point of the study was the incidence of infection. Secondary endpoints included the incidence of SBP, bacteraemia and extraperitoneal bacterial infection requiring antibiotic therapy, among others listed in appendix 1. During the study period there were 19 (23.8%) episodes of infections in both treatment arms. These included 4 episodes of SBP; 2 in the norfloxacin treatment arm and 2 in the co-trimoxazole treatment arm, 4 cases of bacteraemia; 2 in the norfloxacin treatment arm and 2 in the co-trimoxazole treatment arm and 11 cases of extraperitoneal infection; 6 for those treated with norfloxacin and 5 for co-trimoxazole. There were no statistically significant differences in the incidence of SBP, bacteraemia or overall infections between the co-trimoxazole and the norfloxacin treated groups.¹¹ The subgroup analysis of patients who were treated for primary and secondary prophylaxis found no significant difference between co-trimoxazole and norfloxacin in both primary and secondary prophylaxis groups. A significant difference in the rate

of transplantation between the norfloxacin and co-trimoxazole groups was observed (17.5% vs 40% p=0.03) but not in the mortality rate (27.5% vs 17.5%, p=0.28).¹¹

The same authors of the 2014 study had previously conducted a retrospective review, comparing co-trimoxazole and norfloxacin for the prevention of SBP.¹² 69 patients were included and the results showed no statistically significant differences in the rates of SBP, bacteraemia or extraperitoneal infections between the group receiving co-trimoxazole and the those receiving norfloxacin prophylaxis.¹² It was from this retrospective study that the authors determined a total of 80 patients, 40 in each arm, would be required to detect a difference of 20% between the two groups with a power of 80% and a P value of 0.05 for the prospective study detailed above.¹¹

A RCT (n=60), where co-trimoxazole was compared to no treatment, was carried out in 1995 for the prevention of SBP in patients cirrhosis and ascites.¹⁰ See appendix 1 for exclusion criteria. The patients were assigned to either co-trimoxazole 960 mg 5 times a week (Mon-Fri) (n=30) or no treatment (n=30).¹⁰ The primary end points were development of spontaneous bacteraemia or SBP. These infections developed in 8 patients (27%) receiving no prophylaxis and in 1 patient (3%) receiving co-trimoxazole (p=0.025).¹⁰ 6 patients died in the no treatment group and 2 patients in the co-trimoxazole treated group, the paper stated this was not a statistically significant difference.

Other efficacy data:

A study from Brazil published in 2005, compared co-trimoxazole to norfloxacin in the prophylaxis of SBP in hospitalised patients with liver cirrhosis and ascites.¹³ Patient inclusion and exclusion information can be seen in appendix 1. 57 patients were randomly assigned norfloxacin 400 mg daily (n=32) or co-trimoxazole 160/800 mg 5 days a week (n=25).¹³ Patients were followed up for a mean of 163 days. 3 patients (9.4%) on norfloxacin and 4 patients (16%) on co-trimoxazole developed SBP (p=0.68). When looking at infections in general, 23 were recorded: 13 (40%) in the norfloxacin group and 10 (40%) in the co-trimoxazole group (p=1.0)¹³ The overall quality of this trial was assessed as low in a Cochrane review.⁸

Summary of safety data:

In the 2014 study¹¹ there were 17 adverse events (AE)s (norfloxacin versus co-trimoxazole, 17.5% vs 25.0% respectively, p=0.59). Co-trimoxazole was associated with an increased risk of developing a definite or probable AE compared to norfloxacin (22.5% vs 0%, p=0.01). 8 patients out of 40 stopped taking co-trimoxazole during the study due to gastrointestinal (n=4), renal (n=2) and skin (n=2) related side effects, all of which resolved following co-trimoxazole cessation. In comparison, 3 out of 40 patients stopped norfloxacin therapy during the study period, 2 at patients request for reasons unrelated to side effects. The third patient had paranoid delusions, but also had severe chronic hepatic encephalopathy.

