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Antibiotic prophylaxis to prevent spontaneous bacterial peritonitis in people with liver cirrhosis: a network meta-analysis (Protocol)

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Antibiotic prophylaxis to prevent spontaneous bacterial peritonitis in people with liver cirrhosis: a network meta-analysis

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To compare the benefits and harms of different prophylactic antibiotic treatments for prevention of spontaneous bacterial peritonitis in people with liver cirrhosis.

BACKGROUND

Description of the condition

Liver cirrhosis

The liver is a complex organ with multiple functions including carbohydrate metabolism, fat metabolism, protein metabolism, drug metabolism, synthetic functions, storage functions, digestive functions, excretory functions, and immunological functions (Read 1972). Liver cirrhosis is a liver disease in which the normal microcirculation, the gross vascular anatomy, and the hepatic architecture have been variably destroyed and altered, with fibrous

septa surrounding regenerated or regenerating parenchymal nodules (Tsochatzis 2014; NCBI 2018a). The major causes of liver cirrhosis include excessive alcohol consumption, viral hepatitis, non-alcohol related fatty liver disease, autoimmune liver disease, and metabolic liver disease (Williams 2014; Ratib 2015; Setiawan 2016). The global prevalence of liver cirrhosis is difficult to estimate as most estimates correspond to chronic liver disease (which includes liver fibrosis and liver cirrhosis). In studies from the US, the prevalence of chronic liver disease varies between 0.3% and 2.1% (Scaglione 2015; Setiawan 2016); in UK, the prevalence was 0.1% in one study (Fleming 2008). In 2010, liver cirrhosis caused an estimated 2% of all global deaths, equivalent to one million deaths (Mokdad 2014). There is an increasing trend of cirrhosis-related deaths in some countries, like the UK, while there is a decreasing trend in other countries, for example France (Mokdad

2014; Williams 2014). The major cause of complications and deaths in people with liver cirrhosis is due to the development of clinically significant portal hypertension (hepatic venous pressure gradient at least 10 mmHg) (de Franchis 2015). Some of the clinical features of decompensation include jaundice, coagulopathy, ascites, variceal bleeding, hepatic encephalopathy, and renal failure (de Franchis 2015; McPherson 2016; EASL 2018). Decompensated cirrhosis is the most common indication for liver transplantation (Merion 2010; Adam 2012).

Spontaneous bacterial peritonitis

Ascites is accumulation of free fluid in the abdomen (peritoneal cavity) (NCBI 2018b), and it is a feature of liver decompensation (Tsochatzis 2017; EASL 2018). Approximately 20% of people with cirrhosis have ascites (D'Amico 2014). Approximately 1% to 4% of people with cirrhosis develop ascites each year (D'Amico 2006; D'Amico 2014). Ascites is the first sign of liver decompensation in about a third of people with compensated liver cirrhosis (D'Amico 2014). When the ascitic fluid is infected with bacteria without gastrointestinal disease or trauma, it is called spontaneous bacterial peritonitis. However, because of the poor sensitivity of ascitic fluid culture, spontaneous bacterial peritonitis is diagnosed by a polymorphonuclear (PMN) leukocyte count of more than 250 per mm^3 in the ascitic fluid (Rimola 2000; EASL 2018). In the presence of haemorrhagic ascites (ascites with red cell count (RBC) of more than 10,000 per mm^3), one PMN should be subtracted for every RBC 250 to account for the presence of blood in the ascitic fluid (Rimola 2000). Spontaneous bacterial peritonitis may or may not be symptomatic, with symptoms of peritonitis such as abdominal pain, systemic infection, fever and chills, and hypotension (Rimola 2000; Nousbaum 2007; EASL 2010).
The overall incidence and prevalence of spontaneous bacterial peritonitis in people with cirrhosis is difficult to estimate. Approximately 2.5% of all hospitalisations of people with cirrhosis are for spontaneous bacterial peritonitis (Devani 2017). The incidence of spontaneous bacterial peritonitis in people with decompensated liver cirrhosis is about 20% over a period of one to 12 months (Saab 2009).
The short-term mortality (that is, death within 30 days of diagnosis or death in hospital) after spontaneous bacterial peritonitis is about 15% to 40% (Khan 2009; Tandon 2011; Devani 2017). Spontaneous bacterial peritonitis is associated with significant resource utilisation: a study conducted in the US showed that the average length of hospital stay was approximately six days and the average hospital costs per patient were approximately USD 17,000 (Devani 2017).

