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Treatment for ascites in people with decompensated liver cirrhosis: a network meta-analysis (Protocol)

Gurusamy KS, Tsochatzis E

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[Intervention Protocol]

Treatment for ascites in people with decompensated 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 treatments for ascites in people with decompensated 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 USA, the prevalence of chronic liver disease varies between 0.3% to 2.1% (Scaglione 2015; Setiawan 2016); in the UK, the prevalence was 0.1% in one study (Fleming 2008). In 2010, liver cirrhosis was responsible for 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, such as the UK, while there is a decreasing trend in other countries, such as 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).

Ascites

Ascites is accumulation of free fluid in the abdomen (peritoneal cavity) (NCBI 2018b), and is a feature of liver decompensation (Tsochatzis 2017). 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). Ascites can be graded as grade 1 ascites, which is mild ascites only detectable by ultrasound examination; grade 2 ascites or moderate ascites manifests by moderate symmetrical distension of abdomen; and grade 3 ascites is large or gross ascites with marked abdominal distension (Arroyo 1996; Moore 2003). Grade 3 ascites is also called 'tense' ascites (Arroyo 1996). Ascites that is refractory to medical treatment is called 'refractory' ascites (Arroyo 1996; Moore 2003). Table 1 provides detailed criteria for the definition of refractory ascites (Moore 2003).

In people with cirrhosis, the onset of ascites and treatment of ascites result in a decrease in the health-related quality of life (Kim 2006; Les 2010; Orr 2014). Resolution of ascites may result in improvement in health-related quality of life in people with ascites (Orr 2014). The one-year mortality in people with liver cirrhosis and ascites is 20%, which increases to 57% in those with variceal bleeding (D'Amico 2006). Management of ascites and its complications involve significant resources. One study reported that people with liver cirrhosis and ascites required on average one hospital admission per month and a 10 day-stay in hospital per month (Fagan 2014).

Pathophysiology of ascites

The exact mechanism by which ascites develops in people with liver cirrhosis is unknown. Portal hypertension causes arterial vasodilatation of the splanchnic circulation (dilation of the blood vessels supplying the digestive organs in the abdomen such as liver, pancreas, and intestines) (Ginès 2009; Moore 2013). This activates the renin-angiotensin system (Ginès 2009; Moore 2013), leading to fluid retention (Moore 2013). In addition, the vessel wall permeability is increased due to the pathological increase in vascular endothelial growth factor (VEGF) (Colle 2008), and the oncotic pressure is decreased due to decreased albumin synthesis by the diseased liver leading to leaky splanchnic blood vessels in people with portal hypertension (Moore 2013). This results in fluid accumulation in the peritoneal cavity, that is, ascites (Moore 2013).

Description of the intervention

Although people with cirrhosis and grade 2 ascites, grade 3 ascites, and refractory ascites should be considered for liver transplantation (EASL 2010; Runyon 2013; EASL 2016; EASL 2018), cirrhotic ascites alone without other features of end-stage liver disease such as variceal bleeding, spontaneous bacterial peritonitis, or hepatorenal syndrome are usually treated using less invasive methods than liver transplantation (EASL 2010). According to the European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Diseases (AASLD) guidelines, grade 1 ascites does not require any specific treatment; grade 2 requires salt-restricted diet and diuretics; grade 3 requires large volume paracentesis (removal of several litres of ascitic fluid) along with salt-restricted diet and diuretics (EASL 2010; Runyon 2013; EASL 2018).

In people with refractory ascites, paracentesis and transjugular intrahepatic portosystemic shunt (TIPS) are the main treatments according to EASL and AASLD guidelines (EASL 2010; Runyon 2013; EASL 2018). In addition, AASLD guidelines suggests that midodrine (a vasoconstrictor) should be considered in people with refractory ascites (Runyon 2013), while midodrine is not recommended by EASL guidelines (EASL 2018).

