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


[Intervention Review]

Treatment for ascites in adults with decompensated liver cirrhosis: a network meta-analysis

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ABSTRACT

Background

Approximately 20% of people with cirrhosis develop ascites. Several different treatments are available; including, among others, paracentesis plus fluid replacement, transjugular intrahepatic portosystemic shunts, aldosterone antagonists, and loop diuretics. However, there is uncertainty surrounding their relative efficacy.

Objectives

To compare the benefits and harms of different treatments for ascites in people with decompensated liver cirrhosis through a network meta-analysis and to generate rankings of the different treatments for ascites according to their safety and efficacy.

Search methods

We searched CENTRAL, MEDLINE, Embase, Science Citation Index Expanded, World Health Organization International Clinical Trials Registry Platform, and trials registers until May 2019 to identify randomised clinical trials in people with cirrhosis and ascites.

Selection criteria

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

Data collection and analysis

We performed a network meta-analysis with OpenBUGS using Bayesian methods and calculated the odds ratio, rate ratio, and hazard ratio (HR) with 95% credible intervals (CrI) based on an available-case analysis, according to National Institute of Health and Care Excellence Decision Support Unit guidance.
Main results

We included a total of 49 randomised clinical trials (3521 participants) in the review. Forty-two trials (2870 participants) were included in one or more outcomes in the review. The trials that provided the information included people with cirrhosis due to varied aetiologies, without other features of decompensation, having mainly grade 3 (severe), recurrent, or refractory ascites. The follow-up in the trials ranged from 0.1 to 84 months. All the trials were at high risk of bias, and the overall certainty of evidence was low or very low.

Approximately 36.8% of participants who received paracentesis plus fluid replacement (reference group, the current standard treatment) died within 11 months. There was no evidence of differences in mortality, adverse events, or liver transplantation in people receiving different interventions compared to paracentesis plus fluid replacement (very low-certainty evidence). Resolution of ascites at maximal follow-up was higher with transjugular intrahepatic portosystemic shunt (HR 9.44; 95% CI 1.93 to 62.68) and adding aldosterone antagonists to paracentesis plus fluid replacement (HR 30.63; 95% CI 5.06 to 692.98) compared to paracentesis plus fluid replacement (very low-certainty evidence). Aldosterone antagonists plus loop diuretics had a higher rate of other decompensation events such as hepatic encephalopathy, hepatorenal syndrome, and variceal bleeding compared to paracentesis plus fluid replacement (rate ratio 2.04; 95% CI 1.37 to 3.10) (very low-certainty evidence).

None of the trials using paracentesis plus fluid replacement reported health-related quality of life or symptomatic recovery from ascites.

Funding: the source of funding for four trials were industries which would benefit from the results of the study; 24 trials received no additional funding or were funded by neutral organisations; and the source of funding for the remaining 21 trials was unclear.

Authors’ conclusions

Based on very low-certainty evidence, there is considerable uncertainty about whether interventions for ascites in people with decompensated liver cirrhosis decrease mortality, adverse events, or liver transplantation compared to paracentesis plus fluid replacement in people with decompensated liver cirrhosis and ascites. Based on very low-certainty evidence, transjugular intrahepatic portosystemic shunt and adding aldosterone antagonists to paracentesis plus fluid replacement may increase the resolution of ascites compared to paracentesis plus fluid replacement. Based on very low-certainty evidence, aldosterone antagonists plus loop diuretics may increase the decompensation rate compared to paracentesis plus fluid replacement.

Plain Language Summary

Treatments for ascites in people with advanced liver disease

What is the aim of this Cochrane review?

To find out the best available treatment for ascites (abnormal build-up of fluid in the tummy) in people with advanced liver disease (liver cirrhosis, or late-stage scarring of the liver with complications). People with cirrhosis and ascites are at significant risk of death. Therefore, it is important to treat such people, but the benefits and harms of different treatments available are currently unclear. The authors of this review collected and analysed all relevant research studies with the aim of finding what the best treatment is. They found 49 randomised controlled trials (studies where participants are randomly assigned to one of two treatment groups). During analysis of data, authors used standard Cochrane methods, which allow comparison of only two treatments at a time. Authors also used advanced techniques that allow comparison of multiple treatments simultaneously (usually referred as ‘network (or indirect) meta-analysis’).

Date of literature search

May 2019

Key messages

None of the studies were conducted without flaws, and because of this, there is very high uncertainty in the findings. Approximately one in three trial participants with cirrhosis and ascites who received the standard treatment of drainage of fluid (paracentesis) plus fluid replacement died within 11 months of treatment. The funding source for the research was unclear in 21 studies; commercial organisations funded four studies. There were no concerns regarding the source of funding for the remaining 24 trials.

What was studied in the review?

This review looked at adults of any sex, age, and ethnic origin, with advanced liver disease due to various causes and ascites. Participants were given different treatments for ascites. The authors excluded studies in people who had previously had liver transplantation. The average age of participants, when reported, ranged from 43 to 64 years. The treatments used in the trials included paracentesis plus fluid replacement (currently considered the standard treatment), different classes of diuretics (drugs which increase the passing of urine), and transjugular intrahepatic portosystemic shunt (an artificial channel that connects the different blood vessels that carry oxygen-depleted blood (venous system)) within the liver to reduce the pressure built-up in the portal venous system, one of the two venous systems draining the liver. The review authors wanted to gather and analyse data on death (percentage dead at maximal follow-up), quality of life, serious and non-serious adverse events, time to liver transplantation, resolution of ascites, and development of other complications of advanced liver disease.

What were the main results of the review?

Treatment for ascites in adults with decompensated liver cirrhosis: a network meta-analysis (Review)
The 49 studies included a small number of participants (3521 participants). Study data were sparse. Forty-two studies with 2870 participants provided data for analyses. The follow-up of the trial participants ranged from less than a week to seven years. The review shows that there is low- or very low-certainty evidence for the following:

- Approximately one in three people with cirrhosis and ascites who received the standard treatment of drainage of fluid (paracentesis) plus fluid replacement died within 11 months.
- None of the interventions decrease percentage of deaths, number of complications, and liver transplantation compared to paracentesis plus fluid replacement.
- Transjugular intrahepatic portosystemic shunt may be nine times more effective in resolution of ascites compared to paracentesis plus fluid replacement.
- Adding aldosterone antagonists (a class of diuretics) may be 30 times more effective in resolution of ascites compared to paracentesis plus fluid replacement.
- Using aldosterone antagonists plus loop diuretics (another class of diuretics) as a substitute for paracentesis plus fluid replacement may double the development of other liver complications of cirrhosis.
- None of the trials that compared other treatments to paracentesis plus fluid replacement reported health-related quality of life or symptomatic recovery from ascites.
- Future well designed trials are needed to find out the best treatment for people with cirrhosis and ascites.
## SUMMARY OF FINDINGS

### Summary of findings for the main comparison.

**Treatment for ascites in people with decompensated liver cirrhosis**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Aldosterone antagonists plus loop diuretics</th>
<th>Paracentesis plus systemic vasoconstrictors</th>
<th>Aldosterone antagonists plus loop diuretics plus paracentesis plus fluid replacement</th>
<th>Transjugular intrahepatic portosystemic shunt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality at maximal follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paracentesis plus fluid replacement</td>
<td>HR 1.05 (0.70 to 1.69)</td>
<td>18 more per 1000 (109 fewer to 253 more)</td>
<td>HR 1.64 (0.46 to 6.32)</td>
<td>HR 0.84 (0.60 to 1.18)</td>
</tr>
<tr>
<td>Network estimate</td>
<td></td>
<td></td>
<td>Network estimate</td>
<td>Network estimate</td>
</tr>
<tr>
<td>368 per 1000 (36.8%)</td>
<td>235 more per 1000 (200 fewer to 632 more)</td>
<td>88 more per 1000 (141 fewer to 587 more)</td>
<td>59 fewer per 1000 (148 fewer to 65 more)</td>
<td></td>
</tr>
<tr>
<td>Very low&lt;sup&gt;1,2,3&lt;/sup&gt;</td>
<td>Very low&lt;sup&gt;1,2,3&lt;/sup&gt;</td>
<td>Very low&lt;sup&gt;1,2,3&lt;/sup&gt;</td>
<td>Very low&lt;sup&gt;1,2,3&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Based on 211 participants (4 RCTs)</td>
<td>Based on 165 participants (5 RCTs)</td>
<td>No direct RCT</td>
<td>Based on 452 participants (7 RCTs)</td>
<td></td>
</tr>
</tbody>
</table>

### Serious adverse events (number of events)

<table>
<thead>
<tr>
<th>Paracentesis plus fluid replacement</th>
<th>Rate ratio 1.30 (0.27 to 6.99)</th>
<th>Not estimable</th>
<th>-</th>
<th>-</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 per 1000 (0 per 100 participants)</td>
<td>Direct estimate</td>
<td></td>
<td></td>
<td>Not estimable</td>
</tr>
<tr>
<td></td>
<td>(10 serious adverse events in 35 participants)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very low&lt;sup&gt;1,2,3&lt;/sup&gt;</td>
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</tr>
<tr>
<td>Based on 41 participants (1 RCT)</td>
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</tr>
</tbody>
</table>

### Any adverse events (number of people)

<table>
<thead>
<tr>
<th>Paracentesis plus fluid replacement</th>
<th>Rate ratio 1.30 (0.27 to 6.99)</th>
<th>Not estimable</th>
<th>-</th>
<th>-</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 per 1000 (0 per 100 participants)</td>
<td>Direct estimate</td>
<td></td>
<td></td>
<td>Not estimable</td>
</tr>
<tr>
<td></td>
<td>(10 serious adverse events in 35 participants)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very low&lt;sup&gt;1,2,3&lt;/sup&gt;</td>
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<tr>
<td>Based on 70 participants (1 RCT)</td>
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<td></td>
</tr>
<tr>
<td>Outcome</td>
<td>Intervention</td>
<td>Rate ratio</td>
<td>95% CI</td>
<td>Number of events</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>--------------------------------------------------</td>
<td>------------</td>
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<td>------------------</td>
</tr>
<tr>
<td><strong>Paracentesis plus fluid replacement</strong></td>
<td>100 per 1000 (10%)</td>
<td>Rate ratio 4.12 (0.87 to 34.02)</td>
<td>367 more per 1000 (15 fewer to 3885 more)</td>
<td>Based on 84 participants (2 RCTs)</td>
</tr>
<tr>
<td><strong>Any adverse events (number of events)</strong></td>
<td></td>
<td>Rate ratio 1.37 (0.36 to 5.82)</td>
<td>43 more per 1000 (76 fewer to 567 more)</td>
<td>Based on 145 participants (4 RCTs)</td>
</tr>
<tr>
<td><strong>Liver transplantation at maximal follow-up</strong></td>
<td></td>
<td>HR 1.08 (0.11 to 10.35)</td>
<td>10 more per 1000 (108 fewer to 879 more)</td>
<td>Based on 125 participants (3 RCTs)</td>
</tr>
<tr>
<td><strong>Resolution of ascites at maximal follow-up (by ultrasound)</strong></td>
<td></td>
<td>HR 1.17 (0.01 to 98.79)</td>
<td>27 more per 1000 (156 fewer to 842 more)</td>
<td>Based on 125 participants (3 RCTs)</td>
</tr>
</tbody>
</table>

1. Very low evidence: The level of evidence is considered very low due to the small number of participants and the possibility of publication bias. This indicates that the results may not be reliable.
2. HR: Hazard Ratio
3. CI: Confidence Interval
4. RCT: Randomized Controlled Trial
Other features of decompensation at maximal follow-up

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Rate ratio</th>
<th>458 more per 1000</th>
<th>Rate ratio</th>
<th>107 fewer per 1000</th>
<th>Rate ratio</th>
<th>16 more per 1000</th>
<th>Rate ratio</th>
<th>76 more per 1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracentesis plus fluid replacement</td>
<td>2.04</td>
<td>(1.37 to 3.10)</td>
<td>1.07</td>
<td>(0.14 to 3.61)</td>
<td>1.04</td>
<td>(0.56 to 1.93)</td>
<td>1.17</td>
<td>(0.92 to 1.49)</td>
</tr>
<tr>
<td>Network estimate</td>
<td>439 per 1000 (43.9 per 100 participants)</td>
<td>(164 more to 922 more)</td>
<td>377 fewer to 1144 more</td>
<td>(195 fewer to 409 more)</td>
<td>33 fewer to 217 more</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paracentesis</td>
<td></td>
<td></td>
<td>0.76</td>
<td></td>
<td></td>
<td></td>
<td>1.17</td>
<td></td>
</tr>
<tr>
<td>Fluid replacement</td>
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<td></td>
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<tr>
<td>LoopD</td>
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<tr>
<td>OsmoD</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>No active treatment</td>
<td>1.04</td>
<td></td>
<td>0.80</td>
<td></td>
<td>1.06</td>
<td></td>
<td>1.05</td>
<td></td>
</tr>
<tr>
<td>Network estimate</td>
<td>439 per 1000 (43.9 per 100 participants)</td>
<td>(164 more to 922 more)</td>
<td>(377 fewer to 1144 more)</td>
<td>(195 fewer to 409 more)</td>
<td>(33 fewer to 217 more)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paracentesis</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Very low\(^1,2,4\) Very low\(^1,2,3,4\) Very low\(^1,2,3,4\) Very low\(^1,2,3,4\)

Based on 242 participants (4 RCTs) Based on 114 participants (3 RCTs) No direct RCT Based on 452 participants (7 RCTs)

*Ranking was not provided because of the considerable uncertainty in the ranking.

CrI: Credible interval; OR: Odds Ratio; HR: Hazard Ratio.