Pathophysiology of spontaneous bacterial peritonitis

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

Description of the intervention

Antibiotic prophylaxis in the form of norfloxacin (fluoroquinolone) is recommended for people without previous episodes of spontaneous bacterial peritonitis but who have ascites with low protein (primary prophylaxis), and for people with one or more previous episodes of spontaneous bacterial peritonitis (secondary prophylaxis) (EASL 2010; Runyon 2013; EASL 2018). Alternative antibiotic prophylaxis recommended in these people include ciprofloxacin (fluoroquinolone) and a combination of trimethoprim and sulphamethoxazole (folic acid synthesis inhibitors) (EASL 2010; Runyon 2013). Rifamixin is another antibiotic that has been tried (Goel 2017), but it is not currently recommended by the European Association for the Study of the Liver (EASL) for the prophylaxis of spontaneous bacterial peritonitis (EASL 2018).

How the intervention might work

Different antibiotic classes have different mechanisms of action. Cephalosporins inhibit bacterial cell wall synthesis (Yotsuji 1988). Fluoroquinolones are type II topoisomerase inhibitors: type II topoisomerases at appropriate levels are required for normal cellular processes, and altering their levels leads to bacterial cell death (Aldred 2014). Folic acid synthesis inhibitors inhibit folic acid as their names indicate: folic acid is necessary for DNA and bacterial cell replication (Gleckman 1981). Rifamixin inhibits bacterial RNA synthesis (DuPont 2015).

Why it is important to do this review

Spontaneous bacterial peritonitis is associated with significant short-term mortality (Khan 2009; Tandon 2011; Devani 2017). It is important to prevent spontaneous bacterial peritonitis in people at high risk of developing it. This has to be balanced against the development of drug-resistant spontaneous bacterial peritonitis, which is difficult to treat. Several different prophylactic antibiotic treatments are available, however their relative efficacy and optimal combination are not known. There have been two Cochrane Reviews on the role of prophylactic antibiotics in people with cirrhosis (Cohen 2009; Chavez-Tapia 2010); however, there have been no previous network meta-analyses on the topic. Network meta-analysis allows for a combination of direct and indirect evidence and the ranking of different interventions for different outcomes (Salanti 2011; Salanti 2012). With this systematic review and network meta-analysis, we aim to provide the best level of evidence for the benefits and harms of different prophylactic antibiotic treatments for prevention of spontaneous bacterial peritonitis in people with liver cirrhosis. If it is not possible to perform this

review with network meta-analysis methods, we will instead use standard Cochrane methods to perform head-to-head comparison meta-analysis whenever possible. We will also present results from direct comparisons whenever possible, even if we perform the network meta-analysis.

OBJECTIVES

To compare the benefits and harms of different prophylactic antibiotic treatments for prevention of spontaneous bacterial peritonitis in people with liver cirrhosis.

METHODS

Criteria for considering studies for this review

Types of studies

We will consider only randomised clinical trials for this network meta-analysis, irrespective of language, publication status, or date of publication. We will exclude studies of other design because of the risk of bias in such studies. Inclusion of indirect observational evidence could weaken our network meta-analysis, but this could also be viewed as a strength for assessing rare adverse events. It is well established that exclusion of non-randomised studies increases the focus on potential benefits and reduces the focus on the risks of serious adverse events and those of any adverse events. However, because of the exponentially increased amount of work required for non-randomised studies, we will register and perform a new systematic review and meta-analysis of non-randomised studies for adverse events if there is uncertainty in the balance of benefits and harms of effective treatment(s).

Types of participants

We will include randomised clinical trials with adult participants with liver cirrhosis, who are undergoing prophylactic treatment to prevent spontaneous bacterial peritonitis. We will exclude randomised clinical 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.

Types of interventions

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

- Cephalosporins
- Quinolones
- Folic acid synthesis inhibitors
- Rifamixin
- Other classes of antibiotics

The above list is not exhaustive. If we identify classes of antibiotics which we were unaware of, we will consider the eligibility of the treatments for inclusion in the network if they are used primarily for prevention of spontaneous bacterial peritonitis in people with liver cirrhosis. We will report the findings for these interventions in the 'Results' and 'Discussion' sections of the review.