The 1995 trial, upon which European and American guidelines have been based, where co-trimoxazole was compared to no prophylaxis,¹⁰ the authors report that none of the 60 patients developed AEs and that hematologic toxicity caused by the co-trimoxazole was notably absent.¹⁰ One patient developed diarrhoea, C. difficile was found to not be present, which resolved despite continuing co-trimoxazole therapy. The investigators suggested that the

diarrhoea could be potentially related to the study drug.¹⁰

The 2005 paper of co-trimoxazole vs. norfloxacin reported that AEs only occurred in patients receiving co-trimoxazole. There were 5 instances (20%) p=0.01: one patient had a skin rash which disappeared spontaneously, 2 patients complained about epigastric pain, the remaining 2 patients showed worsening of the renal function which was not attributed to any other causes.¹³

The reduced risk of *Clostridium difficile* infection when co-trimoxazole is used for prophylaxis rather than quinolones had been put forward as a potential benefit of its use. A NICE “Evidence Summary” reviewed the data from three meta-analyses looking at antibiotics and the risk of hospital and community-associated clostridium difficile infection. The following risk of *C. difficile* was found for quinolone antibiotics; in one paper (Slimings and Riley 2014 which reviewed data from 10 studies in hospital associated *C. difficile*) there was an OR 1.66 (95% CI 1.17 to 2.35), the second meta-analysis (Brown et al. 2013, reviewing 5 studies in community associated *C. difficile*), found an OR 5.50 (95% CI 4.26 to 7.11) and the third paper (Deshpande et al. 2013, with data taken from 3 studies in community *C. difficile*), found an OR 5.65 (95% CI 4.38 to 7.28). For sulphonamides and trimethoprim the results for the three meta-analyses were; Slimings and Riley (5 studies) OR 1.78 (95% CI 1.04 to 3.05), the second study Brown et al. (4 studies) OR 1.81 (95% CI 1.34 to 2.43) and the third meta-analysis Deshpande et al. (3 studies) OR 1.84 (95% CI 1.48 to 2.29).¹⁴ The evidence summary concluded that for community associated infection, the strongest association was seen with clindamycin, cephalosporins and quinolones. It also stated that trimethoprim and sulfonamides were also associated with an increased risk of infection in all three meta-analyses.¹⁴

The SPC for co-trimoxazole³ includes in the list of undesirable effects, blood and lymphatic system disorders to which patients with hepatic or renal failure are more susceptible. In addition severe skin sensitivity reactions, Stevens-Johnson syndrome and Lyell syndrome have occurred infrequently.³ Deaths have occurred with severe skin, hepatic and blood disorders, aplastic anaemia and hypersensitivity of the respiratory tract.³ The SPC advises that co-trimoxazole should be discontinued immediately with the first appearance of skin rash.³ Use for SBP prophylaxis is unlicensed and as such is not covered in the SPC. Information on the safety issues of co-trimoxazole observed when used in this way is discussed within the published trials summarised above. For further information on adverse effects and contraindications of co-trimoxazole the SPC and the current edition of the BNF should be consulted.^{1,3}

Strengths and limitations of the evidence:

Strengths

- The patient populations included in the trials, although small, were applicable to where prophylactic antibiotics would be used in practice.
- Appropriate patient orientated end-points were used in the trials; incidence of SBP.

Weaknesses

- Small numbers of patients were included in the trials; total of 197 patients for the prospective studies (95 treated with co-trimoxazole for SBP prophylaxis). For reliable conclusions to be drawn the sample would ideally be larger.

- The retrospective study only included 69 patients. However, the paper did state a power calculation.
- There was no blinding in any of the trials.
- Both the 1995 and 2005 papers co-trimoxazole was taken for 5 days a week compared to the proposed daily use. Results cannot necessarily be extrapolated to daily use of the medication as advocated in available guidelines and in the request.
- There were no trials identified comparing co-trimoxazole against ciprofloxacin, which is the antibiotic currently used prophylactically for SBP and is mentioned in current guidance.
- A Cochrane review assessed the quality of the trials as low.

Summary of evidence on cost effectiveness:

There is no published data for cost effectiveness of co-trimoxazole in the prophylaxis of SBP in the UK.