## GRADE Working Group grades of evidence

**High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect.

**Moderate certainty:** we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

**Low certainty:** our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

**Very low certainty:** we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

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1. Downgraded one level for risk of bias because the trial(s) included in the analysis was/were at high risk of bias
2. Downgraded one level for imprecision because the sample size was small
3. Downgraded one level for imprecision because the credible intervals were wide (included clinical benefit and harms)
4. Downgraded one level for inconsistency because there was evidence of statistical heterogeneity

**Figure 1.** A high resolution version of this image can be found at: https://doi.org/10.5281/zenodo.3604788. The network plots showing the outcomes for which network meta-analysis was performed. The size of the node (circle) provides a measure of the number of trials in which the particular intervention was included as one of the intervention groups. The thickness of the line provides a measure of the number of direct comparisons between two nodes (Interventions). A higher resolution image of this picture is available at: http://doi.org/10.5281/zenodo.3531818. Abbreviations

- Alb = Albumin
- AldoAnt = Aldosterone antagonists
- Fluid = Fluid replacement
- LoopD = Loop diuretics
- No active treatment = No active treatment
- OsmoD = Osmotic diuretics
- Paracen = Paracentesis
- PVShunt = Peritoneovenous shunt
- Reinf = Reinfusion
- Vasocons = Systemic vasoconstrictors
Summary of findings 2.

### Treatment for ascites in people with decompensated liver cirrhosis

**Patient or population:** people with liver cirrhosis and ascites  
**Settings:** secondary or tertiary care  
**Intervention:** various interventions  
**Comparison:** paracentesis plus fluid replacement  
**Follow-up period:** 0.1 to 84 months  
**Network geometry plots:** Figure 1

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Relative effect (95% CrI)</th>
<th>Anticipated absolute effect* (95% CrI)</th>
<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Paracentesis plus fluid replacement</td>
<td>Various interventions</td>
</tr>
<tr>
<td>Paracentesis plus fluid replacement</td>
<td></td>
<td>368 per 1000</td>
<td>387 per 1000</td>
</tr>
<tr>
<td>Aldosterone antagonists plus loop diuretics (4 RCTs; 211 participants)</td>
<td>HR 1.05 (0.70 to 1.69) Network estimate</td>
<td>368 per 1000</td>
<td>387 per 1000</td>
</tr>
<tr>
<td>Paracentesis plus systemic vasoconstrictors (5 RCTs; 165 participants)</td>
<td>HR 1.64 (0.46 to 6.32) Network estimate</td>
<td>368 per 1000</td>
<td>604 per 1000</td>
</tr>
<tr>
<td>Intervention</td>
<td>HR</td>
<td>95% CI</td>
<td>Network estimate</td>
</tr>
<tr>
<td>----------------------------------------------------------------------------</td>
<td>--------</td>
<td>-----------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Aldosterone antagonists plus loop diuretics plus paracentesis plus fluid replacement (No direct RCT)</td>
<td>1.24</td>
<td>(0.62 to 2.59)</td>
<td>368 per 1000</td>
</tr>
<tr>
<td>Transjugular intrahepatic portosystemic shunt (7 RCTs; 452 participants)</td>
<td>0.84</td>
<td>(0.60 to 1.18)</td>
<td>368 per 1000</td>
</tr>
<tr>
<td>No active treatment (No direct RCT)</td>
<td>1.66</td>
<td>(0.46 to 6.59)</td>
<td>368 per 1000</td>
</tr>
<tr>
<td>Loop diuretics (No direct RCT)</td>
<td>0.71</td>
<td>(0.23 to 1.64)</td>
<td>368 per 1000</td>
</tr>
<tr>
<td>Paracentesis plus reinfusion (1 RCT; 24 participants)</td>
<td>0.77</td>
<td>(0.23 to 2.68)</td>
<td>368 per 1000</td>
</tr>
<tr>
<td>Aldosterone antagonists plus loop diuretics plus albumin (No direct RCT)</td>
<td>1.06</td>
<td>(0.57 to 2.16)</td>
<td>368 per 1000</td>
</tr>
<tr>
<td>Aldosterone antagonists plus loop diuretics plus peritoneovenous shunt (No direct RCT)</td>
<td>0.97</td>
<td>(0.40 to 2.43)</td>
<td>368 per 1000</td>
</tr>
<tr>
<td>Aldosterone antagonists plus loop diuretics plus systemic vasoconstrictors (No direct RCT)</td>
<td>0.42</td>
<td>(0.15 to 1.22)</td>
<td>368 per 1000</td>
</tr>
<tr>
<td>Aldosterone antagonists (No direct RCT)</td>
<td>1.92</td>
<td>(0.24 to 20.64)</td>
<td>368 per 1000</td>
</tr>
<tr>
<td>Aldosterone antagonists plus loop diuretics plus systemic vasoconstrictors plus paracentesis plus fluid replacement (No direct RCT)</td>
<td>1.11</td>
<td>(0.02 to 39.77)</td>
<td>368 per 1000</td>
</tr>
<tr>
<td>Aldosterone antagonists plus loop diuretics plus systemic vasoconstrictors plus systemic vasodilator</td>
<td>0.61</td>
<td>(0.02 to 9.17)</td>
<td>368 per 1000</td>
</tr>
</tbody>
</table>

**HR:** Hazard Ratio

**95% CI:** 95% Confidence Interval

**Network estimate:** Estimated number in the intervention group for every 1000 participants.
### Treatment for ascites in adults with decompensated liver cirrhosis: a network meta-analysis

**Aldosterone antagonists plus loop diuretics plus systemic vasodilator**  
*(No direct RCT)*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rate ratio</th>
<th>Network estimate</th>
<th>228 per 1000 (12 to 1000)</th>
<th>140 fewer per 1000 (357 fewer to 632 more)</th>
<th>Very low(^1,2,3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldosterone antagonists plus loop diuretics plus systemic vasodilator</td>
<td>HR 0.62</td>
<td>(0.03 to 9.10)</td>
<td>368 per 1000</td>
<td>228 per 1000</td>
<td>140 fewer per 1000</td>
</tr>
</tbody>
</table>

**Systemic vasoconstrictors plus albumin**  
*(No direct RCT)*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rate ratio</th>
<th>Network estimate</th>
<th>965 per 1000 (151 to 1000)</th>
<th>596 more per 1000 (218 fewer to 632 more)</th>
<th>Very low(^1,2,3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic vasoconstrictors plus albumin</td>
<td>HR 2.62</td>
<td>(0.41 to 19.28)</td>
<td>368 per 1000</td>
<td>965 per 1000</td>
<td>596 more per 1000</td>
</tr>
</tbody>
</table>

**Serious adverse events (number of people)**  
None of the trials with paracentesis plus fluid replacement as an intervention reported this outcome.

**Serious adverse events (number of events)**  
Total studies: 1  
Total participants: 41

**Paracentesis plus fluid replacement**  
Reference

**Aldosterone antagonists plus loop diuretics**  
*(1 RCT; 41 participants)*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rate ratio</th>
<th>Network estimate</th>
<th>0 per 1000</th>
<th>Not estimable</th>
<th>Very low(^1,2,3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldosterone antagonists plus loop diuretics</td>
<td>Rate ratio 1.30</td>
<td>(0.27 to 6.99)</td>
<td>0 per 1000</td>
<td>Not estimable</td>
<td>Very low(^1,2,3)</td>
</tr>
</tbody>
</table>

**Transjugular intrahepatic portosystemic shunt**  
*(1 RCT; 70 participants)*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rate ratio</th>
<th>Network estimate</th>
<th>0 per 1000</th>
<th>Not estimable</th>
<th>Very low(^1,2,3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transjugular intrahepatic portosystemic shunt</td>
<td>Rate ratio 1.63</td>
<td>(0.30 to 11.66)</td>
<td>0 per 1000</td>
<td>Not estimable</td>
<td>Very low(^1,2,3)</td>
</tr>
</tbody>
</table>

**Health-related quality of life**  
None of the trials with paracentesis plus fluid replacement as an intervention reported this outcome.

**Any adverse events (number of people)**  
Total studies: 3

**Any adverse events (number of events)**  
Total studies: 6

**Paracentesis plus fluid replacement**  
Reference

**Paracentesis plus systemic vasoconstrictors**  
*(4 RCTs; 145 participants)*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>OR</th>
<th>Network estimate</th>
<th>153 per 1000 (32 to 564)</th>
<th>53 more per 1000 (68 fewer to 464 more)</th>
<th>Very low(^1,2,3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracentesis plus systemic vasoconstrictors</td>
<td>OR 1.63</td>
<td>(0.30 to 11.66)</td>
<td>100 per 1000</td>
<td>153 per 1000</td>
<td>53 more per 1000</td>
</tr>
</tbody>
</table>

**Aldosterone antagonists plus loop diuretics**  
*(2 RCT; 84 participants)*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>OR</th>
<th>Network estimate</th>
<th>282 per 1000 (46 to 753)</th>
<th>182 more per 1000 (54 fewer to 653 more)</th>
<th>Very low(^1,2,3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldosterone antagonists plus loop diuretics</td>
<td>OR 3.54</td>
<td>(0.43 to 27.41)</td>
<td>100 per 1000</td>
<td>282 per 1000</td>
<td>182 more per 1000</td>
</tr>
</tbody>
</table>
### Total participants: 116

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Reference</th>
<th>Rate ratio</th>
<th>Network estimate</th>
<th>High level harms</th>
<th>Evidence quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldosterone antagonists plus loop diuretics (1 RCT; 31 participants)</td>
<td></td>
<td>4.12 (0.87 to 34.02)</td>
<td>118 per 1000: (103 to 4003)</td>
<td>367 more per 1000: (15 fewer to 3885 more)</td>
<td>Very low¹,²,³</td>
</tr>
<tr>
<td>Paracentesis plus systemic vasoconstrictors (1 RCT; 25 participants)</td>
<td></td>
<td>1.37 (0.36 to 5.82)</td>
<td>118 per 1000: (42 to 685)</td>
<td>43 more per 1000: (76 fewer to 567 more)</td>
<td>Very low¹,²,³</td>
</tr>
<tr>
<td>Aldosterone antagonists plus loop diuretics plus systemic vasoconstrictors (No direct RCT)</td>
<td></td>
<td>3.30 (0.38 to 38.51)</td>
<td>118 per 1000: (45 to 4531)</td>
<td>271 more per 1000: (55 fewer to 4413 more)</td>
<td>Very low¹,²,³</td>
</tr>
<tr>
<td>Aldosterone antagonists plus loop diuretics plus systemic vasoconstrictors plus systemic vasodilator (No direct RCT)</td>
<td></td>
<td>4.25 (0.53 to 46.99)</td>
<td>118 per 1000: (62 to 5529)</td>
<td>383 more per 1000: (55 fewer to 5411 more)</td>
<td>Very low¹,²,³</td>
</tr>
<tr>
<td>Aldosterone antagonists plus loop diuretics plus systemic vasodilator (No direct RCT)</td>
<td></td>
<td>2.41 (0.24 to 29.67)</td>
<td>118 per 1000: (28 to 3490)</td>
<td>166 more per 1000: (89 fewer to 3372 more)</td>
<td>Very low¹,²,³</td>
</tr>
</tbody>
</table>

### Liver transplantation at maximal follow-up

**Total studies: 11**

**Total participants: 596**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Reference</th>
<th>HR</th>
<th>Network estimate</th>
<th>High level harms</th>
<th>Evidence quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracentesis plus fluid replacement (4 RCTs; 145 participants)</td>
<td></td>
<td>1.08 (0.11 to 10.35)</td>
<td>121 per 1000: (14 to 1000)</td>
<td>10 more per 1000: (108 fewer to 879 more)</td>
<td>Very low¹,²,³</td>
</tr>
<tr>
<td>Transjugular intrahepatic portosystemic shunt (6 RCTs; 427 participants)</td>
<td></td>
<td>0.87 (0.52 to 1.44)</td>
<td>121 per 1000: (63 to 175)</td>
<td>15 fewer per 1000: (58 fewer to 54 more)</td>
<td>Very low¹,²,³</td>
</tr>
<tr>
<td>Paracentesis plus reinfusion (1 RCT; 24 participants)</td>
<td></td>
<td>2.56 (0.20 to 90.92)</td>
<td>121 per 1000: (25 to 1000)</td>
<td>189 more per 1000: (97 fewer to 879 more)</td>
<td>Very low¹,²,³</td>
</tr>
</tbody>
</table>

### Symptomatic resolution of ascites at maximal follow-up

None of the trials reported this outcome.
## Resolution of ascites at maximal follow-up (by ultrasound)

*Total studies: 17
*Total participants: 1007

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Reference</th>
<th>Network estimate</th>
<th>HR (95% CI)</th>
<th>Events per 1000 (95% CI)</th>
<th>Very low 1,2,3,4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracentesis plus fluid replacement</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aldosterone antagonists plus loop diuretics</td>
<td>HR 1.10 (0.12 to 10.74)</td>
<td>158 per 1000</td>
<td>174 per 1000 (18 to 1000)</td>
<td>16 more per 1000 (140 fewer to 842 more)</td>
<td>Very low 1,2,3,4</td>
</tr>
<tr>
<td>Aldosterone antagonists plus loop diuretics plus paracentesis plus fluid replacement</td>
<td>HR 1.17 (0.01 to 98.79)</td>
<td>158 per 1000</td>
<td>185 per 1000 (2 to 1000)</td>
<td>27 more per 1000 (156 fewer to 842 more)</td>
<td>Very low 1,2,3,4</td>
</tr>
<tr>
<td>Transjugular intrahepatic portosystemic shunt</td>
<td>HR 9.44 (1.93 to 62.68)</td>
<td>158 per 1000</td>
<td>1000 per 1000 (305 to 1000)</td>
<td>842 more per 1000 (147 more to 842 more)</td>
<td>Very low 1,2,3,4</td>
</tr>
<tr>
<td>No active treatment</td>
<td>HR 0.16 (0.00 to 17.37)</td>
<td>158 per 1000</td>
<td>26 per 1000 (0 to 1000)</td>
<td>132 fewer per 1000 (158 fewer to 842 more)</td>
<td>Very low 1,2,3,4</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>HR 2.26 (0.01 to 846.41)</td>
<td>158 per 1000</td>
<td>357 per 1000 (1 to 1000)</td>
<td>199 more per 1000 (157 fewer to 842 more)</td>
<td>Very low 1,2,3,4</td>
</tr>
<tr>
<td>Aldosterone antagonists plus loop diuretics plus albumin</td>
<td>HR 3.28 (0.09 to 118.39)</td>
<td>158 per 1000</td>
<td>517 per 1000 (15 to 1000)</td>
<td>360 more per 1000 (143 fewer to 842 more)</td>
<td>Very low 1,2,3,4</td>
</tr>
<tr>
<td>Aldosterone antagonists plus loop diuretics plus systemic vasoconstrictors</td>
<td>HR 8.81 (0.06 to 1908.36)</td>
<td>158 per 1000</td>
<td>1000 per 1000 (10 to 1000)</td>
<td>842 more per 1000 (148 fewer to 842 more)</td>
<td>Very low 1,2,3,4</td>
</tr>
<tr>
<td>Aldosterone antagonists plus paracentesis plus fluid replacement</td>
<td>HR 30.63 (5.06 to 692.98)</td>
<td>158 per 1000</td>
<td>1000 per 1000 (799 to 1000)</td>
<td>842 more per 1000 (641 more to 842 more)</td>
<td>Low 1,2</td>
</tr>
</tbody>
</table>