We will evaluate the plausibility of transitivity assumption by looking at the inclusion and exclusion criteria in the studies. Transitivity assumption means that participants included in the different trials with different antibiotic prophylaxis can be considered to be a part of a multi-arm randomised clinical trial and could potentially have been randomised to any of the interventions (Salanti 2012). In other words, any participant that meets the inclusion criteria is, in principle, equally likely to be randomised to any of the above eligible interventions. This necessitates that information on potential effect-modifiers, such as the reason why the patients were considered to be at high risk of developing spontaneous bacterial peritonitis (ascites with low protein or previous episodes of spontaneous bacterial peritonitis), is the same across trials. If there is any concern about the transitivity assumption, we will perform separate meta-analysis for people considered to be at high risk of spontaneous bacterial peritonitis due to different reasons.

Types of outcome measures

Primary outcomes

- All-cause mortality at maximal follow-up (time to death)
- Health-related quality of life using a validated scale such as the EQ-5D or 36-Item Short Form Health Survey (SF-36) (EuroQol 2018; Optum 2018), at maximal follow-up
- Serious adverse events (during or within six months after cessation of intervention). We define a serious adverse event as any event that would increase mortality; is life-threatening; requires hospitalisation; results in persistent or significant disability; is a congenital anomaly/birth defect; or any important medical event that might jeopardise the person or require intervention to prevent it (ICH-GCP 1997). However, we will use the definitions used by study authors for serious adverse events.
  ○ 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): we define an adverse event as any untoward medical occurrence not necessarily having a causal relationship with the intervention but resulting in a dose reduction or discontinuation of intervention (any time after commencement of the intervention) (ICH-GCP 1997). However, we will use the definition used by study authors for adverse events.
  - Proportion of people with one or more adverse event
  - Number of any adverse events per participant
- Time to liver transplantation (maximal follow-up)
- Time to development of spontaneous bacterial peritonitis (however defined by study authors at maximal follow-up)
  - According to definitions used for spontaneous bacterial peritonitis
  - Symptomatic spontaneous bacterial peritonitis
- Time to other features of decompensation (maximal follow-up)

Exploratory outcomes

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

We have chosen the outcomes of this protocol based on their importance to patients in a survey related to research priorities for people with liver diseases (Gurusamy 2018), based on feedback of the patient and public representative of the project, and based on an online survey about the outcomes promoted through the Cochrane Consumer Network.

Search methods for identification of studies

Electronic searches

We will search the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, MEDLINE Ovid, Embase Ovid, and Science Citation Index Expanded (Web of Science) from inception to date of search, without applying any language restrictions (Royle 2003). We will search for all possible comparisons formed by the interventions of interest. To identify further ongoing or completed trials, we will also search clinicaltrials.gov, and the World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch/) which searches various trial registers, including ISRCTN and ClinicalTrials.gov. We will also search the European Medical Agency (EMA) (

www.ema.europa.eu/ema/) and US Food and Drug Administration (FDA) (www.fda.gov) registries for randomised clinical trials. The provisional search strategies are provided in Appendix 1.

Searching other resources

We will search the references of the identified trials and the existing Cochrane Reviews on prophylactic antibiotic treatments in liver cirrhosis to identify additional trials for inclusion (Cohen 2009; Chavez-Tapia 2010).

Data collection and analysis

Selection of studies

Two review authors (KG and a research assistant) will independently identify trials for inclusion by screening the titles and abstracts, and will seek full-text articles for any references identified by at least one of the review authors for potential inclusion. We will select trials for inclusion based on the full-text articles. We will provide the list of references that we excluded and the reasons for their exclusion in the 'Characteristics of excluded studies' table. We will also list any ongoing trials identified primarily through the search of the clinical trial registers for further follow-up. We will resolve any discrepancies through discussion.

Data extraction and management

Two review authors (KG and a research assistant) will independently extract the provided below data in a piloted Microsoft Excel-based data extraction form (after translation of non-English articles).