The role of vasoconstrictors, spontaneous ultrafiltration and reinfusion (filter the removed ascitic fluid and reinfuse the proteins), and low-flow ascites fluid pump (automatically diverts ascitic fluid to the urinary bladder, from where it is excreted in urine) in the treatment of people with ascites is unclear and neither EASL nor AASLD guidelines recommend their routine use (EASL 2010; Runyon 2013). Surgical portosystemic shunts are currently recommended only in people with refractory ascites unsuitable for TIPS, repeated paracentesis, or liver transplantation (Runyon 2013).

How the intervention might work

Diuretics increase fluid excretion, thereby decreasing the fluid accumulation: fluid accumulation is one of the mechanisms of developing ascites, and decreasing fluid accumulation can lead to resolution of ascites. Systemic vasoconstrictor drugs decrease the splanchnic vasodilation which is another mechanism of developing ascites.

Paracentesis involves removing the ascitic fluid. Removal of up to 5 litres of fluid in one session of paracentesis is unlikely to cause circulatory shock (EASL 2010; Runyon 2013), but removal of more than this volume can lead to circulatory shock. Various methods to overcome this is to administer albumin, colloids such as hydroxyethyl starch, vasoconstrictors such as midodrine, or reinfusing the proteins in the ascitic fluid (Bruno 1992; Altman 1998; Appenrodt 2008).

TIPS procedures and other surgical forms of portosystemic shunt are aimed at decreasing portal venous pressure, the major cause of ascites in people with liver cirrhosis.

Why it is important to do this review

It is important to provide optimal treatment to people with ascites to improve their survival and health-related quality of life.

Several different treatments are available but their relative efficacy and optimal combinations are not known. One Cochrane Review on TIPS versus paracentesis for people with cirrhosis and having refractory ascites is available (Saab 2006); however, to date, there have not been any 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 treatments for ascites in people with decompensated 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 treatments for ascites in people with decompensated 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 designs 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 trial participants undergoing treatment for ascites with decompensated liver cirrhosis. We will exclude randomised clinical trials in which participants had previously undergone liver transplantation.

Types of interventions

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

- Diuretics (different classes of diuretics based on their mechanism of action will be treated as separate interventions, for example, loop diuretics such as furosemide, torsemide; aldosterone antagonists such as spironolactone or potassium canrenoate).
- Large volume paracentesis (removes ascitic fluid) with different fluids to prevent circulatory dysfunction (for example, albumin, hydroxyethyl starch, etc).
- Spontaneous ultrafiltration and reinfusion (filter the removed ascitic fluid and reinfuse the proteins).
- Low-flow ascites fluid pump (automatically diverts ascitic fluid to the urinary bladder, from where it is excreted in urine).
- Systemic vasoconstrictor (for example, terlipressin, midodrine).
- TIPS procedure (decrease portal hypertension).
- Other forms of portosystemic shunt (decrease portal hypertension).
- No active intervention (no intervention or placebo).

The above list is not exhaustive. If we identify treatments of which we were unaware, we will consider eligibility of the treatments for inclusion in the network if they are used primarily for treatment of ascites. We will report the findings for these interventions in the 'Results' and 'Discussion' sections of the review.

We will exclude trials that evaluate cointerventions such as fluid restriction, restricted-salt diet, or drugs such as vasopressin-antagonists which are used as supplements to diuretics to overcome their adverse effects such as hyponatraemia. However, we will include trials in which such cointerventions are administered equally in both trial arms.

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 treatments (in this case, ascites) 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 grade of ascites (grade 2 ascites, grade 3 ascites, or refractory ascites) are the same across trials. If there is any concern about the transitivity assumption, we will perform separate meta-analysis for each of these different types of ascites.

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) at maximal follow-up (EuroQol 2018; Optum 2018).
- 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 events;
    - 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 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 events;
    - number of any adverse events per participant.
- Time-to-liver transplantation (maximal follow-up).
- Time-to-resolution of ascites (however defined by authors at maximal follow-up):
    - symptomatic recovery;
    - resolution as per ultrasound.
- 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 this project, and based on an online survey about the outcomes promoted through 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 for randomised clinical trials comparing two or more of the above interventions 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. We have provided the provisional search strategies in Appendix 1.