Prescribing and risk management issues:

The use of co-trimoxazole in this indication is not licensed and there is not a large amount of data for its use for prophylaxis. There are concerns over the increased incidence of *C. difficile* with the use of co-trimoxazole.

Commissioning considerations:

Comparative unit costs:

Drug	Example regimen	Pack cost	Cost per patient per course/ per year (ex VAT)
Co-trimoxazole 960 mg (Septrin Forte)	1 tablet daily	£23.46 for 100	£86
Ciprofloxacin 500 mg	1 tablet daily	£1.09 for 10	£40

Costs based on MIMS list prices April 2015.
This table does not imply therapeutic equivalence of drugs or doses.

Associated additional costs or available discounts:

No available discounts known.

Productivity, service delivery, implementation:

The service is already in place. The proposal is to prescribe an alternative antibiotic.

Anticipated patient numbers and net budget impact:

The request stated that it was anticipated co-trimoxazole would be used in 1-2 patients per month; this would be up to 24 a year. 24 patients using co-trimoxazole over ciprofloxacin would equate to an additional £1104 annually.

Innovation, need, equity:

Co-trimoxazole is not an innovative treatment; however it would be additional alternative prophylactic antibiotic for SBP. It would be particularly useful for those patients for which the organism is sensitive to co-trimoxazole..

References

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Appendix 1: Summary of key antibiotic and co-trimoxazole RCTs relevant to use in SBP prophylaxis

Ref	Trial design	Patients / Trial subjects	Trial intervention and comparison	Outcomes: Primary endpoint (mITT)	Outcomes: Key secondary / exploratory endpoints	Grading of evidence / risk of bias
10	Randomised controlled trial.	60 patients with cirrhosis and ascites. Excluded if: <ul style="list-style-type: none"> allergic to sulphonamides had renal failure with a creatinine clearance of less than 15 mL/min had active spontaneous bacterial peritonitis or extraperitoneal infection at the time of enrolment. 	30 patients received no prophylaxis. 30 patients received trimethoprim-sulfamethoxazole (co-trimoxazole) one double-strength tablet five times a week (Monday to Friday) Entry to groups was stratified by serum bilirubin level, renal function and ascitic fluid protein level so that high-risk patients were not disproportionately allocated to either group. Paracentesis was carried out on patients in whom ascitic fluid infection was suspected – fever, abdominal pain or tenderness, leucocytosis, or worsening encephalopathy.	Development of spontaneous bacteremia or spontaneous bacterial peritonitis (defined as: ascitic fluid polymorphnuclearnuclear cell count $\geq 250/\text{mm}^3$ and negative ascitic fluid culture). Infectious complications developed in: No prophylaxis - 9 patients (30%) Co-trimoxazole – 1 patient – (3%) (p=0.012) Spontaneous bacterial peritonitis or spontaneous bacteraemia developed in: No prophylaxis – 8 patients (27%) Co-trimoxazole – 1 patient (3%) (p=0.025)	Adverse events noted were: Diarrhoea – 1 patient – in co-trimoxazole group. Mortality in: No prophylaxis – 6 patients (20%) (causes were gastrointestinal bleeding, hepatic insufficiency, hepatic insufficiency with respiratory failure) Co-trimoxazole – 2 patients (7%) (causes were gastrointestinal bleeding, hepatic insufficiency) (not statistically significant).	Patient-oriented outcome measure?: Yes Allocation concealment?: Not clear Blinded if possible?: No Intention to treat analysis?: yes Adequate power/size?: No Adequate follow-up (>80%)?: Yes Level 2 evidence based on unclear risk of bias. Risk of bias: unclear based on no blinding, small number of patients, no placebo
11	Randomised non-blinded comparator trial	80 cirrhotic patients (both inpatients and outpatients) with ascites at high risk of SBP (defined as a presence of at least	80 patients consecutively recruited. Computer generated randomisation in sealed opaque envelopes. Assigned to receive either:	Primary end-point: incidence of infection. 19 (23.8%) episodes of infections occurred during the study period;	Secondary end-points: incidence of SBP, bacteraemia, extraperitoneal bacterial infection requiring antibiotic therapy, liver transplantation, death, side	Patient-oriented outcome measure?: Yes Allocation concealment?: Yes