## Other features of decompensation at maximal follow-up

*Total studies: 25
*Total participants: 1756

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Reference</th>
<th>Events per 1000 (95% CI)</th>
<th>Very low 1,2,3,4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracentesis plus fluid replacement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aldosterone antagonists plus loop diuretics</td>
<td>Rate ratio 2.04</td>
<td>439 per 1000</td>
<td>896 per 1000</td>
</tr>
<tr>
<td>Aldosterone antagonists plus loop diuretics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>Rate ratio</td>
<td>Network estimate</td>
<td>Event rate</td>
</tr>
<tr>
<td>---------------------------------------------------------------------------</td>
<td>----------------</td>
<td>------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Paracentesis plus systemic vasoconstrictors (3 RCTs; 114 participants)</td>
<td>0.76</td>
<td>(0.14 to 3.61)</td>
<td>439 per 1000</td>
</tr>
<tr>
<td>Aldosterone antagonists plus loop diuretics plus paracentesis plus fluid replacement (No direct RCT)</td>
<td>1.04</td>
<td>(0.56 to 1.93)</td>
<td>439 per 1000</td>
</tr>
<tr>
<td>Transjugular intrahepatic portosystemic shunt (7 RCTs; 452 participants)</td>
<td>1.17</td>
<td>(0.92 to 1.49)</td>
<td>439 per 1000</td>
</tr>
<tr>
<td>No active treatment (No direct RCT)</td>
<td>3.34</td>
<td>(0.85 to 13.94)</td>
<td>439 per 1000</td>
</tr>
<tr>
<td>Loop diuretics (No direct RCT)</td>
<td>0.95</td>
<td>(0.40 to 2.23)</td>
<td>439 per 1000</td>
</tr>
<tr>
<td>Aldosterone antagonists plus loop diuretics plus albumin (No direct RCT)</td>
<td>1.56</td>
<td>(0.84 to 2.87)</td>
<td>439 per 1000</td>
</tr>
<tr>
<td>Aldosterone antagonists plus loop diuretics plus peritoneovenous shunt (No direct RCT)</td>
<td>0.84</td>
<td>(0.41 to 1.70)</td>
<td>439 per 1000</td>
</tr>
<tr>
<td>Aldosterone antagonists plus loop diuretics plus systemic vasoconstrictors (No direct RCT)</td>
<td>0.53</td>
<td>(0.02 to 4.98)</td>
<td>439 per 1000</td>
</tr>
<tr>
<td>Aldosterone antagonists plus loop diuretics plus systemic vasoconstrictors plus systemic vasodilator (No direct RCT)</td>
<td>0.53</td>
<td>(0.02 to 4.99)</td>
<td>439 per 1000</td>
</tr>
<tr>
<td>Aldosterone antagonists plus loop diuretics plus systemic vasodilator (No direct RCT)</td>
<td>0.53</td>
<td>(0.02 to 5.11)</td>
<td>439 per 1000</td>
</tr>
</tbody>
</table>
### Systemic vasoconstrictors plus albumin

| Rate ratio 3.90 | Network estimate | 439 per 1000 | 1712 per 1000 | 1274 more per 1000 | Very low
|----------------|------------------|--------------|---------------|-------------------|---------
| 0.96 to 16.98  |                  | 422 to 7447  | (422 to 7447) | (16 fewer to 7009 more) | 1,2,3,4 |

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

**Ranking is not provided because of the considerable uncertainty in the ranking.

Crl: Credible interval; OR: Odds Ratio; HR: Hazard Ratio.

### GRADE Working Group grades of evidence

**High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect.

**Moderate certainty:** we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

**Low certainty:** our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

**Very low certainty:** we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

1. Downgraded one level for risk of bias because the trial(s) included in the analysis was/were at high risk of bias
2. Downgraded one level for imprecision because the sample size was small
3. Downgraded one level for imprecision because the credible intervals were wide (includes clinical benefit and harms)
4. Downgraded one level for inconsistency because there was evidence of statistical heterogeneity
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 (Tsachatzis 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 (Tsachatzis 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 or moderate ascites which is manifested by moderate symmetrical distension of the abdomen; and grade 3 ascites which 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 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 ascites and 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 splanchic 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 splanchic 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 jaundice, 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; and 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 diuretic-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 suggest 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 try to overcome this are to administer albumin, colloids such as hydroxyethyl starch, vasoconstrictors such as midodrine, or reinfusing the proteins from the ascitic fluid into systemic circulation (Bruno 1992; Altman 1998; Appenrodt 2008). However, the benefits of plasma expanders for people with cirrhosis and large ascites treated with abdominal paracentesis is questionable (Simonetti 2019).

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 with refractory ascites was available at the start of this project (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 provide the best level of evidence for the benefits and harms of different treatments for ascites in people with decompensated liver cirrhosis. We have also presented results from direct comparisons whenever possible, as well as performing the network meta-analysis.

OBJECTIVES

To compare the benefits and harms of different treatments for ascites in people with decompensated liver cirrhosis through a network meta-analysis and to generate rankings of the different treatments for ascites according to their safety and efficacy.

METHODS

Criteria for considering studies for this review

Types of studies

We considered only randomised clinical trials (including cross-over, cluster-randomised clinical trials) for this network meta-analysis irrespective of language, publication status, or date of publication. We excluded 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, we did not include these studies because of the findings of this review, i.e. there is considerable uncertainty about the benefits of the different treatments for ascites.

Types of participants

We included randomised clinical trials with adult trial participants (18 years old and above) undergoing treatment for ascites with decompensated liver cirrhosis. We excluded randomised clinical trials in which participants had previously undergone liver transplantation.

Types of interventions

We included 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 canrenone);
- Large volume paracentesis (removal of ascitic fluid) with different fluids to prevent circulatory dysfunction (for example, albumin, hydroxyethyl starch, etc.) ('paracentesis plus fluid replacement');
- Spontaneous ultrafiltration and reinfusion (filtering the removed ascitic fluid and reinfusing the proteins);
- Low-flow ascites fluid pump (automatic diversion of ascitic fluid to the urinary bladder, from where it is excreted in urine);
- Systemic vasoconstrictor (for example, terlipressin, midodrine);
- TIPS procedure (decrease in portal hypertension);
- Other forms of portosystemic shunt (decrease in portal hypertension);
- No active intervention (no ascites-related intervention or placebo).

We considered 'paracentesis plus fluid replacement' as the reference group. Each of the above categories was considered as a 'treatment node'; the only exception was the diuretics, where we considered different classes of diuretics as different treatment nodes. We considered variations in drugs within the same class of diuretics, doses of drugs, frequency and duration of interventions as the same treatment node. We treated each different combination of the categories as different treatment nodes.

We excluded trials that evaluated co-interventions 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 included trials in which such co-interventions were administered equally in both trial arms.

We evaluated the plausibility of the network meta-analysis transitivity assumption by looking at the inclusion and exclusion criteria in the studies. The 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.
performed separate meta-analysis for each of these different types of ascites, when possible, to ensure that the concerns about the transitivity assumption were minimised.

Types of outcome measures

Primary outcomes

- All-cause mortality at maximal follow-up, i.e. the outcome measured at the last time when the participant was followed 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 the intervention). We defined a serious adverse event as any event that would increase mortality; is life-threatening; requires hospitalisation; results in persistent or significant disability; is a congenital anomaly/birth defect; or any important medical event that might jeopardise the person or require intervention to prevent it (ICH-GCP 1997). However, none of the trial authors defined serious adverse events. Therefore, we used the list provided by trial authors for serious adverse events (as indicated in the protocol).
  * 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 the intervention): We defined an adverse event as any untoward medical occurrence not necessarily having a causal relationship with the intervention but resulting in a dose reduction or discontinuation of the intervention (any time after commencement of the intervention) (ICH-GCP 1997). However, none of the trial authors defined ‘adverse event’. Therefore, we used the list provided by trial authors for adverse events (as indicated in the protocol).
  * 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.
- Number of decompensation episodes (maximal follow-up).

Exploratory outcomes

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

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

Search methods for identification of studies

Electronic searches

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

Searching other resources

We searched 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 AB, DR, LP, or MP) independently identified trials for inclusion by screening the titles and abstracts of articles identified by the literature search, and sought full-text articles of any references identified by at least one review author for potential inclusion. We selected trials for inclusion based on the full-text articles. We listed the references that we excluded and the reasons for their exclusion in the Characteristics of excluded studies table. We also listed any ongoing trials identified primarily through the search of the clinical trial registers for further follow-up. We resolved any discrepancies through discussion. We illustrated the study selection process in a PRISMA diagram.

Data extraction and management

Two review authors (KG and AB, DR, LP, or MP) independently extracted 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 the 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 collected 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 was available.

We attempted to contact the trial authors in the case of unclear or missing information. We resolved any differences in opinion through discussion.

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

Allocation sequence generation

Low risk of bias: 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.

Unsure 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 excluded such quasi-randomised studies.

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. We excluded such quasi-randomised studies.

Blinding of participants and personnel

Low risk of bias: 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: all-cause mortality, adverse events, and time to resolution of ascites. If the original trial protocol was available, the outcomes should have been those called for in that protocol. If we obtained 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 did 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.
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 considered a trial to be at low risk of bias if we assessed the trial to be at low risk of bias across all listed bias risk domains. Otherwise, we considered trials to be at high risk of bias. At the outcome level, we classified an outcome to be at low risk of bias if the allocation sequence generation, allocation concealment, blinding of participants, healthcare professionals, and outcome assessors, incomplete outcome data, and selective outcome reporting (at the outcome level) were at low risk of bias for objective and subjective outcomes (Savović 2018).

Measures of treatment effect

Relative treatment effects

For dichotomous variables (e.g. proportion of participants with serious adverse events or any adverse events), we calculated the odds ratio (OR) with 95% credible interval (CrI) (or Bayesian confidence interval) (Severini 1993). For continuous variables (e.g. health-related quality of life reported on the same scale), we calculated the mean difference (MD) with 95% CrI. We planned to use standardised mean difference (SMD) values with 95% CrI for health-related quality of life if included trials used different scales. If we calculated the SMD, we planned to convert it to a common scale, for example, EQ-5D or SF-36 (using the standard deviation of the common scale) for the purpose of interpretation. For count outcomes (e.g. number of serious adverse events or number of any adverse events), we calculated the rate ratio (RR) with 95% CrI. This assumes that the events are independent of each other, i.e. if a person has had an event, they are not at an increased risk of further outcomes, which is the assumption in Poisson likelihood. For time-to-event data (e.g. all-cause mortality at maximal follow-up), we calculated hazard ratios (HRs) with 95% CrI.

Relative ranking

We estimated the ranking probabilities for all interventions of being at each possible rank for each intervention for each outcome when NMA (network meta-analysis) was performed. We obtained the surface under the cumulative ranking curve (SUCRA) (cumulative probability), rankogram, and relative ranking table with CrI for the ranking probabilities for each outcome when NMA was performed (Salanti 2011; Chaimani 2013).

Unit of analysis issues

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

Cluster-randomised clinical trials

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

Cross-over randomised clinical trials

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

Trials with multiple intervention groups

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

Dealing with missing data

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

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

Assessment of heterogeneity

We assessed clinical and methodological heterogeneity by carefully examining the characteristics and design of included trials. We also planned to assess the presence of clinical heterogeneity by comparing effect estimates (please see Subgroup analysis and investigation of heterogeneity) in trial reports of different drug dosages, 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 assessed statistical heterogeneity by comparing the results of the fixed-effect model meta-analysis and the random-effects model meta-analysis, between-study standard deviation (tau² and comparing this with values reported in a study of the distribution of between-study heterogeneity estimates) (Turner 2012), and by calculating the NMA-specific I² statistic (Jackson 2014) using Stata/SE 15.1. When possible, we explored substantial clinical, methodological, or statistical heterogeneity and addressed the heterogeneity in subgroup analysis (see ‘Subgroup analysis and investigation of heterogeneity’).

Assessment of transitivity across treatment comparisons
We assessed the transitivity assumption by comparing the distribution of the potential effect modifiers (clinical: grade of ascites (grade 2 versus grade 3) and whether refractory or recurrent ascites; and methodological: risk of bias, year of randomisation, duration of follow-up) across the different pairwise comparisons.