- Outcome data (for each outcome and for each intervention group whenever applicable):
  - number of participants randomised;
  - number of participants included for the analysis;
  - number of participants with events for binary outcomes, mean and standard deviation for continuous outcomes, number of events and the mean follow-up period for count outcomes, and number of participants with events and the mean follow-up period for time-to-event outcomes;
  - natural logarithm of hazard ratio and its standard error, if this was reported, rather than the number of participants with events and the mean follow-up period for time-to-event outcomes;
  - definition of outcomes or scale used if appropriate.
- Data on potential effect modifiers:
  - participant characteristics such as age, sex, presence of other features of decompensation (hepatorenal syndrome, hepatic encephalopathy, and variceal bleeding), the aetiology for

cirrhosis, and the interval between diagnosis of ascites and prophylactic treatment;

- ○ details of the intervention and control (including dose, frequency, and duration);
- ○ length of follow-up;
- ○ information related to 'Risk of bias' assessment (please see Assessment of risk of bias in included studies).
- Other data:
  - ○ year and language of publication;
  - ○ country in which the participants were recruited;
  - ○ year(s) in which the trial was conducted;
  - ○ inclusion and exclusion criteria.

We will collect outcomes at maximum follow-up but also at short-term (up to three months) and medium-term (from three months to five years) if this is available.

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

Assessment of risk of bias in included studies

We will follow the guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and as described in the Cochrane Hepato-Biliary Group Module (Gluud 2018), to assess the risk of bias in the included trials. Specifically, we will assess sources of bias as defined below (Schulz 1995; Moher 1998; Kjaergard 2001; Wood 2008; Savović 2012a; Savović 2012b; Lundh 2017; Savović 2018).

Allocation sequence generation

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

Allocation concealment

- Low risk of bias: the participant allocations could not have been foreseen in advance of, or during, enrolment. A central and independent randomisation unit controlled allocation. The investigators are unaware of the allocation sequence (e.g. if the allocation sequence was hidden in sequentially numbered, opaque, and sealed envelopes).
- Unclear risk of bias: the study authors did not describe the method used to conceal the allocation so that the intervention allocations may have been foreseen before, or during, enrolment.
- High risk of bias: it is likely that the investigators who assigned the participants knew the allocation sequence. We will exclude such quasi-randomised studies.

Blinding of participants and personnel

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

Blinded outcome assessment

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

Incomplete outcome data

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

- High risk of bias: the results were likely to be biased due to missing data.

Selective outcome reporting

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

For-profit bias

- Low risk of bias: the trial appeared to be free of industry sponsorship or other type of for-profit support that could manipulate the trial design, conductance, or results of the trial (industry-sponsored trials overestimate the efficacy by about 25%) (Lundh 2017).
- Unclear risk of bias: the trial may or may not have been free of for-profit bias, as no information on clinical trial support or sponsorship was provided.
- High risk of bias: the trial was sponsored by industry or received other type of for-profit support.

Other bias

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

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

Measures of treatment effect

Relative treatment effects

For dichotomous variables (e.g. proportion of participants with serious adverse events or any adverse events), we will calculate the odds ratio (OR) with 95% credible interval (CrI) (or Bayesian confidence interval) (Severini 1993). For continuous variables (e.g. health-related quality of life reported on the same scale), we will calculate the mean difference (MD) with 95% CrI. We will use standardised mean difference (SMD) values with 95% CrI for health-related quality of life if the included trials have used different scales. For count outcomes (e.g. number of serious adverse events or number of any adverse events), we will calculate the rate ratio (RaR) with 95% CrI. For time-to-event data (e.g. all-cause mortality at maximal follow-up), we will calculate hazard ratio (HR) with 95% CrI.

Relative ranking

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

Unit of analysis issues

The unit of analysis is the participant receiving antibiotic prophylaxis for spontaneous bacterial peritonitis according to the intervention group to which the participant was randomly assigned.

Cluster-randomised clinical trials

We will include cluster-randomised clinical trials, provided that the effect estimate adjusted for cluster correlation is available. If this is not available, we will include such trials if sufficient information to calculate the design effect is available from the trial because this will allow us to take clustering into account. We will also assess additional domains of risk of bias for cluster-randomised trials according to guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Cross-over randomised clinical trials

If we identify any cross-over randomised clinical trials, we will include the outcome data after the period of first intervention because the included treatments can have residual effects.