Searching other resources

We will search the references of the identified trials and the existing Cochrane Reviews on ascites in liver cirrhosis to identify additional trials for inclusion.

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 of articles identified by the literature search, and will seek full-text articles of any references identified by at least one review author for potential inclusion. We will select trials for inclusion based on the full-text articles. We will list the 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. We will illustrate the study selection process in a PRISMA diagram.

Data extraction and management

Two review authors (KG and a research assistant) will independently extract the following data onto a pre-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, grade of ascites, whether refractory or recurrent ascites, the aetiology for cirrhosis, and the interval between diagnosis of ascites and treatment;
  - details of the intervention and control (including dose, frequency, and duration);
  - length of follow-up;
  - information related to risk of bias assessment (please see below).
- Other data:
  - year and language of publication;
  - country in which the participants were recruited;
  - year(s) in which the trial was conducted;
  - inclusion and exclusion criteria.

We 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 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: sequence generation was achieved using computer random number generation or a random number table. Drawing lots, tossing a coin, shuffling cards, and throwing dice were adequate if performed by an independent person not otherwise involved in the trial.
- Unclear risk of bias: the method of sequence generation was not specified.
- High risk of bias: the sequence generation method was not random or only quasi-randomised. We will only use these studies for the assessment of harms and not of benefits.

Allocation concealment

- Low risk of bias: the allocation sequence was described as unknown to the investigators. Hence, the participants' allocations could not have been foreseen in advance of, or during, enrolment. Allocation was controlled by a central and independent randomisation unit, an onsite locked computer, identical-looking numbered sealed opaque envelopes, drug bottles or containers prepared by an independent pharmacist, or an independent investigator.
- Unclear risk of bias: it was unclear if the allocation was hidden or if the block size was relatively small and fixed so that intervention allocations may have been foreseen in advance of, or during, enrolment.
- High risk of bias: the allocation sequence was likely to be known to the investigators who assigned the participants.

Blinding of participants and personnel

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

Incomplete outcome data

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

Selective outcome reporting

- Low risk of bias: the trial reported the following predefined outcomes: at least one of the outcomes related to the main reason for treatment of people with ascites, namely, mortality or resolution of ascites along with adverse events. If the original trial protocol was available, the outcomes should have been those called for in that protocol. If we obtain the trial protocol 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, we will not consider those outcomes 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).
- Uncertain 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).
- Uncertain 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 (Savovic 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 included trials use 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 undergoing treatment for ascites 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 outcomes 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 for analysis, that we will use, 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 (good outcome in intervention group and bad outcome in control group) and worst-best case scenario analysis (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, different grades of ascites (grade 2 or grade 3), refractory or recurrent ascites, different aetiologies for cirrhosis (for example, alcohol-related liver disease, viral liver diseases, autoimmune liver disease), and based on the co-interventions (for example, both groups receive prophylactic antibiotics to decrease the risk of subacute bacterial peritonitis). 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 the I^2 statistic 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: grade of ascites (grade 2 versus grade 3) and whether refractory or recurrent ascites; 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 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 OpenBUGS 3.2.3 as per 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 the 'no active intervention' as the reference group. We will perform 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 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 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. 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 is 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 we include at least two trials 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 as per 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 as per 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 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.
- Based on the grade of ascites (grade 2 or grade 3 or refractory/recurrent ascites).
- Based on the aetiology for cirrhosis (for example, alcohol-related liver disease, viral liver diseases, autoimmune liver disease).
- Based on the interval between the diagnosis of ascites and the start of treatment.
- Based on the co-interventions (for example, both groups receive prophylactic antibiotics to decrease the risk of subacute bacterial peritonitis).
- Based on 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).
- Based on 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% Crl 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 analyses 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 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 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 also 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 will provide a link within the review.

Grading of evidence

We will present 'Summary of findings' tables for all the primary and secondary outcomes. We will follow the approach suggested by Puhan 2014. First, we will calculate the direct and indirect effect estimates and 95% CrI using the node-splitting approach (Dias 2010), that is calculating the direct estimate for each comparison by including only trials in which there was direct comparison of interventions and the indirect estimate for each comparison by excluding the trials in which there was direct comparison of interventions. 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 as per the standard 'Summary of findings' table.