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

Data synthesis

Methods for indirect and mixed comparisons
We conducted network meta-analyses to compare multiple interventions simultaneously for each of the primary and secondary outcomes. When two or more interventions were combined, we considered this as a separate intervention (‘node’). Network meta-analysis combines direct evidence within trials and indirect evidence across trials (Mills 2013). We obtained a network plot to ensure that the trials were connected by interventions using Stata/SE 15.1 (Chaimani 2013). We excluded any trials that were not connected to the network from the network meta-analysis, and we reported only the direct pairwise meta-analysis for such comparisons. We summarised the population and methodological characteristics of the trials included in the network meta-analysis in a table based on pairwise comparisons. We conducted a Bayesian network meta-analysis using the Markov chain Monte Carlo method in OpenBUGS 3.2.3, according to guidance from the National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) documents (Dias 2016). We modelled the treatment contrast (i.e. log odds ratio for binary outcomes, mean difference or standardised mean difference for continuous outcomes, log rate ratio for count outcomes, and log hazard ratio for time-to-event outcomes) for any two interventions (‘functional parameters’) as a function of comparisons between each individual intervention and the reference group (‘basic parameters’) using appropriate likelihood functions and links (Lu 2006). We used binomial likelihood and logit link for binary outcomes, Poisson likelihood and log link for count outcomes, binomial likelihood and complementary log-log link (a semiparametric model which excludes censored individuals from the denominator of ‘at risk’ individuals at the point when they are censored) for time-to-event outcomes, and normal likelihood and identity link for continuous outcomes. We used ‘paracentesis plus fluid replacement’ as the reference group across the networks, as this was the commonest intervention compared in the trials. We performed a fixed-effect model and random-effects model for the network meta-analysis. We reported both models for comparison with the reference group in a forest plot when the results were different between the models. For each pairwise comparison in a table, we reported the fixed-effect model if the two models reported similar results; otherwise, we reported the more conservative model, i.e. usually using the random-effects model in the absence of ‘small-study’ bias.

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

Assessment of inconsistency
We assessed inconsistency (statistical evidence of the violation of the transitivity assumption) by fitting both an inconsistency model and a consistency model. We used inconsistency models employed in the NICE DSU manual, as we used a common between-study standard deviation (Dias 2014). In addition, we used design-by-treatment full interaction model and inconsistency factor (IF) plots to assess inconsistency (Higgins 2012; Chaimani 2013), when applicable. We used Stata/SE 15.1 to create IF plots. In the presence of inconsistency, we assessed 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 or limited network meta-analysis to a more compatible subset of trials, when possible.

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

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

- Trials at low risk of bias (risk of bias in all domains were low) compared to trials at high risk of bias (risk of bias was unclear or high in at least one of the domains).
- The grade of ascites (grade 2 or grade 3 or refractory/recurrent ascites).
- 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 treatment.
- The co-interventions (for example, both groups received prophylactic antibiotics to decrease the risk of subacute bacterial peritonitis).
- 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 compared to other definitions).

We calculated a single common interaction term which assumes that each relative treatment effect compared to a common comparator treatment (i.e. paracentesis plus fluid replacement) is impacted in the same way by the covariate in question, when applicable (Dias 2012a). If the 95% CI of the interaction term did not overlap zero, we considered this statistically significant heterogeneity or inconsistency (depending upon the factor being used as covariate).

Sensitivity analysis

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

Presentation of results

We followed the PRISMA-NMA statement while reporting (Hutton 2015). We presented the effect estimates with 95% CrI for each pairwise comparison calculated from the direct comparisons and network meta-analysis. We originally planned to present the cumulative probability of the treatment ranks (i.e. the probability that the intervention was within the top two, the probability that the intervention was within the top three, etc) but we did not present these because of the sparse data which can lead to misinterpretation of results due to large uncertainty in the rankings (the CrI was 0 to 1 for all the ranks). We uploaded all the raw data and the codes used for analysis in the European Organization for Nuclear Research open source database (Zenodo): the link is: http://doi.org/10.5281/zenodo.3531818.

Grading of evidence

We presented 'Summary of findings' tables for all the primary and secondary outcomes (see Primary outcomes; Secondary outcomes). We followed the approach suggested by Yepes-Nunez and colleagues (Yepes-Nunez 2019). First, we calculated the direct and indirect effect estimates (when possible) and 95% CrI using the node-splitting approach (Dias 2010), that is, calculating the direct estimate for each comparison by including only trials in which there was direct comparison of interventions and the indirect estimate for each comparison by excluding the trials in which there was direct comparison of interventions (and ensuring a connected network). Next, we rated the quality of direct and indirect effect estimates using GRADE methodology which takes into account the risk of bias, inconsistency (heterogeneity), directness of evidence (including incoherence, the term used in GRADE methodology for inconsistency in network meta-analysis), imprecision, and publication bias (Guyatt 2011). We then presented the relative and absolute estimates of the meta-analysis with the best certainty of evidence (Yepes-Nunez 2019). We also presented the 'Summary of findings' tables in a second format presenting all the outcomes for selected interventions (Yepes-Nunez 2019): we selected the four interventions (aldosterone antagonists plus loop diuretics, paracentesis plus systemic vasconstrictors, aldosterone antagonists plus loop diuretics plus paracentesis plus fluid replacement, and transjugular intrahepatic portosystemic shunt) which were compared in the most trials (Table 1).

Recommendations for future research

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

RESULTS

Description of studies

Results of the search

We identified 4877 references through electronic searches of CENTRAL (n = 1095), MEDLINE Ovid (n = 2093), Embase Ovid (n = 875), Science Citation Index expanded (n = 779), ClinicalTrials.gov (n = 35), and WHO Trials register (n = 0). After removing duplicate references, there were 3890 references. We excluded 3713 clearly irrelevant references through reading titles and abstracts. We identified no additional references by reference searching and by searching the EMA and FDA. We retrieved a total of 177-full text references for further assessment in detail. We excluded 97 references (78 studies) for the reasons stated in the Characteristics of excluded studies. There were six ongoing trials (seven references) without interim data (Characteristics of ongoing studies). Thus, we included a total of 49 trials described in 73 references (Characteristics of included studies). The reference flow is shown in Figure 2.
Figure 2. Study flow diagram.

- 4877 records identified through database searching
- No additional records identified through other sources

3890 records after duplicates removed

3890 records screened
3713 records excluded

- 97 references (78 studies) of full-text articles excluded, with reasons in Characteristics of excluded studies
- 7 references (6 ongoing trials) without interim data

177 full-text articles assessed for eligibility

49 studies (73 references) included in qualitative synthesis

42 studies included in
Included studies

Forty-nine trials were included (Gregory 1977; Fogel 1981; Descos 1983; Gines 1987; Salerno 1987; Mchutchison 1989; Stanley 1989b; Chesta 1990; Ginès 1991; Strauss 1991; Acharya 1992; Bruno 1992; Hague 1992; Ljubici 1994; Sola 1994; Ginès 1995; Schaub 1995; Lebrec 1996; Chang 1997; Fernandez-Esparrach 1997; Graziotto 1997; Mehta 1998; Gentilini 1999a; Rossle 2000; Ginès 2002; Morreau 2002; Sanyal 2003; Salerno 2004; Romanelli 2006; Singh 2006a; Singh 2006b; Lata 2007; Apprenrodt 2008; Singh 2008; Licata 2009; Narahara 2011; Raza 2011; Al Sebaey 2012; Amin 2012; Singh 2013; Ali 2014; Hamdy 2014; Tuttolomondo 2016; Rai 2017); 19 trials had medium-term follow-up (Gines 1987; Salerno 1987; Chesta 1990; Ginès 1991; Sola 1994; Ginès 1995; Lebrec 1996; Graziotto 1997; Gentilini 1999a; Rossle 2000; Ginès 2002; Sanyal 2003; Salerno 2004; Narahara 2011; Bari 2012; Singh 2012a; Bureau 2017c; Caraceni 2018; Sola 2018); only two trials had long-term follow-up (Stanley 1989b; Romanelli 2006).

Twenty-five trials reported the proportion of participants who had ascites grade 2: in 23 trials, none of the participants had ascites grade 2; these trials included only participants with grade 3 (Descos 1983; Gines 1987; Salerno 1987; Chesta 1990; Acharya 1992; Bruno 1992; Ljubici 1994; Sola 1994; Chang 1997; Fernandez-Esparrach 1997; Graziotto 1997; Rossle 2000; Morreau 2002; Singh 2006a; Singh 2006b; Lata 2007; Apprenrodt 2008; Singh 2008; Al Sebaey 2012; Amin 2012; Ali 2014; Hamdy 2014; Bureau 2017c); in the remaining two trials, the proportion of participants who had ascites grade 2 ranged from 65.0% to 83.1% (Romanelli 2006; Caraceni 2018). Twenty trials reported the proportion of participants who had refractory or recurrent ascites: in 19 trials, all the participants had refractory or recurrent ascites (Ginès 1991; Strauss 1991; Bruno 1992; Ginès 1995; Lebrec 1996; Rossle 2000; Ginès 2002; Sanyal 2003; Salerno 2004; Licata 2009; Narahara 2011; Raza 2011; Bari 2012; Singh 2012a; Singh 2013; Ali 2014; Hamdy 2014; Tuttolomondo 2016; Bureau 2017c; Rai 2017; Caraceni 2018; Sola 2018). The mean or median age in the trials ranged from 43 to 64 years in the trials that reported this information (Gregory 1977; Fogel 1981; Descos 1983; Gines 1987; Salerno 1987; Chesta 1990; Ginès 1991; Strauss 1991; Acharya 1992; Bruno 1992; Hague 1992; Ljubici 1994; Sola 1994; Ginès 1995; Lebrec 1996; Chang 1997; Fernandez-Esparrach 1997; Graziotto 1997; Mehta 1998; Gentilini 1999a; Rossle 2000; Ginès 2002; Morreau 2002; Sanyal 2003; Salerno 2004; Romanelli 2006; Singh 2006a; Singh 2006b; Lata 2007; Apprenrodt 2008; Singh 2008; Licata 2009; Narahara 2011; Raza 2011; Al Sebaey 2012; Bari 2012; Singh 2012a; Singh 2013; Ali 2014; Hamdy 2014; Tuttolomondo 2016; Bureau 2017c; Rai 2017; Caraceni 2018; Sola 2018). The proportion of females ranged from 0.0% to 47.6% in the trials that reported this information (Gregory 1977; Fogel 1981; Descos 1983; Gines 1987; Salerno 1987; Chesta 1990; Ginès 1991; Strauss 1991; Acharya 1992; Bruno 1992; Hague 1992; Ljubici 1994; Sola 1994; Ginès 1995; Lebrec 1996; Chang 1997; Fernandez-Esparrach 1997; Graziotto 1997; Mehta 1998; Gentilini 1999a; Rossle 2000; Ginès 2002; Morreau 2002; Sanyal 2003; Salerno 2004; Romanelli 2006; Singh 2006a; Singh 2006b; Lata 2007; Apprenrodt 2008; Singh 2008; Licata 2009; Narahara 2011; Raza 2011; Al Sebaey 2012; Bari 2012; Singh 2012a; Singh 2013; Hamdy 2014; Tuttolomondo 2016; Bureau 2017c; Rai 2017; Caraceni 2018; Sola 2018). The follow-up period in the trials ranged from 0.1 to 84 months in the trials that reported this information. Twenty-eight trials had short-term follow-up (Gregory 1977; Fogel 1981; Descos 1983; Mchutchison 1989; Strauss 1991; Acharya 1992; Bruno 1992; Hague 1992; Ljubici 1994; Schaub 1995; Chang 1997; Fernandez-Esparrach 1997; Mehta 1998; Morreau 2002; Singh 2006b; Lata 2007; Apprenrodt 2008; Singh 2008; Licata 2009; Raza 2011; Al Sebaey 2012; Amin 2012; Singh 2013; Ali 2014; Hamdy 2014; Tuttolomondo 2016; Rai 2017); 19 trials had medium-term follow-up (Gines 1987; Salerno 1987; Chesta 1990; Ginès 1991; Sola 1994; Ginès 1995; Lebrec 1996; Graziotto 1997; Gentilini 1999a; Rossle 2000; Ginès 2002; Sanyal 2003; Salerno 2004; Narahara 2011; Bari 2012; Singh 2012a; Bureau 2017c; Caraceni 2018; Sola 2018); only two trials had long-term follow-up (Stanley 1989b; Romanelli 2006).
Treatment for ascites in adults with decompensated liver cirrhosis: a network meta-analysis (Review)
Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.
Figure 4. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.
### Figure 4. (Continued)

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</tbody>
</table>
Allocation

With regards to sequence generation, twenty-two trials were at low risk of bias (Gines 1987; Ginès 1991; Strauss 1991; Bruno 1992; Hagege 1992; Ljubici 1994; Sola 1994; Chang 1997; Romaneli 2006; Singh 2006a; Singh 2006b; Singh 2008; Licata 2009; Narahara 2011; Bari 2012; Singh 2012a; Singh 2013; Ali 2014; Bureau 2017c; Rai 2017; Caraceni 2018; Sola 2018); the remaining 27 trials, which did not provide sufficient information, were at unclear risk of bias (Gregory 1977; Fogel 1981; Descos 1983; Salerno 1987; Mchutchison 1988; Stanley 1988b; Chesta 1990; Acharya 1992; Ginès 1995; Schaub 1995; Lebrec 1996; Fernandez-Esparrach 1997; Graziotto 1997; Mehta 1998; Gentilini 1999a; Rossle 2000; Ginès 2002; Sanyal 2003; Narahara 2011; Bari 2012; Singh 2013; Ai 2014; Bureau 2017c; Rai 2017); 25 trials were at unclear risk of bias (Descos 1983; Gines 1987; Mchutchison 1988; Chesta 1990; Ginès 1991; Strauss 1991; Acharya 1992; Hagege 1992; Ljubici 1994; Sola 1994; Ginès 1995; Schaub 1995; Lebrec 1996; Chang 1997; Mehta 1998; Moreau 2002; Singh 2006b; Lata 2007; Raza 2011; Al Sebaey 2012; Amin 2012; Hamdy 2014; Tuttolomondo 2016; Bureau 2017c).