		<p>one of the following: history of SBP, ascitic protein concentration of < 15 g/L or serum bilirubin > 43 µmol/L. Exclusion criteria were:</p> <ul style="list-style-type: none"> • Allergies to sulfur-containing drugs or quinolones • Documented failure of either study drug in the past while on prophylaxis • Antibiotic therapy in the 2 weeks prior to the inclusion • Severe renal impairment, CrCl < 15 mL/min • Presence of hepatocellular carcinoma or other conditions with an expected survival of less than 3 months • Current bacterial infection • Secondary peritonitis • Active autoimmune hepatitis • HIV infection • Previous liver transplantation 	<ul style="list-style-type: none"> • Norfloxacin 400 mg orally daily (n=40) • Trimethoprim-sulfamethoxazole (co-trimoxazole) 160/800 mg orally daily (n=40) <p>Ascitic tap was performed prior to enrolment to exclude active SBP. Those with SBP were treated with ceftriaxone and ampicillin and albumin, with a repeat test 2/52 after completion to confirm resolution before commencement of trial antibiotics.</p> <p>Patients were followed up at 3-month intervals or at any hospitalisation.</p> <p>Total follow period was 12 months or earlier if an endpoint such as bacterial infection, liver transplantation or death was reached.</p>	<p>norfloxacin = 10 patients co-trimoxazole = 9 patients (p=0.79)</p>	<p>effects of the therapies, incidence of drug resistance to norfloxacin or co-trimoxazole in organisms isolated during the study.</p> <p>SBP = 4 (5.0%); norfloxacin = 2, co-trimoxazole = 2 (p=0.60)</p> <p>Bacteraemia = 4 (5.0%); norfloxacin = 2, co-trimoxazole = 2 (p=0.60)</p> <p>Extraperitoneal infection = 11 (13.8%); norfloxacin n=6, co-trimoxazole n=5 (p=0.74)</p> <p>A subgroup analysis of infection and incidence of SBP for those on treatment for primary prophylaxis and secondary prophylaxis. (NB/ subgroup analysis not powered to demonstrate statistical significance)</p> <p>Primary prophylaxis: Overall infection; norfloxacin n= 5, co-trimoxazole = 7 (p=0.80) SBP; norfloxacin = 1, co-trimoxazole = 1 (p=0.49)</p> <p>Secondary prophylaxis: Overall infection; norfloxacin n= 5, co-trimoxazole = 2 (p=0.44) SBP; norfloxacin = 1, co-trimoxazole = 1 (p=0.50)</p> <p>Adverse events: 17 total; 7 (22.5%) for norfloxacin, 10 for co-trimoxazole (p=0.59).</p>	<p>Blinded if possible?: No</p> <p>Intention to treat analysis?: Yes</p> <p>Adequate power/size?: yes – study stated a power calculation 80 patients (40 in each arm) would be required to detect a difference of 20% between the two groups with a power of 80% and p value of 0.05.</p> <p>Adequate follow-up (>80%)?: Not stated</p> <p>Level 2 evidence based on unclear risk of bias.</p> <p>Risk of bias: unclear</p>
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					8 discontinued co-trimoxazole therapy due to AEs, which all resolved on discontinuations. (gastrointestinal n = 4, renal n=2, skin n=2). The paper states that co-trimoxazole was associated with definite or probable AEs compared to norfloxacin (22.5% vs 0% p=0.01).	
12	Retrospective analysis in high risk patients with cirrhosis and ascites: Previous episode of SBP, serum bilirubin > μ 43 mol/L, or ascitic protein , 15g/L	Records of all patients in Austin Health, Melbourne Australia, prescribed norfloxacin or co-trimoxazole who had cirrhosis and ascites and were prescribed these medications for SBP prophylaxis between 1 st April 2001 and 1 st May 2004. 69 patients (18 female, 51 male) mean age 53.9 \pm 10.6 years. Follow up period was up to 1 st May 2004, liver transplantation or death	Patients were prescribed either norfloxacin 400 mg orally daily (n=37) or co-trimoxazole 180 mg/800 mg* orally daily (n=32) Follow-up period was until 1 st May 2004 or until liver transplantation or death. * as appears in paper, likely misprint as standard is 160 mg/800 mg.		Incidence of SBP: Norfloxacin = 8 (22%) Co-trimoxazole = 9 (28%) p=0.532 Incidence of bacteremia: Norfloxacin = 3 (8%) Co-trimoxazole = 2 (6%) p=1.00 Incidence of extraperitoneal infection: Norfloxacin = 3 (8%) Co-trimoxazole = 5 (16%) p=0.457 Death: Norfloxacin = 13 (35%) Co-trimoxazole = 14 (44%) p=0.465 Adverse events: Norfloxacin; paranoid delusions =1, erythema multiforme =1 Co-trimoxazole; pruritus =1, nausea and vomiting =1	Patient-oriented outcome measure?: Yes Allocation concealment?: No Blinded if possible?: No Intention to treat analysis?: No Adequate power/size?: No Adequate follow-up (>80%)?: Yes Level 2 evidence based on retrospective analysis, high risk of bias Risk of bias: High, retrospective analysis.
13	Randomised clinical trial (n=57)	Hospitalised patients with liver cirrhosis and ascites. Inclusion criteria:1) previous episode of SBP or 2) total protein	Randomly assigned to: norfloxacin 400 mg daily (n=32) or co-trimoxazole 160/800 mg 5 days per week (n=25). Patients followed up on		Development of SBP: Norfloxacin = 3 patients (9.4%) Co-trimoxazole = 4 patients (16%) (4 of these were on primary prophylaxis and 3 on secondary	Patient-oriented outcome measure?: Yes Allocation concealment?: Yes