Trials with multiple intervention groups

We will collect data for all trial intervention groups that meet the inclusion criteria. The codes we will use for analysis will account for the correlation between the effect sizes from studies with more than two groups.

Dealing with missing data

We will perform an intention-to-treat analysis whenever possible (Newell 1992); otherwise, we will use the data available to us. This may result in the use of 'per-protocol' analyses. Since these may be biased, particularly if the data are not missing at random (for example, treatment was withdrawn due to adverse events or duration of treatment was shortened because of lack of response and such participants were excluded from analysis), we will conduct best-worst case scenario analysis (assuming a good outcome in intervention group and bad outcome in control group) and worst-best case scenario analysis (assuming a bad outcome in intervention group and good outcome in control group) as sensitivity analyses whenever possible for dichotomous outcomes.

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

Assessment of heterogeneity

We will assess clinical and methodological heterogeneity by carefully examining the characteristics and design of included trials. We will assess the presence of clinical heterogeneity by comparing effect estimates (please see 'Subgroup analysis and investigation of heterogeneity') in trial reports of different drug dosages, reasons why the trial participants were considered to be at high risk of developing spontaneous bacterial peritonitis (ascites with low protein or previous episodes of spontaneous bacterial peritonitis), different aetiologies for cirrhosis (e.g. alcohol-related liver disease, viral liver diseases, autoimmune liver disease), and based on the cointerventions (e.g. both groups receive albumin). Different study designs and risk of bias can contribute to methodological heterogeneity.

We will assess statistical heterogeneity by comparing the results of the fixed-effect model meta-analysis and the random-effects model meta-analysis, between-study standard deviation (tau^2, and comparing this with values reported in study of the distribution of between-study heterogeneity) (Turner 2012), and by calculating I^2 using Stata/SE 14.2. If we identify substantial clinical, methodological, or statistical heterogeneity, we will explore and address the heterogeneity in subgroup analysis (see 'Subgroup analysis and investigation of heterogeneity').

Assessment of transitivity across treatment comparisons

We will assess the transitivity assumption by comparing the distribution of the potential effect modifiers (clinical: reasons why the trial participants were considered to be at high risk of developing spontaneous bacterial peritonitis, i.e. ascites with low protein or previous episodes of spontaneous bacterial peritonitis; methodological: risk of bias, year of randomisation, duration of follow-up) across the different pairwise comparisons.

Assessment of reporting biases

For the network meta-analysis, we will perform a comparison-adjusted funnel plot. If there is no meaningful way in which to rank these studies (i.e. there was no specific change in the risk of bias in the studies, sample size, or the control group used over time), we will judge the reporting bias by the completeness of the search (Chaimani 2012).

Data synthesis

Methods for indirect and mixed comparisons

We will conduct network meta-analyses to compare multiple interventions simultaneously for each of the primary and secondary outcomes. Network meta-analysis combines direct evidence within trials and indirect evidence across trials (Mills 2012). We will obtain a network plot to ensure that the trials are connected by interventions using Stata/SE 14.2 (Chaimani 2013). We will exclude any trials that are not connected to the network from the network meta-analysis, and we will report only the direct pairwise meta-analysis for such comparisons. We will summarise the population and methodological characteristics of the trials included in the network meta-analysis in a table based on pairwise comparisons. We will conduct a Bayesian network meta-analysis using the Markov chain Monte Carlo method in Open-BUGS 3.2.3, according to guidance from the National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) documents (Dias 2016). We will model the treatment contrast (i.e. log odds ratio for binary outcomes, mean difference or standardised mean difference for continuous outcomes, log rate

ratio for count outcomes, and log hazard ratio for time-to-event outcomes) for any two interventions ('functional parameters') as a function of comparisons between each individual intervention and the reference group ('basic parameters'), using appropriate likelihood functions and links (Lu 2006). We will use binomial likelihood and logit link for binary outcomes, Poisson likelihood and log link for count outcomes, binomial likelihood and complementary log-log link (a semiparametric model which excludes censored individuals from the denominator of 'at risk' individuals at the point when they are censored), and normal likelihood and identity link for continuous outcomes. We will use 'no active intervention' as the reference group. We will use a fixed-effect model and random-effects model for the network meta-analysis. We will report both models for comparison with the reference group in a forest plot. For each pairwise comparison in a table, we will report the fixed-effect model if the two models report similar results; otherwise, we will report the more conservative model.