With regards to allocation concealment, twenty-two trials were at low risk of bias (Stanley 1989b; Strauss 1991; Bruno 1992; Hagege 1992; Lebrec 1996; Graziotto 1997; Ginès 2002; Sanyal 2003; Salerno 2004; Romaneli 2006; Singh 2006a; Singh 2006b; Singh 2008; Licata 2009; Narahara 2011; Bari 2012; Singh 2012a; Singh 2013; Ali 2014; Rai 2017; Caraceni 2018; Sola 2018); the remaining 27 trials, which did not provide sufficient information, were at unclear risk of bias (Gregory 1977; Fogel 1981; Descos 1983; Ginès 1987; Salerno 1987; Mchutchison 1988; Chesta 1990; Ginès 1991; Acharya 1992; Ljubici 1994; Sola 1994; Ginès 1995; Schaub 1995; Chang 1997; Fernandez-Esparrach 1997; Mehta 1998; Gentilini 1999a; Rossle 2000; Moreau 2002; Lata 2007; Appenrodt 2008; Raza 2011; Al Sebaey 2012; Amin 2012; Hamdy 2014; Tuttolomondo 2016; Bureau 2017c).

Blinding

With regards to the blinding of patients and healthcare providers, five trials were at low risk of bias (Appenrodt 2008; Raza 2011; Bari 2012; Ali 2014; Sola 2018); 34 trials, which did not provide sufficient information, were at unclear risk of bias (Gregory 1977; Descos 1983; Ginès 1987; Salerno 1987; Mchutchison 1988; Stanley 1988b; Chesta 1990; Ginès 1991; Strauss 1991; Acharya 1992; Bruno 1992; Ljubici 1994; Sola 1994; Ginès 1995; Schaub 1995; Lebrec 1996; Chang 1997; Fernandez-Esparrach 1997; Graziotto 1997; Gentilini 1999a; Rossle 2000; Ginès 2002; Moreau 2002; Sanyal 2003; Narahara 2011; Bari 2012; Singh 2012a; Singh 2013; Ali 2014; Rai 2017; Caraceni 2018). The remaining 10 trials were at high risk of bias (Fogel 1981; Hagege 1992; Mehta 1998; Salerno 2004; Singh 2006a; Singh 2006b; Singh 2008; Singh 2013; Rai 2017; Caraceni 2018).

Incomplete outcome data

With regards to incomplete data, twenty-three trials were at low risk of bias (Gregory 1977; Fogel 1981; Salerno 1987; Stanley 1989b; Bruno 1992; Fernandez-Esparrach 1997; Graziotto 1997; Gentilini 1999a; Rossle 2000; Ginès 2002; Sanyal 2003; Salerno 2004; Romaneli 2006; Singh 2006a; Appenrodt 2008; Singh 2008; Licata 2009; Narahara 2011; Singh 2012a; Singh 2013; Tuttolomondo 2016; Bureau 2017c; Rai 2017); 25 trials were at unclear risk of bias (Descos 1983; Ginès 1987; Mchutchison 1988; Chesta 1990; Ginès 1991; Strauss 1991; Acharya 1992; Hagege 1992; Ljubici 1994; Sola 1994; Ginès 1995; Schaub 1995; Lebrec 1996; Chang 1997; Mehta 1998; Moreau 2002; Singh 2006b; Lata 2007; Raza 2011; Al Sebaey 2012; Amin 2012; Bari 2012; Ali 2014; Hamdy 2014; Tuttolomondo 2016; Bureau 2017c), because it was not clear whether there were post-randomisation dropouts or whether the post-randomisation dropouts were related to the outcomes (if there were post-randomisation dropouts); the remaining trial was at high risk of bias (Sola 2018), as the post-randomisation dropouts were probably related to the intervention and the outcomes.

Selective reporting

Eight trials were at low risk of selective outcome reporting bias (Hagege 1992; Singh 2006a; Singh 2006b; Singh 2008; Singh 2012a; Singh 2013; Ali 2014; Sola 2018), as the important clinical outcomes expected to be reported in such trials were reported; 40 trials were at unclear risk of selective outcome reporting bias (Gregory 1977; Fogel 1981; Descos 1983; Ginès 1987; Salerno 1987; Mchutchison 1988; Chesta 1990; Ginès 1991; Acharya 1992; Ljubici 1994; Sola 1994; Ginès 1995; Schaub 1995; Chang 1997; Fernandez-Esparrach 1997; Mehta 1998; Gentilini 1999a; Rossle 2000; Moreau 2002; Lata 2007; Appenrodt 2008; Raza 2011; Al Sebaey 2012; Amin 2012; Hamdy 2014; Tuttolomondo 2016; Bureau 2017c). As a protocol published prior to recruitment was not available; the remaining trial was at high risk of selective outcome reporting bias (Caraceni 2018), as adverse events were clearly collected, but not reported adequately.

Other potential sources of bias

No other bias was noted in the trials.

Effects of interventions

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

The network plots (where relevant) are available in Figure 1. The inconsistency factor plots (where relevant) are available in Figure 5. The differences in the fixed-effect versus random-effects model, where relevant, are available in Figure 6. The model fit is available in Table 4. The effect estimates are available in Table 5. A formal subgroup analysis was not possible for grade of ascites because the trials that provided this information included only grade 3 ascites or included a mixture of grade 2 and grade 3 ascites, i.e. there were no trials that included grade 2 ascites only. However, there was evidence of inconsistency in some outcomes when all studies were synthesised.
Figure 5. Inconsistency factor plots showing the inconsistency factors for the outcomes with direct and indirect evidence available for one or more comparisons. There was no evidence of inconsistency except for hospital stay. A higher resolution image of this picture is available at: http://doi.org/10.5281/zenodo.3531818. Abbreviations: Alb = Albumin
AldoAnt = Aldosterone antagonists
Fluid = Fluid replacement
LoopD = Loop diuretics
No active treatment = No active treatment
OsmoD = Osmotic diuretics
Paracen = Paracentesis
PVShunt = Peritoneovenous shunt
Reinf = Reinfusion
Vasocons = Systemic vasoconstrictors
Vasodil = Systemic vasodilator
ThiazD = Thiazide diuretics
TIPS = Transjugular intrahepatic portosystemic shunt
Figure 5. (Continued)

Figure 6. Forest plots showing the outcomes for which the random-effects model were different from the fixed-effect model. The more conservative random-effects model was used. In this figure, mortality at maximal follow-up, any adverse events (number of people), and resolution of ascites are shown. Figure 7 shows the remaining outcomes (other decompensation events and length of hospital stay), the other outcomes in which the fixed-effect and random-effects model were different. A higher resolution image of this picture is available at: http://doi.org/10.5281/zenodo.3531818. Abbreviations: Alb = Albumin, AldoAnt = Aldosterone antagonists, Fluid = Fluid replacement, LoopD = Loop diuretics, No active treatment = No active treatment, OsmoD = Osmotic diuretics, Paracen = Paracentesis, PVShunt = Peritoneovenous shunt, Reinf = Reinfusion, Vasocons = Systemic vasoconstrictors, Vasodil = Systemic vasodilator, ThiazD = Thiazide diuretics.
TIPS = Transjugular intrahepatic portosystemic shunt
Figure 6. (Continued)
Figure 7. Forest plots showing the outcomes for which the random-effects model were different from the fixed-effect model. The more conservative random-effects model was used. In this figure, other decompen sation events and length of hospital stay are shown. Figure 6 shows the remaining outcomes (mortality at maximal follow-up, any adverse events (number of people), and resolution of ascites), the other outcomes in which the fixed-effect and random-effects model were different. A higher resolution image of this picture is available at: http://doi.org/10.5281/zenodo.3531818. Abbreviations: Alb = Albumin

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Vasodil = Systemic vasodilator
ThiazD = Thiazide diuretics
TIPS = Transjugular intrahepatic portosystemic shunt

### Other decompen sation events

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Rate Ratio)</th>
<th>SE</th>
<th>IV, Fixed, 95% CI</th>
<th>Rate Ratio IV, Fixed, 95% CI</th>
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</thead>
<tbody>
<tr>
<td>AldoAnt+LoopD+Vascons+Vasodilator</td>
<td>-0.6525 1.4873 0.52 [0.03, 8.24]</td>
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<td>AldoAnt+LoopD+Vasodilator</td>
<td>-0.683 1.4538 0.53 [0.03, 8.08]</td>
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<tr>
<td>AldoAnt+LoopD+Vascons</td>
<td>-0.6399 1.463 0.53 [0.03, 8.26]</td>
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<tr>
<td>Paracen+Vascons</td>
<td>-0.2012 0.8304 0.75 [0.15, 3.64]</td>
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<tr>
<td>AldoAnt+LoopD+PVShunt</td>
<td>-0.18 0.3574 0.84 [0.41, 1.92]</td>
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<tr>
<td>LoopD</td>
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</tr>
<tr>
<td>AldoAnt+LoopD+Paracen+Fluid</td>
<td>0.0339 0.3117 1.03 [0.56, 1.91]</td>
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</tr>
<tr>
<td>TIPS</td>
<td>0.1903 0.122 1.17 [0.92, 1.49]</td>
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<tr>
<td>AldoAnt+LoopD+Alb</td>
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<tr>
<td>AldoAnt+LoopD</td>
<td>0.7078 0.2023 2.03 [1.37, 3.02]</td>
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<td>NoActiveTreatment</td>
<td>1.189 0.7036 3.22 [0.91, 11.76]</td>
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<td>Vascons+Alb</td>
<td>1.321 0.7153 3.75 [0.92, 15.23]</td>
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</table>

### Length of hospital stay

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<th>Study or Subgroup</th>
<th>Mean Difference</th>
<th>SE</th>
<th>IV, Fixed, 95% CI</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
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<td>TIPS</td>
<td>-3.79 4.2791 -0.79 [-12.17, 8.59]</td>
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<td></td>
</tr>
<tr>
<td>LoopD</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AldoAnt+LoopD</td>
<td>13.21 1.2526 13.21 [10.75, 15.67]</td>
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</tbody>
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Treatmen t for ascites in adults with decompen sated liver cirrhosis: a network meta-analysis (Review)

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The 95% credible intervals of the probability ranks were wide and included 0 and 1 in most comparisons for all the primary and secondary outcomes. This was probably because of the sparse data from small trials. Therefore, we did not present the ranking probabilities (in a table), rankograms, and SUCRA plots as we considered that presenting this information would be unhelpful and potentially misleading and would ignore the differences in systematic errors in the trials.

The certainty of evidence was low or very low for all the comparisons. This was because most of the trials included in the comparison were at unclear or high risk of bias for at least one risk of bias domain at the outcome level (downgraded one level) and the sample size was small (downgraded one level). This resulted in low-certainty evidence. In comparisons where the wide credible intervals overlapped significant clinical effect and no effect, we downgraded one more level for imprecision (downgraded one level). There was also evidence of heterogeneity (called inconsistency in the GRADE system; not to be confused with inconsistency in direct and indirect estimates in the context of network meta-analysis) for resolution of ascites and other decomposition events (downgraded one level)

**Mortality at maximal follow-up**

Thirty-four trials (2548 participants) reported mortality at maximal follow-up (Gregory 1977; Fogel 1981; Descos 1983; Gines 1987; Salerno 1987; Chesta 1990; Ginés 1991; Acharya 1992; Hagege 1992; Ljubicic 1994; Sola 1994; Ginès 1995; Lebrecc 1996; Graziotto 1997; Gentilini 1999a; Rossle 2000; Ginès 2002; Moreau 2002; Sanyal 2003; Salerno 2004; Romanelli 2006; Singh 2006a; Singh 2006b; Singh 2008; Licata 2009; Naraheara 2011; Bari 2012; Singh 2012a; Singh 2013; Ali 2014; Bureau 2017c; Rai 2017; Caraceni 2018; Sola 2018). A total of 18 treatments were compared in these trials. Two trials were not connected to the network because they were the only trials for the comparison and had zero events in one of the intervention groups (Acharya 1992; Sola 2018). Therefore, random-effects, network meta-analysis, checking for inconsistency, or subgroup analyses were not applicable.

There was no evidence of differences in any of the direct comparisons for which it was possible to calculate the effect estimates (i.e. there was no statistically significant difference in any of the comparisons).

- Aldosterone antagonists plus paracentesis plus fluid replacement versus aldosterone antagonists plus loop diuretics: OR 0.68 (95% CI 0.11 to 3.83; 1 trial; 40 participants; very low-certainty evidence);
- Aldosterone antagonists plus loop diuretics plus systemic vasodilator versus aldosterone antagonists plus loop diuretics plus systemic vasodilators: OR 0.84 (95% CI 0.46 to 1.55; 1 trial; 173 participants; very low-certainty evidence);
- Aldosterone antagonists plus loop diuretics plus paracentesis plus fluid replacement (0/10; 0%) versus aldosterone antagonists plus loop diuretics (1/11; 9.1%) (1 trial; 21 participants; very low-certainty evidence);
- Paracentesis plus systemic vasodilators (0/84; 0%) versus paracentesis plus fluid replacement (1/85; 1.2%) (4 trials; 169 participants; very low-certainty evidence).

There was no change in the results by using the best-worst and worst-best scenarios for imputing missing data.

Two trials (111 participants) reported serious adverse events (with respect to number of events) (Salerno 1987; Ginés 2002). A total of three treatments were compared in these trials. One trial was not connected to the network because it was the only trial for the comparison and had zero events in one of the intervention groups (Ginés 2002). Only two treatments were compared in the remaining trial (Salerno 1987; 41 participants). Therefore, random-effects, network meta-analysis, checking for inconsistency, or subgroup analyses were not applicable.

There was no evidence of differences in the only direct comparison for which it was possible to calculate the effect estimates (i.e. there was no statistically significant difference): aldosterone antagonists
plus loop diuretics versus paracentesis plus fluid replacement: rate ratio: 1.30 (95% CrI 0.27 to 7.16; 1 trial; 41 participants; very low-certainty evidence; Summary of findings 2). In the remaining comparison, transjugular intrahepatic portosystemic shunt versus paracentesis plus fluid replacement, there were 10 serious adverse events in 35 participants receiving transjugular intrahepatic portosystemic shunt (28.6 serious adverse events per 100 participants) compared to no serious adverse events in 35 participants receiving paracentesis plus fluid replacement (1 trial; 70 participants; very low-certainty evidence).