		<p>in ascitic fluid \leq 1 g/dL &/or total serum bilirubin \geq 2.5 mg/dL</p> <p>Exclusion criteria were: allergy to sulphonamides or quinolones; antibiotic therapy in the 2 weeks preceding inclusion; episode of digestive haemorrhage within the previous 7 days; diagnosis of hepatocellular carcinoma or other neoplasias able to shorten life expectancy and patient refusal to take part in the study.</p>	<p>outpatient basis monthly for 3 months then if stable at 3 monthly intervals.</p> <p>Followed prospectively for period of 3 to 547 days.</p> <p>Mean follow up was 163 days for the norfloxacin group and 182 days for the co-trimoxazole group.</p>		<p>prophylaxis)</p> <p>Extraperitoneal infections; Norfloxacin = 10 patients (31.3%) Co-trimoxazole = 6 patients (24%) ($p=0.42$)</p> <p>Time from initiation of prophylactic antibiotics: Norfloxacin = 23 days Co-trimoxazole = 64 days ($p=0.59$)</p> <p>Deaths: Norfloxacin = 7 patients (21.9%) Co-trimoxazole = 5 patients (20%) ($p=1.00$)</p> <p>Adverse events: Norfloxacin = 0 patients Co-trimoxazole = 5 patients (20%) ($p=0.01$) (included skin rash, epigastric pain, worsening renal function)</p>	<p>Blinded if possible?:no</p> <p>Intention to treat analysis?: unclear</p> <p>Adequate power/size?: no</p> <p>Adequate follow-up (>80%)?:</p> <p>Level 2 evidence based on small sample, unclear risk of bias</p> <p>Risk of bias: unclear</p>
Footnotes						

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: <ul style="list-style-type: none"> • high quality randomised controlled trials (RCTs) with low risk of bias • systematic reviews or meta-analyses of RCTs with consistent findings 	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: <ul style="list-style-type: none"> • clinical trials at moderate or high risk of bias • systematic reviews or meta-analyses of such clinical trials or with inconsistent findings • cohort studies • case-control studies 	
Level 3	Disease-oriented evidence, or evidence from: <ul style="list-style-type: none"> • consensus guidelines • expert opinion • case series 	Any trial with disease-oriented evidence is Level 3, irrespective of quality

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