Recommendations for future research

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

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* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1. Revised 'International Ascites Club' criteria for refractory ascites

1. Treatment duration: patients must be on intensive diuretic therapy (spironolactone 400 mg/day and furosemide 160 mg/day) for at least 1 week and on a salt-restricted diet of less than 90 mmol or 5.2 g of salt/day
2. Lack of response: mean weight loss of less than 0.8 kg over 4 days and urinary sodium output less than the sodium intake
3. Early ascites recurrence: reappearance of grade 2 or 3 ascites within 4 weeks of initial mobilisation
4. Diuretic-induced complications: • Diuretic-induced hepatic encephalopathy is the development of encephalopathy in the absence of any other precipitating factor. • Diuretic-induced renal impairment is an increase of serum creatinine by more than 100% to a value more than 2 mg/dL in patients with ascites responding to treatment. • Diuretic-induced hyponatraemia is defined as a decrease of serum sodium by more than 10 mmol/L to a serum sodium of less than 125 mmol/L. • Diuretic induced hypo- or hyperkalaemia is defined as a change in serum potassium to less than 3 mmol/L or more than 6 mmol/L despite appropriate measures.

From: Moore 2003.

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: [Ascites] this term only #2 ascites #3 #1 or #2 #4 MeSH descriptor: [Liver Cirrhosis] explode all trees #5 ((hepatic or liver) and (fibrosis or cirrhosis or cirrhotic)) #6 #4 or #5 #7 #3 and #6
MEDLINE Ovid	January 1947 to date of search	1. ascites/ 2. ascites.ti,ab. 3. 1 or 2 4. exp Liver Cirrhosis/

(*Continued*)

		5. ((hepatic or liver) and (fibrosis or cirrhosis or cirrhotic)).ti,ab 6. 4 or 5 7. 3 and 6 8. randomized controlled trial.pt. 9. controlled clinical trial.pt. 10. randomized.ab. 11. placebo.ab. 12. drug therapy.fs. 13. randomly.ab. 14. trial.ab. 15. groups.ab. 16. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 17. exp animals/ not humans.sh. 18. 16 not 17 19. 7 and 18
Embase Ovid	January 1974 to date of search	1. exp ascites/ 2. ascites.ti,ab. 3. 1 or 2 4. exp liver cirrhosis/ 5. ((hepatic or liver) and (fibrosis or cirrhosis or cirrhotic)).ti,ab 6. 4 or 5 7. 3 and 6 8. exp crossover-procedure/ or exp double-blind procedure/ or exp randomized controlled trial/ or single-blind procedure/ 9. (((((random* or factorial* or crossover* or cross over* or cross-over* or placebo* or double*) adj blind*) or single*) adj blind*) or assign* or allocat* or volunteer*).af 10. 8 or 9 11. 7 and 10
Science Citation Index Expanded (Web of Science)	January 1945 to date of search	#1 TS=(ascites) #2 TS=((hepatic or liver) and (fibrosis or cirrhosis or cirrhotic)) #3 TS=(random* OR rct* OR crossover OR masked OR blind* OR placebo* OR meta-analysis OR systematic review* OR meta-analys*) #4 #1 AND #2 AND #3
World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch/Default.aspx)	Date of search to be provided at the review stage	ascites

(*Continued*)

ClinicalTrials.gov	Date of search to be provided at the review stage	cirrhosis | Interventional Studies | Ascites | 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	ascites; cirrhosis; random

Appendix 2. Sample size calculation

Approximately 20% of people with cirrhotic ascites die within a year (D'Amico 2006). 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

Coordinating the protocol: KG

Designing search strategies: KG

Writing the protocol: KG

Providing general advice on the protocol: ET

Securing funding for the protocol: KG

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DECLARATIONS OF INTEREST

None known for any of the authors

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Internal sources

- University College London, UK.

Writing equipment, software, etc

External sources

- National Institute for Health Research (NIHR), UK.

Payment for writing reviews, writing equipment, software

NOTES

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