### Health-related quality of life

One trial (431 participants) reported health-related quality of life (EQ-5D) (Caraceni 2018). For EQ-5D, a higher score indicates better health-related quality of life. A total of two treatments were compared in this trial. Since only one trial reported the outcome, random-effects, network meta-analysis, checking for inconsistency, or subgroup analyses were not applicable. Aldosterone antagonists plus loop diuretics plus albumin had better health-related quality of life than aldosterone antagonists plus loop diuretics plus paracentesis plus fluid replacement: MD 0.06 (95% CrI 0.03 to 0.09; 1 trial; 431 participants; low-certainty evidence). The standard deviation was reported in the trial: therefore, sensitivity analysis of excluding trials in which standard deviations were imputed was not applicable.

### Any adverse events

Eight trials (462 participants) reported any adverse events (with respect to number of people) (Chesta 1990; Hagege 1992; Singh 2006a; Singh 2006b; Singh 2008; Narahara 2011; Bari 2012; Sola 2018). A total of six treatments were compared in these trials. Two trials were not connected to the network because they were the only trials for the comparisons and had zero events in one of the intervention groups (Narahara 2011) or had unconnected treatments (Sola 2018). The network had three connected treatments (6 trials; 229 participants). There were no triangular or quadrangular loops; therefore, inconsistency was not checked. The random-effects model was used because it was more conservative, even though the model fit was similar to the fixed-effect model. The ‘between-study variance’ was 0.37 (95% CrI 0.00 to 10.82).

There was no evidence of differences in any of the direct comparisons or network meta-analysis (i.e. there was no statistically significant difference in any of the comparisons included in the network meta-analysis) (Table 5) (very low-certainty evidence; Summary of findings 2). There was no change in the results by using the best-best and worst-worst scenarios for imputing missing data.

The results of the remaining two comparisons which could not be included in the network meta-analysis are as follows.

- 10 participants among 30 participants (10/30; 33.3%) receiving transjugular intrahepatic portosystemic shunt compared to no participant of 30 participants (0/30; 05) receiving paracentesis plus fluid replacement developed ‘any adverse events’ (1 trial; 60 participants; very low-certainty evidence).
- There was no evidence of differences between systemic vasoconstrictors plus albumin versus no active intervention OR 0.45 (95% CrI 0.05 to 2.61; 1 trial; 173 participants; very low-certainty evidence).

Five trials (314 participants) reported any adverse events (number of events) (Chesta 1990; Bari 2012; Singh 2013; Rai 2017; Sola 2018). A total of 10 treatments were compared in these trials. Two trials were not connected to the network because of unconnected treatments (Rai 2017; Sola 2018). The network had six connected treatments (3 trials; 116 participants). There was no evidence of inconsistency according to model fit and the ‘between-design’ variance 0.17 (95% CrI 0.00 to 3.49). The inconsistency factor plot could not be obtained since there was only one trial for the closed loops and heterogeneity could not be calculated. The fixed-effect model was used because there was only one trial for each of the comparisons.

The following direct comparisons were statistically significant (both comparisons not included in the network meta-analysis because of unconnected treatments):

- Aldosterone antagonists plus loop diuretics plus systemic vasoconstrictors plus paracentesis plus fluid replacement versus aldosterone antagonists plus loop diuretics plus paracentesis plus fluid replacement: rate ratio 0.07 (95% CrI 0.00 to 0.47; 1 trial; 25 participants; low-certainty evidence);
- Systemic vasoconstrictors plus albumin versus no active treatment: rate ratio 1.17 (95% CrI 1.03 to 1.33; 1 trial; 173 participants; low-certainty evidence).

There was no evidence of differences between the treatments in the remaining direct comparisons (i.e. the remaining direct comparisons were not statistically significant) or in the network meta-analysis (Table 5) (very low-certainty evidence; Summary of findings 2). The sensitivity analysis indicated that the different scenarios (best-worst and worst-best scenarios) for imputing missing data showed different interpretation of results; therefore, the results have to be interpreted with caution.

### Liver transplantation at maximal follow-up

Nineteen trials (1568 participants) reported liver transplantation at maximal follow-up (Fogel 1981; Hagege 1992; Graziotto 1997; Rossle 2000; Ginès 2002; Sanyal 2003; Sarzolo 2004; Romanelli 2006; Singh 2006a; Singh 2006b; Singh 2008; Narahara 2011; Bari 2012; Singh 2012a; Singh 2013; Burello 2017a; Rai 2017; Caraceni 2018; Sola 2018). A total of 14 treatments were compared in these trials. Five trials were not connected to the network because they had zero events in both intervention groups (Fogel 1981; Hagege 1992; Singh 2012a; Singh 2013; Rai 2017); three trials were not connected to the network because of unconnected treatments (Romanelli 2006; Caraceni 2018; Sola 2018). The network had four connected treatments (11 trials; 596 participants). There were no triangular or quadrangular loops; therefore, inconsistency was not checked. The fixed-effect model was used because it had equivalent results and model fit to the random-effects model.

There was no evidence of differences in any of the direct comparisons or network meta-analysis (i.e. there was no statistically significant difference in any of the comparisons) (Table 5) (very low-certainty evidence; Summary of findings 2). There was no change in the results by using the best-worst and worst-best scenarios for imputing missing data.

The effect estimates in the comparisons with unconnected treatments were as follows.
• Aldosterone antagonists plus loop diuretics plus albumin versus aldosterone antagonists plus loop diuretics: HR 0.22 (95% CrI 0.01 to 1.99; 1 trial; 100 participants; very low-certainty evidence);
• Aldosterone antagonists plus loop diuretics plus albumin versus aldosterone antagonists plus loop diuretics plus paracentesis plus fluid replacement: HR 1.03 (95% CrI 0.54 to 2.00; 1 trial; 431 participants; very low-certainty evidence);
• Systemic vasoconstrictors plus albumin versus no active intervention: HR 1.44 (95% CrI 0.96 to 2.15; 1 trial; 173 participants; very low-certainty evidence).

The number of people who underwent liver transplantation in the trials with zero events are as follows.

- Aldosterone antagonists plus loop diuretics (0/27; 0%) versus paracentesis plus fluid replacement (0/26; 0%) (1 trial; 53 participants; very low-certainty evidence);
- Aldosterone antagonists plus loop diuretics (0/61; 0%) versus loop diuretics (0/29; 0%) (1 trial; 90 participants; very low-certainty evidence);
- Aldosterone antagonists plus loop diuretics (0/35; 0%) versus aldosterone antagonists plus loop diuretics (0/35; 0%) (2 trials; 70 participants; very low-certainty evidence);
- Aldosterone antagonists plus loop diuretics (0/35; 0%) versus aldosterone antagonists plus loop diuretics (0/15; 0%) (1 trial; 30 participants; very low-certainty evidence);
- Aldosterone antagonists plus loop diuretics plus systemic vasoconstrictors plus systemic vasodilator (0/15; 0%) versus aldosterone antagonists plus loop diuretics (0/15; 0%) (1 trial; 30 participants; very low-certainty evidence);
- Aldosterone antagonists plus loop diuretics plus systemic vasoconstrictors plus systemic vasodilator (0/15; 0%) versus aldosterone antagonists plus loop diuretics (0/15; 0%) (1 trial; 30 participants; very low-certainty evidence);
- Aldosterone antagonists plus loop diuretics plus systemic vasoconstrictors plus systemic vasodilator (0/15; 0%) versus aldosterone antagonists plus loop diuretics plus systemic vasoconstrictors (0/15; 0%) (1 trial; 30 participants; very low-certainty evidence);
- Aldosterone antagonists plus loop diuretics plus systemic vasoconstrictors plus systemic vasodilator (0/15; 0%) versus aldosterone antagonists plus loop diuretics plus systemic vasoconstrictors (0/15; 0%) (1 trial; 30 participants; very low-certainty evidence);
- Aldosterone antagonists plus loop diuretics plus systemic vasoconstrictors plus systemic vasodilator (0/15; 0%) versus aldosterone antagonists plus paracentesis plus fluid replacement (0/13; 0%) versus aldosterone antagonists plus loop diuretics plus paracentesis plus fluid replacement (0/12; 0%) (1 trial; 25 participants; very low-certainty evidence);
- Aldosterone antagonists plus loop diuretics plus systemic vasoconstrictors plus systemic vasodilator (0/15; 0%) versus aldosterone antagonists plus loop diuretics plus systemic vasoconstrictors (0/15; 0%) (1 trial; 30 participants; very low-certainty evidence);
- Aldosterone antagonists plus loop diuretics plus systemic vasoconstrictors plus systemic vasodilator (0/15; 0%) versus aldosterone antagonists plus loop diuretics plus systemic vasoconstrictors (0/15; 0%) (1 trial; 30 participants; very low-certainty evidence);
- Aldosterone antagonists plus loop diuretics plus systemic vasoconstrictors plus systemic vasodilator (0/15; 0%) versus aldosterone antagonists plus loop diuretics plus systemic vasoconstrictors (0/15; 0%) (1 trial; 30 participants; very low-certainty evidence).

Resolution of ascites at maximal follow-up

None of the trials reported symptomatic resolution of ascites (for example, resolution of shortness of breath) at maximal follow-up. Twenty trials (1217 participants) reported resolution of ascites (by ultrasound) at maximal follow-up (Gregory 1977; Descos 1983; Salerno 1987; Chesta 1990; Strauss 1991; Hagege 1992; Lebrec 1996; Fernandez-Esparrach 1997; Graziotto 1997; Gentili 1999a; Ginès 2002; Sanyal 2003; Salerno 2004; Romanelli 2006; Licata 2009; Narahara 2011; Singh 2012a; Singh 2013; Bureau 2017c; Rai 2017). A total of 14 treatments were compared in these trials. Two trials were not connected to the network because they were the only trials for the comparison and had zero events in one of the intervention groups (Graziotto 1997; Rai 2017) and another trial was not connected because of unconnected treatments. One more trial had four arms with zero events in all four arms (Singh 2013). One comparison could be included in the network meta-analysis as there were some events in the remaining trials of the same comparison, but the other comparisons could not be included (Singh 2013). The network had nine connected treatments (17 trials; 1007 participants). There were no triangular or quadrangular loops; therefore, inconsistency was not checked. The random-effects model was used because it was more conservative and had better model fit. The ‘between-study variance’ was 2.60 (95% CrI 0.68 to 12.29).

The following direct comparisons which could be estimated were in favour of:

- Transjugular intrahepatic portosystemic shunt versus paracentesis plus fluid replacement: HR 8.37 (95% CrI 1.97 to 62.68; 6 trials; 392 participants; very low-certainty evidence);
- Aldosterone antagonists plus paracentesis plus fluid replacement versus paracentesis plus fluid replacement alone: HR 30.63 (95% CrI 5.06 to 692.98; 1 trial; 36 participants; low-certainty evidence);
- No active treatment versus aldosterone antagonists plus loop diuretics: HR 0.15 (95% CrI 0.04 to 0.43; 1 trial; 43 participants; low-certainty evidence) (i.e. aldosterone antagonists plus loop diuretics versus no active treatment: HR 6.67 (95% CrI 2.33 to 25));
- Loop diuretics versus aldosterone antagonists plus loop diuretics plus paracentesis plus fluid replacement: HR 1.90 (95% CrI 1.03 to 3.76; 1 trial; 84 participants; low-certainty evidence).

There was no evidence of differences between the treatments in the remaining direct comparisons (i.e. the remaining direct comparisons were not statistically significant) (Table 5) (very low-certainty evidence). In the network meta-analysis, the following comparisons were statistically significant:

- Transjugular intrahepatic portosystemic shunt versus paracentesis plus fluid replacement: HR 9.44 (95% CrI 1.93 to 62.68) (similar effect as in direct comparison; very low-certainty evidence).

There was no evidence of differences between the treatments in the remaining comparisons in the network meta-analysis (Table 5) (very low-certainty evidence; Summary of findings 2). There was no change in the results by using the best-worst and worst-best scenarios for imputing missing data.

The effect estimates in the comparisons with unconnected treatments were as follows.

- Aldosterone antagonists versus paracentesis plus reinfusion: HR 1.11 (95% CrI 0.69 to 1.79; 1 trial; 131 participants; very low-certainty evidence).

The number of people who had resolution of ascites in the trials with zero events are as follows.
• Paracentesis plus rein infusion (2/12; 16.7%) versus paracentesis plus fluid replacement (0/12; 0%) (1 trial; 24 participants; very low-certainty evidence)

• Aldosterone antagonists plus loop diuretics plus systemic vasconstrictors plus systemic vasodilator (0/15; 0%) versus aldosterone antagonists plus loop diuretics plus paracentesis plus fluid replacement (0/12; 0%) (1 trial; 30 participants; very low-certainty evidence)

• Aldosterone antagonists plus loop diuretics plus systemic vasodilator (0/15; 0%) versus aldosterone antagonists plus loop diuretics (0/15; 0%) (1 trial; 30 participants; very low-certainty evidence)

• Aldosterone antagonists plus loop diuretics plus systemic vasodilator plus systemic vasocconstrictors plus paracentesis plus fluid replacement (5/15; 38.5%) versus aldosterone antagonists plus loop diuretics plus paracentesis plus fluid replacement (0/12; 0%) (1 trial; 25 participants; very low-certainty evidence)

• Aldosterone antagonists plus loop diuretics plus systemic vasodilator plus systemic vasodilator (0/15; 0%) versus aldosterone antagonists plus loop diuretics plus systemic vasocconstrictors (0/15; 0%) (1 trial; 30 participants; very low-certainty evidence)

• Aldosterone antagonists plus loop diuretics plus systemic vasodilator (0/15; 0%) versus aldosterone antagonists plus loop diuretics plus systemic vasocconstrictors (0/15; 0%) (1 trial; 30 participants; very low-certainty evidence)

Other features of decompen sation at maximal follow-up


The number of decompen sation events in the trials with zero events are as follows.