We will use a hierarchical Bayesian model using three different initial values, employing codes provided by the NICE DSU (Dias 2016). We will use a normal distribution with large variance (10,000) for treatment effect priors (vague or flat priors). For the random-effects model, we will use a prior distributed uniformly (limits: 0 to 5) for between-trial standard deviation but will assume the same between-trial standard deviation across treatment comparisons (Dias 2016). We will use a 'burn-in' of 10,000 simulations, check for convergence (of effect estimates and between-study heterogeneity) visually (i.e. to check whether the values in different chains mix very well by visualisation), and run the models for another 10,000 simulations to obtain effect estimates. If we do not obtain convergence, we will increase the number of simulations for the 'burn-in'. If we still do not obtain convergence, we will use alternate initial values and priors employing methods suggested by van Valkenhoef 2012. We will estimate the probability that each intervention ranks at one of the possible positions using the NICE DSU codes (Dias 2016).

Assessment of inconsistency

We will assess inconsistency (statistical evidence of the violation of transitivity assumption) by fitting both an inconsistency model and a consistency model. We will use inconsistency models employed in the NICE DSU manual, as we will use a common between-study standard deviation (Dias 2014). In addition, we will use design-by-treatment full interaction model and inconsistency factor (IF) plots to assess inconsistency (Higgins 2012; Chaimani 2013). We will use Stata/SE 14.2 to create IF plots. In the presence of inconsistency, we will assess whether the inconsistency was due to clinical or methodological heterogeneity by performing separate analyses for each of the different subgroups mentioned in the Subgroup analysis and investigation of heterogeneity section.

If there was evidence of inconsistency, we will identify areas in the network where substantial inconsistency might be present in terms

of clinical and methodological diversities between trials and, when appropriate, limit network meta-analysis to a more compatible subset of trials.

Direct comparison

We will perform the direct comparisons using the same codes and the same technical details.

Calculation of required information size and Trial Sequential Analysis

For calculation of the required information size, see Appendix 2. We will perform Trial Sequential Analysis for direct comparisons to control the risk of random errors when at least two trials were included for the comparison of other interventions versus no active intervention ('control') for the outcomes all-cause mortality at maximal follow-up and health-related quality of life, the two outcomes that determine whether the intervention should be given (Wetterslev 2008; Thorlund 2011; TSA 2011; Wetterslev 2017). For all-cause mortality at maximal follow-up, we will use an alpha error according to the guidance of Jakobsen 2014 (i.e. 0.033), power of 90% (beta error of 10%) (Castellini 2017), a relative risk reduction of 20%, the median control group proportion observed in the trials, and the heterogeneity observed in the meta-analysis using Stata/SE 14.2, employing methods suggested by Miladinovic 2013. For health-related quality of life, a continuous outcome, we will use an alpha error according to the guidance of Jakobsen 2014 (i.e. 0.033), power of 90% (beta error of 10%) (Castellini 2017), a standardised mean difference of 0.2, the median health-related quality of life in the control group in the trials, and the heterogeneity observed in the meta-analysis.

Subgroup analysis and investigation of heterogeneity

We plan to assess the differences in the effect estimates between the following subgroups, and investigate heterogeneity and inconsistency using meta-regression with the help of the codes provided in the NICE DSU guidance, if we include a sufficient number of trials (Dias 2012a). We plan to use the following trial-level covariates for meta-regression.

- Trials at low risk of bias compared to trials at high risk of bias
- The reasons why the trial participants were considered to be at high risk of developing spontaneous bacterial peritonitis (ascites with low protein or previous episodes of spontaneous bacterial peritonitis)
- The aetiology for cirrhosis (for example, alcohol-related liver disease, viral liver diseases, autoimmune liver disease)
- The interval between the diagnosis of ascites and the start of prophylactic treatment

- Different types of cointervention (for example, both groups receive treatment for ascites or vasoactive drugs to decrease portal pressure, as cointerventions)
- The period of follow-up (short-term: up to three months, medium term: more than three months to five years, long-term: more than five years)
- The definition used by authors for serious adverse events and any adverse event (ICH-GCP 1997 versus other definitions)

We will calculate a single common interaction term when applicable (Dias 2012a). If the 95% CrI of the interaction term does not overlap zero, we will consider this statistically significant heterogeneity or inconsistency (depending upon the factor being used as covariate).