• Aldosterone antagonists plus loop diuretics versus paracentesis plus fluid replacement: rate ratio 2.04 (95% CrI 1.39 to 3.08; 4 trials; 242 participants; very low-certainty evidence) (i.e. paracentesis plus fluid replacement versus aldosterone antagonists plus loop diuretics: rate ratio 0.49 (95% CrI 0.72 to 0.32))

• Aldosterone antagonists plus loop diuretics plus paracentesis plus fluid replacement versus aldosterone antagonists plus loop diuretics: rate ratio 0.48 (95% CrI 0.29 to 0.77; 2 trials; 102 participants; low-certainty evidence)

• Aldosterone antagonists plus paracentesis plus fluid replacement versus aldosterone antagonists plus loop diuretics plus systemic vasocconstrictors: 7/12 (0.6 other decompen sation events per participant) versus 0/13 (no decompen sation events per participant) (1 trial; 15 participants).

There was no evidence of differences between the treatments in the remaining direct comparisons (i.e. the remaining direct comparisons were not statistically significant (Table 5) (very low-certainty). In the network meta-analysis, the following comparisons were in favour of:

• Aldosterone antagonists plus loop diuretics versus paracentesis plus fluid replacement: rate ratio 2.04 (95% CrI 1.37 to 3.10) (i.e. paracentesis plus fluid replacement versus aldosterone antagonists plus loop diuretics: rate ratio 0.49 (95% CrI 0.73 to 0.32))

• Aldosterone antagonists plus loop diuretics versus paracentesis plus fluid replacement versus aldosterone antagonists plus loop diuretics plus systemic vasodilator: rate ratio 0.51 (95% CrI 0.32 to 0.80)

• Transjugular intrahepatic portosystemic shunt versus aldosterone antagonists plus loop diuretics: rate ratio 0.57 (95% CrI 0.35 to 0.92)

• Loop diuretics versus aldosterone antagonists plus loop diuretics: rate ratio 0.47 (95% CrI 0.22 to 0.96)

• Aldosterone antagonists plus loop diuretics plus peritoneovenous shunt versus aldosterone antagonists plus loop diuretics: rate ratio 0.41 (95% CrI 0.23 to 0.73)

• Systemic vasocconstrictors plus albumin versus aldosterone antagonists plus loop diuretics plus peritoneovenous shunt: rate ratio 4.65 (95% CrI 1.06 to 20.84) i.e. aldosterone antagonists plus loop diuretics plus peritoneovenous shunt versus systemic vasocconstrictors plus albumin: rate ratio: 0.22 (95% CrI 0.05 to 0.94).

There was no evidence of differences between the treatments in the remaining comparisons in the network meta-analysis (Table 5) (very low-certainty evidence; Summary of findings 2).

Length of hospital stay (days)

Fifteen trials (1086 participants) reported length of hospital stay (days) (all admissions until maximal follow-up) (Fogel 1981; Descos 1983; Gines 1987; Chesta 1990; Ginès 1991; Hagege 1992; Ginès 1995; Schaub 1995; Gentilini 1999a; Rossle 2000; Moreau 2002; Salerno 2004; Licata 2009; Tuttolomondo 2016;
Bureau 2017c). A total of 10 treatments were compared in these trials. One trial was not connected to the network because it had treatments unconnected to network (Descos 1983). The network had eight connected treatments. There was evidence of inconsistency according to the ‘between-design’ variance 11.04 (95% CrI 0.05 to 24.30) and inconsistency factor, but not by model fit; therefore, there is uncertainty in the validity of NMA results: direct comparisons are more reliable. The random-effects model was used because it had better model fit. The ‘between-study variance’ was 20.10 (95% CrI 8.86 to 24.79).

The following direct comparisons were in favour of:

- Aldosterone antagonists plus loop diuretics versus paracentesis plus fluid replacement: MD 14.00 days (95% CrI 9.19 to 18.52; 4 trials; 218 participants; low-certainty evidence), i.e. paracentesis plus fluid replacement versus aldosterone antagonists plus loop diuretics versus paracentesis (MD -14.00 days (95% CrI -18.52 to -9.19)
- Aldosterone antagonists plus loop diuretics plus albumin versus aldosterone antagonists plus loop diuretics: MD -9.28 days (95% CrI -14.11 to -4.40; 1 trial; 126 participants; low-certainty evidence).

There was no evidence of differences between the treatments in the remaining direct comparisons (i.e. the remaining direct comparisons were not statistically significant) (Table 5). In the network meta-analysis, the following comparisons were in favour of:

- Aldosterone antagonists plus loop diuretics versus paracentesis plus fluid replacement: MD 11.81 days (95% CrI 6.92 to 16.67; low-certainty evidence), i.e. paracentesis plus fluid replacement versus aldosterone antagonists plus loop diuretics versus paracentesis (MD -11.81 days (95% CrI -16.67 to -6.92)
- Paracentesis plus systemic vasoconstrictors versus aldosterone antagonists plus loop diuretics: MD -11.60 days (95% CrI -21.67 to -1.68; low-certainty evidence)
- Transjugular intrahepatic portosystemic shunt versus aldosterone antagonists plus loop diuretics: MD -17.25 days (95% CrI -28.47 to -6.17; low-certainty evidence).

There was no evidence of differences between the treatments in the remaining comparisons in the network meta-analysis (Table 5). There was no imputation of mean or standard deviation in the trials. Therefore, sensitivity analysis excluding trials in which mean or standard deviation were to be imputed was not applicable.

**Work days lost**

None of the trials reported work days lost.

**Treatment costs**

Four trials (150 participants) reported treatment costs (Mehta 1998; Singh 2006a; Singh 2008; Hamdy 2014). We used an international exchange rate based on purchasing power parities (PPP) to convert cost estimates to USA dollars (USD), and we used the gross domestic product (GDP) deflators (or implicit price deflators for GDP) to convert cost estimates to 2018 USD using PPP conversion rates and GDP deflator values available from the International Monetary Fund in the World Economic Outlook Database (www.imf.org/external/data.htm (accessed in July 2019)).

A total of three treatments were compared in the four trials. All the trials were connected to the network (after imputation of standard deviation for one trial). There were no triangular or quadrangular loops; therefore, inconsistency was not checked. The random-effects model was used because of the model fit and because the random-effects model was the more conservative model. The ‘between-study variance’ was 2,458,624 (95% CrI 265,431 to 64,689,849). Given the extremely high between-study variance, we have presented the results in a table, without meta-analysing the results.

Treatment costs for paracentesis plus systemic vasoconstrictors was lower than that for paracentesis plus fluid replacement in all the three trials that reported this information (Table 6). For the other comparison, paracentesis plus reinfusion versus paracentesis plus fluid replacement, the standard deviation was not reported; therefore, it was not clear whether there were differences in treatment costs between the two interventions.

**Subgroup analysis**

Data were sufficient to perform only the following subgroup analysis: duration of follow-up (short-term, medium-term, and long-term). There were no subgroup differences for any of the outcomes where there were at least two different subgroups represented in the analyses.

There were insufficient data for the remaining subgroup analyses or only one subgroup was represented in the analyses. Although a formal test for subgroup differences was not relevant for grade of ascites, as the trials included either only ascites 3 or a mixture of ascites 2 and ascites 3 (or did not provide information on the grade of ascites), we have presented the subgroup estimates of grade 3 ascites only in Table 7, when possible. Similarly, we have presented the results for recurrent and refractory ascites only in Table 8, when possible. Some comparisons became statistically nonsignificant, as could be expected when fewer than 50% trials were included for the analysis, but there were no major differences that would have resulted in alterations in the overall interpretation of the results.

**Sensitivity analysis**

All sensitivity analyses were presented under the outcome.

**Assessment of reporting biases**

Since there was no meaningful way in which to rank these studies (i.e. there was no specific change in the risk of bias in the studies, sample size, or the control group used over time), we were unable to perform the comparison-adjusted funnel plot. However, important outcomes such as all-cause mortality and adverse events were not reported in some trials indicating the possibility of reporting biases.

**D I S C U S S I O N**

**Summary of main results**

We performed a systematic review and network meta-analysis of all the treatments available for ascites in people with decompensated liver cirrhosis. A total of 49 trials, including a total of 3521 participants, were included in this review. A total of 21 interventions were compared in these trials. A total of 42 trials including 2870 participants were included for one or more outcomes of this review (Gregory 1977; Fogel 1981; Descos 1983; Gines 1987; Salerno 1987;
Overall, 36.8% of the trial participants who received the standard treatment of paracentesis plus fluid replacement died during the follow-up period ranging from one week to 11 months. There was no evidence of differences in mortality or serious adverse events in any of the direct comparisons or network meta-analysis. However, the credible intervals were wide, and clinically important differences in mortality or serious adverse events cannot be ruled out.

The health-related quality of life was reported in only one trial comparing aldosterone antagonists plus loop diuretics plus albumin versus aldosterone antagonists plus loop diuretics plus paracentesis plus fluid replacement. The mean difference was 0.06. The minimum clinically important difference for EQ-5D in people with cirrhosis is not known. In other conditions, a difference of 0.04 to 0.20 is clinically important [Asher 2018; Sims 2018; Hoehle 2019; Kato 2019]. Therefore, it is not clear whether the difference of 0.06 with aldosterone antagonists plus loop diuretics plus albumin and aldosterone antagonists plus loop diuretics plus paracentesis plus fluid replacement is clinically important. It should also be pointed out that there is no information on whether this difference was reproducible, as this was the only trial for this comparison. Therefore, there is considerable uncertainty about the difference between the groups.

There were differences between the different groups in 'any' adverse events, but none of the comparisons in which there were differences could be considered as 'standard of care'; therefore the implications of these findings are not clinically relevant. The resolution of ascites was greater with transjugular intrahepatic portosystemic shunt versus paracentesis plus fluid replacement. While the resolution of ascites was greater by adding aldosterone antagonists to paracentesis plus fluid replacement, this was based on a single small trial of high risk of bias (sample size: 36 participants), indicating that there is high uncertainty about this issue.

The number of other decompenation events and the length of hospital stay were more with aldosterone antagonists plus loop diuretics versus paracentesis plus fluid replacement. In the network meta-analysis, a number of other treatments including transjugular intrahepatic portosystemic shunt had fewer other decompenation events and shorter length of hospital stay than aldosterone antagonists plus loop diuretics without paracentesis. Therefore, aldosterone antagonists plus loop diuretics without paracentesis seems to be the worst among the common treatments compared in this review.

Treatment costs with paracentesis plus systemic vasoconstrictors was lower than that for paracentesis plus fluid replacement in all three trials that reported this information, although the between study variance was extremely high and meta-analysis was not performed. Furthermore, in the presence of considerable uncertainty in benefits and harms of different treatments, treatment costs alone cannot determine whether one intervention is better than another.

The weighted median mortality in the paracentesis plus fluid replacement group was 36.8% in 11 months. The sample size required to detect a relative risk reduction of 20% in the experimental group, with type I error of 5%, and type II error of 20%, is 1282 participants. Although approximately 20% of people with liver cirrhosis develop ascites, the majority may be grade 2 and may be amenable to treatment with diuretics. However, a significant proportion may be grade 3, refractory, or recurrent. There is paucity of information on the incidence or prevalence of grade 3 refractory or recurrent ascites. One small study in Tunisia estimated that about 20% of all hospital admissions in people with cirrhosis was due to refractory ascites [Ennaifer 2014]. If even 5% of hospital admissions due to liver cirrhosis relate to grade 3 refractory or recurrent ascites in UK, a trial like the stipulated one, is very much feasible.

There were approximately 44 other decompenation events per 100 participants in the paracentesis plus fluid replacement group. In addition to causing death, decomposition usually results in hospital admissions and significant costs to the health service. Therefore, any decompenation event is another possible primary outcome. Assuming that the variance was equal to the mean in an ordinary Poisson distribution commonly used to analyse recurrent events (that happen independently, although this is a questionable assumption), for a 20% relative risk reduction in the experimental group, with type I error of 5%, and type II error of 20%, the sample size required in a trial using any decompenation event is 786 participants.

In terms of the interventions to be compared in future trials, paracentesis plus fluid replacement was the commonest intervention in this review. So, it should be considered as one of the interventions in future trials. Aldosterone antagonists plus loop diuretics instead of paracentesis plus fluid replacement appears to increase the other decompenation events and length of hospital stay (and paracentesis or TIPS may be required in people who do not respond to diuretics), although this is based on trials at high risk of bias. However, adding diuretics to paracentesis plus fluid replacement is one of the options for intervention (particularly, because this is currently the recommended treatment by AASLD and EASL, although there is no evidence to consider this superior to paracentesis plus fluid replacement alone); transjugular intrahepatic portosystemic shunt may be another option. Such shunts may be effective in preventing variceal rebleeding [Qi 2016], but they may increase hepatic encephalopathy [Saab 2006; Zhou 2019]. Therefore, the impact of decompenation events on quality of life and ability to perform daily activities, social activities, and work should be evaluated as part of future trials.

Overall completeness and applicability of evidence

There did not seem to be any restrictions based on the etiology or the presence of other features of decomposition in the trials that provided this information. Therefore, the results of the study are applicable in people with cirrhosis resulting from varied aetiologies having ascites. However, it appears that the trials included mainly people with grade 3, refractory, or recurrent ascites. Therefore, the findings of this review are applicable only to such people. There is currently no information on which diuretic is better for people with cirrhosis and grade 2 ascites which is not refractory.
or recurrent. Therefore, feasible randomised clinical trials which look at the potential effects of different diuretics are necessary. The incidence of grade 3, recurrent, or refractory ascites may be a suitable outcome for such a trial.

Furthermore, 38 trials excluded participants with active other decomposition features such as active variceal bleeding, hepatorenal syndrome, and grade III or grade IV hepatic encephalopathy, while the remaining 11 trials did not report whether they included any participants with active other decomposition features. Therefore, the results of the review are only applicable to people without active other decomposition events. Accordingly, more evidence on ascites treatment seems to be needed in populations with ascites and other signs of decomposition.