Sensitivity analysis

If a trial reports only per-protocol analysis results, we plan to re-analyse the results using the best-worst case scenario and worst-best case scenario as sensitivity analyses whenever possible. We will also perform a sensitivity analysis excluding the trials in which mean or standard deviation (or both) were imputed, and we will use the median standard deviation in the trials to impute missing standard deviations.

Presentation of results

We will follow the PRISMA-NMA statement while reporting (Hutton 2015). We will present the effect estimates with 95% CrI for each pairwise comparison calculated from the direct comparisons and network meta-analysis. We will also present the cumulative probability of the treatment ranks (i.e. the probability that the intervention is within the top two, the probability that the intervention is within the top three, etc.) in graphs (SUCRA) (Salanti 2011). We will also plot the probability that each intervention was best, second best, third best, etc. for each of the different outcomes (rankograms), which are generally considered more informative (Salanti 2011; Dias 2012b). We will provide the CrI of the probabilities in the ranking probability tables. We will upload all the raw data and the codes used for analysis in The European Organization for Nuclear Research open source database (Zenodo) and provide a link within the review.

Grading of evidence

We will present 'Summary of findings' tables for all the primary and secondary outcomes (see Primary outcomes; Secondary outcomes). We will follow the approach suggested by Puhan and colleagues (Puhan 2014). First, we will calculate the direct and indirect effect estimates and 95% CrI using the node-splitting approach, that is calculating the direct estimate for each comparison by including only trials in which there was direct comparison of

interventions and the indirect estimate for each comparison by excluding the trials in which there was direct comparison of interventions (Dias 2010). Next, we will rate the quality of direct and indirect effect estimates using GRADE methodology which takes into account the risk of bias, inconsistency, directness of evidence, imprecision, and publication bias (Guyatt 2011). We will then present the estimates of the network meta-analysis and rate the quality of network meta-analysis effect estimates as the best quality of evidence between the direct and indirect estimates (Puhan 2014). In addition, we will present information on the absolute measures (i.e. proportion of people with the outcome in each intervention group based on the direct estimates, indirect estimates, and network meta-analysis estimates). We will also present information on the number of trials and participants, according to the standard 'Summary of findings' table.

Recommendations for future research

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

Department of Health disclaimer

The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the 16/114/17 Programme, NIHR, NHS or the Department of Health.

Danish State and The Copenhagen Trial Unit disclaimer

The views and opinions expressed in this review are those of the authors and do not necessarily reflect those of the Danish State or The Copenhagen Trial Unit.

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* *Indicates the major publication for the study*

Antibiotic prophylaxis to prevent spontaneous bacterial peritonitis in people with liver cirrhosis: a network meta-analysis (Protocol)   13

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APPENDICES

Appendix 1. Search strategies

Database	Time span	Search strategy
Central Register of Controlled Trials (CENTRAL) in the Cochrane Library	Latest issue	#1 MeSH descriptor: [Antibiotic Prophylaxis] explode all trees #2 antibiotic* #3 antibacteri* near prophyl* #4 #1 or #2 or #3 #5 MeSH descriptor: [Liver Cirrhosis] explode all trees #6 ((hepatic or liver) and (fibrosis or cirrhosis or cirrhotic)) #7 #5 or #6 #8 #4 and #7
MEDLINE Ovid	January 1947 to date of search	1. exp antibiotic prophylaxis/ 2. antibiotic*.ti,ab. 3. (antibacteri* adj prophyl*).ti,ab. 4. 1 or 2 or 3 5. exp Liver Cirrhosis/ 6. ((hepatic or liver) and (fibrosis or cirrhosis or cirrhotic)).ti,ab 7. 5 or 6 8. 4 and 7 9. randomized controlled trial.pt. 10. controlled clinical trial.pt. 11. randomized.ab. 12. placebo.ab. 13. drug therapy.fs. 14. randomly.ab. 15. trial.ab. 16. groups.ab. 17. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 18. exp animals/ not humans.sh. 19. 17 not 18 20. 8 and 19
Embase Ovid	January 1974 to date of search	1. exp antibiotic prophylaxis/ 2. antibiotic*.ti,ab. 3. (antibacteri* adj prophyl*).ti,ab. 4. 1 or 2 or 3 5. exp liver cirrhosis/ 6. ((hepatic or liver) and (fibrosis or cirrhosis or cirrhotic)).ti,ab 7. 5 or 6

		8. 4 and 7 9. exp crossover-procedure/ or exp double-blind procedure/ or exp randomized controlled trial/ or single-blind procedure/ 10. (((((random* or factorial* or crossover* or cross over* or cross-over* or placebo* or double*) adj blind*) or single*) adj blind*) or assign* or allocat* or volunteer*).af 11. 9 or 10 12. 8 and 11
Science Citation Index Expanded (Web of Science)	January 1945 to date of search	#1 TS=(antibiotic*) #2 TS=(antibacteri* near prophyl*) #3 #2 OR #1 #4 TS=((hepatic or liver) and (fibrosis or cirrhosis or cirrhotic)) #5 TS=(random* OR rct* OR crossover OR masked OR blind* OR placebo* OR meta-analysis OR systematic review* OR meta-analys*) #6 #3 AND #4 AND #5
World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch/Default.aspx)	Date of search to be provided at the review stage	Condition: cirrhosis; intervention: antibiotic*
ClinicalTrials.gov	Date of search to be provided at the review stage	antibiotic | Interventional Studies | Cirrhosis | Phase 2, 3, 4
European Medical Agency (www.ema.europa.eu/ema/) and US Food and Drug Administration (www.fda.gov)	Date of search to be provided at the review stage	spontaneous bacterial peritonitis

Appendix 2. Sample size calculation

The mortality in cirrhotic patients with decompensated liver cirrhosis (in whom prophylaxis for spontaneous bacterial peritonitis is considered) is approximately 20% (Saab 2009). The required information size based on a control group proportion of 20%, a relative risk reduction of 20% in the experimental group, type I error of 5%, and type II error of 20% is 2894 participants. Network analyses are more prone to risk of random errors than direct comparisons (Del Re 2013). Accordingly, a greater sample size is required in indirect comparisons than in direct comparisons (Thorlund 2012). The power and precision in indirect comparisons depend upon various factors, such as the number of participants included for each comparison and the heterogeneity between the trials (Thorlund 2012). If there is no heterogeneity across the trials, the sample size in indirect comparisons would be equivalent to the sample size in direct comparisons. The effective indirect sample size can be calculated using the number of participants included in each direct comparison (Thorlund 2012). For example, a sample size of 2500 participants in the direct comparison A versus C (n_{AC}) and a sample size of 7500 participants in the direct comparison B versus C (n_{BC}) results in an effective indirect sample size of 1876 participants. However, in the presence of heterogeneity within the comparisons, the required sample size is higher. In the above scenario, for an I^2 statistic for each of the comparisons A versus C ($I_{AC}{}^2$) and B versus C ($I_{BC}{}^2$) of 25%, the effective indirect sample size is 1407 participants. For an I^2 statistic for each of the comparisons A versus C and B versus C of 50%, the effective indirect sample size is 938 participants (Thorlund

2012). If there are only three groups, and the sample size in the trials is more than the required information size, we will calculate the effective indirect sample size using the following generic formula (Thorlund 2012):

$(n_{AC} \times (1 - I_{AC}^2)) \times (n_{BC} \times (1 - I_{BC}^2))/(n_{AC} \times (1 - I_{AC}^2)) + (n_{BC} \times (1 - I_{BC}^2))$.

Currently, there is no method to calculate the effective indirect sample size for a network analysis involving more than three intervention groups.

CONTRIBUTIONS OF AUTHORS

Conceiving the protocol: KG

Designing the protocol: KG

Co-ordinating the protocol: KG

Designing search strategies: KG

Writing the protocol: KG

Providing general advice on the protocol: ET, PW

Securing funding for the protocol: KG

Performing previous work that was the foundation of the current study: not applicable

DECLARATIONS OF INTEREST

KG: none known

PW: none known

ET: none known

SOURCES OF SUPPORT

Internal sources

- University College London, UK.
Writing equipment, software, etc.

External sources

- National Institute for Health Research, UK.
Payment for writing reviews, writing equipment, software

NOTES

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