**Quality of the evidence**

The overall certainty (quality) of evidence was very low. One of the main reasons for the very low certainty of evidence was the unclear or high risk of bias in all the trials. It is possible to perform trials at low risk of bias in certain comparisons: randomisation can be performed using standard methods, for example, web-based central randomisation; an intention-to-treat analysis can be performed; and a protocol should be published prior to recruitment. However, blending of healthcare providers and participants may not be possible if TIPS is used as one of the interventions. It is possible to achieve blinding with careful planning for other comparisons, for example by using placebos for diuretics if the trial was about adding diuretics to paracentesis plus fluid replacement. Outcome assessor blinding can be achieved for all comparisons.

Another major reason for the very low certainty of evidence was imprecision: the trials had small sample sizes and the credible intervals overlapped clinically significant benefits and clinically significant harms for most comparisons. Therefore, future trials should be adequately powered with sample sizes as described above.

We used clinical outcomes; therefore, there is no issue of indirectness due to outcomes. There was no suggestion that the potential effect modifiers were systematically different across comparisons (i.e. there was no concern about the transitivity assumption). While there was evidence of inconsistency according to the model fit, inconsistency in factor plots, and between-design variance, an analysis of a subset of participants with grade 3 ascites (when possible) did not result in major differences in the interpretation of findings. Similarly, an analysis of a subset of participants with refractory or recurrent ascites (when possible) did not result in major differences in the interpretation of findings. However, one cannot rule out inconsistency (‘incoherence’ according to GRADE terminology).

There was no meaningful way to rank these studies (i.e. there was no specific change in the risk of bias in the studies, sample size, or the control group used over time); we have completed a thorough search for studies on effectiveness. However, different sets of trials were included for different outcomes: only 30% to 70% of the trials reported mortality, serious adverse events, liver transplantation, resolution of ascites, and other decomposition events, even though these outcomes would have been routinely measured in trials of this nature. This may suggest reporting bias for these outcomes.

**Potential biases in the review process**

We selected a range of databases to search without using any language restrictions and conducted the network meta-analysis according to NICE DSU guidance. In addition, we have analysed using the fixed-effects model and random-effects model and assessed and reported inconsistency whenever possible. These are the strengths of the review process.

We have excluded studies that compared variations in duration or dose in the different interventions. Hence, this review does not provide information on whether one variation is better than another. Another major limitation of this review was the paucity of data: the trials were small. This paucity of data decreases the confidence in the results.

All of the network meta-analyses included only sparse data from trials, most of which were at high risk of bias. However, the potential effect modifiers in the trials that reported them were broadly similar across comparisons. The results of direct comparisons and indirect comparisons were similar for the most outcomes where we could assess this. Therefore, the concern about the transitivity assumption was low. However, this cannot be ruled out.

We included only randomised clinical trials, which were known to focus mostly on benefits and did not collect and report harms in a detailed manner. A significant effort was required to identify nonrandomised studies that reported on harm. It was also challenging to assess the risk of bias in those studies. If future randomised clinical trials are powered on mortality or other decomposition events, a systematic review on adverse events from observational studies will likely be unnecessary.

**Agreements and disagreements with other studies or reviews**

This is the first network meta-analysis on the topic. There have been several systematic reviews and direct comparisons of different interventions for treating people with cirrhosis and ascites.

Guo and colleagues assessed the role of midodrine in people with cirrhosis and ascites (Guo 2016). They did not find any benefits of midodrine in terms of clinical outcomes despite improving surrogate outcomes such as response rates and plasma renin activity (Guo 2016). They also found that midodrine could be potentially harmful when used as a substitute for fluid replacement after paracentesis (Guo 2016). We did not find any evidence of benefit or harms of systemic vasoconstrictors in people with ascites and cirrhosis. This may be because of the different methods used for meta-analysis: we have considered that the co-interventions such as the diuretics or vasodilators used could influence the effect of systemic vasoconstrictors and treated these as different ‘nodes’ in the network meta-analysis, while Guo and colleagues combined the trials despite differences in diuretics or vasodilators used. The method used for meta-analysis (Bayesian versus frequentist method) could be an additional reason for the difference.

Simonetti and colleagues assessed the role of different fluids after paracentesis and found no evidence of difference in outcomes between different fluids used after paracentesis including reinfusion of ascitic fluid (Simonetti 2019). While we are
unable to comment on different fluids after paracentesis since we did not explore this, we agree that there was no evidence of differences between paracentesis plus reinfusion and paracentesis plus fluid replacement.

Saab and colleagues found that TIPS was more effective in the resolution of ascites than paracentesis and fluid replacement, but found that the incidence of hepatic encephalopathy was increased (Saab 2006). However, they did not find evidence of differences in other decomposition events. Our network meta-analysis also demonstrated that TIPS may be more effective in the resolution of ascites than paracentesis plus fluid replacement. We did not analyse the individual decomposition events separately. Therefore, we are unable to comment on whether hepatic encephalopathy was increased with TIPS compared to paracentesis plus fluid replacement.

A U T H O R S ' C O N C L U S I O N S

Implications for practice

Based on very low-certainty evidence, there is considerable uncertainty about whether other interventions decrease mortality, adverse events, or liver transplantation compared to paracentesis plus fluid replacement in people with decompensated liver cirrhosis and ascites. Based on very low-certainty evidence, transjugular intrahepatic portosystemic shunt and adding aldosterone antagonists to paracentesis plus fluid replacement may increase the resolution of ascites compared to paracentesis plus fluid replacement. Based on very low-certainty evidence, aldosterone antagonists plus loop diuretics may increase the decompensation rate compared to paracentesis plus fluid replacement.

Implications for research

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

Study design: parallel, randomised clinical trial

Participants: people with liver cirrhosis and grade 3 or diuretic-refractory ascites

Interventions/control: transjugular intrahepatic portosystemic shunt versus diuretics plus paracentesis plus fluid replacement versus paracentesis plus fluid replacement.

Outcomes:

Primary outcome: medium-term mortality (one-year all-cause mortality)

Secondary outcomes: health-related quality of life, decompensation events, adverse events, resolution of ascites, and resource utilisation measures including length of hospital stay, costs

Minimum length of follow-up: one year

Sample size:

For a simple two-arm parallel randomised clinical trial, the sample size required to detect or reject a relative risk reduction of 20% in the experimental group from the control group proportion of 36.8% mortality, with type I error of 5%, and type II error of 20%, 1282 participants are required.

Other aspects:

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

A C K N O W L E D G E M E N T S

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Danish State and the Copenhagen Trial Unit Disclaimer

The views and opinions expressed in this Cochrane Review are those of the review authors and do not necessarily reflect those of the Danish State or the Copenhagen Trial Unit.
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Ennaifer 2014

EuroQol 2018

Fagan 2014

Fleming 2008

Ginès 2009

Guo 2016

**Gurusamy 2019**


**Guyatt 2011**


**Higgins 2011**


**Higgins 2012**


**Hoehle 2019**


**Hutton 2015**


**ICH-GCP 1997**


**Jackson 2014**


**Kato 2019**


**Kim 2006**


**Kjaergard 2001**


**Les 2010**


**Lu 2006**


**McPherson 2016**


**Merion 2010**


**Mills 2012**


**Moher 1998**


**Mokdad 2014**


**Moore 2003**


**Moore 2013**

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

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NCBI 2018a

NCBI 2018b

Newell 1992

Optum 2018

Orr 2014

Puhan 2014

Qi 2016

Ratib 2015

Read 1972

Royle 2003

Runyon 2013

Saab 2006

Salanti 2011

Salanti 2012

Savović 2012a

Savović 2012b

Savović 2018

Scaglione 2015

Schulz 1995

Schulz 2010

Setiawan 2016
**Severini 1993**

**Simonetti 2019**

**Sims 2018**

**Stata/SE 15.1 [Computer program]**
StataCorp LLC. Stata/SE. Version 15.1. Texas, USA: StataCorp LLC, 2017.

**Tsocatzis 2014**

**Tsocatzis 2017**

**Turner 2012**

**References to other published versions of this review**

**Gurusamy 2018**

* Indicates the major publication for the study

**CHARACTERISTICS OF STUDIES**

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

**Acharya 1992**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised clinical trial</th>
</tr>
</thead>
</table>
| Participants | Country: India  
Period of recruitment: 1988-1989  
Number randomised: 40  
Post-randomisation dropouts: not stated  
Revised sample size: 40  
Average age (years): 43  
Females: 10 (25.0%)  
Ascites grade 2: 0 (0.0%)  
Ascites grade 3: 40 (100.0%)  
Refractory or recurrent ascites: 34 (85.0%)  
Alcohol-related cirrhosis: 11 (27.5%)  
Viral-related cirrhosis: 19 (47.5%) |

**Van Valkenhoef 2012**

**Williams 2014**

**Wood 2008**

**Yepes-Nunez 2019**

**Zhou 2019**

**Treatment for ascites in adults with decompensated liver cirrhosis: a network meta-analysis (Review)**

Copyright © 2020 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
### Acharya 1992 (Continued)

Autoimmune disease-related cirrhosis: not stated  
Other causes for cirrhosis: 10 (25.0%)  
Prophylactic antibiotics for subacute bacterial peritonitis: not stated

#### Exclusion
- 1. Other features of decompensation  
- 2. Cardiac, renal, or respiratory diseases  
- 3. Hyponatraemia

#### Interventions

<table>
<thead>
<tr>
<th>Group 1: Aldosterone antagonists plus paracentesis plus fluid replacement (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Further details: Spironolactone 100 mg/day after resolution of ascites + large volume paracentesis 5 litres daily and supported by dextran (30% to 50% of ascitic fluid removed)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group 2: Aldosterone antagonists plus loop diuretics (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Further details: Spironolactone 200 mg/day + furosemide 40 mg/day doubled after third day for 15 days (route not stated)</td>
</tr>
</tbody>
</table>

#### Outcomes

Outcomes reported: mortality at maximal follow-up, serious adverse events (number of people), other features of decompensation at maximal follow-up  
Follow-up (months): 0.5

#### Notes

Source of funding: not stated  
Trial name/trial registry number: not stated  
Attempts were made to contact the authors in November 2018.

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
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<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td></td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td></td>
</tr>
</tbody>
</table>
| Blinding of participants and personnel (performance bias)  
All outcomes | Unclear risk |
| Blinding of outcome assessment (detection bias)  
All outcomes | Unclear risk |
| Incomplete outcome data (attrition bias)  
All outcomes | Unclear risk |
| Selective reporting (reporting bias) | Unclear risk |
| Other bias | Low risk |

### Al Sebaey 2012

Methods  
Randomised clinical trial
Al Sebaey 2012 (Continued)

**Participants**
- Country: Egypt
- Period of recruitment: not stated
- Number randomised: 125
- Post-randomisation dropouts: not stated
- Revised sample size: 125
- Average age (years): 50
- Females: 56 (44.8%)
- Ascites grade 2: 0 (0.0%)
- Ascites grade 3: 125 (100.0%)
- Refractory or recurrent ascites: not stated
- Alcohol-related cirrhosis: not stated
- Viral-related cirrhosis: not stated
- Autoimmune disease-related cirrhosis: not stated
- Other causes for cirrhosis: not stated
- Prophylactic antibiotics for subacute bacterial peritonitis: not stated

**Exclusion**
1. Hypertension
2. Cardiac or respiratory disease
3. Other features of decompensation

**Interventions**
- **Group 1: Paracentesis plus systemic vasoconstrictors (n = 50)**
  - Further details: Large volume paracentesis (details not available) + terlipressin 1 mg at onset of LVP, 8 hours, and 16 hours or midodrine 5 to 10 mg orally TDS for 3 days
- **Group 2: Paracentesis plus fluid replacement (n = 75)**
  - Further details: Large volume paracentesis (no further details) + HES or low dose albumin or high dose albumin

**Outcomes**
- None of the outcomes of interest were reported.

**Notes**
- Source of funding: not stated
- Trial name/trial registry number: not stated
- Attempts were made to contact the authors in November 2018.

**Risk of bias**

<table>
<thead>
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<th>Authors’ judgement</th>
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<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Comment: this information was not available.</td>
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<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Comment: this information was not available.</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Unclear risk</td>
<td>Comment: this information was not available.</td>
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<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Comment: this information was not available.</td>
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<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Unclear risk</td>
<td>Comment: this information was not available.</td>
</tr>
</tbody>
</table>
Al Sebaey 2012 (Continued)

Selective reporting (reporting bias) | Unclear risk | Comment: pre-published protocol was not available.
---|---|---
Other bias | Low risk | Comment: no other bias noted

Ali 2014

Methods
Randomised clinical trial

Participants
Country: Egypt
Period of recruitment: 2012
Number randomised: 66
Post-randomisation dropouts: 6 (9.1%)
Revised sample size: 60
Reasons for post-randomisation dropouts: lost to follow-up
Average age (years): 57
Females: not stated
Ascites grade 2: 0 (0.0%)
Ascites grade 3: 60 (100.0%)
Refractory or recurrent ascites: not stated
Alcohol-related cirrhosis: not stated
Viral-related cirrhosis: not stated
Autoimmune disease-related cirrhosis: not stated
Other causes for cirrhosis: not stated
Prophylactic antibiotics for subacute bacterial peritonitis: not stated
Exclusion
1. Acute or chronic renal failure
2. Hypertension
3. Heart diseases
4. Other features of decompensation
5. Hepatocellular carcinoma (HCC)
6. Portal vein thrombosis

Interventions
Group 1: Systemic vasoconstrictors (n = 30)
Further details: Midodrine (dose not clear, but probably 2.5 mg TDS) for 2 weeks
Group 2: No active treatment (n = 30)
Further details: placebo

Outcomes
Outcomes reported: mortality at maximal follow-up, serious adverse events (number of people)
Follow-up (months): 0.5

Notes
Source of funding (quote): "No funding (author replies)"
Trial name/trial registry number: not stated
Attempts were made to contact the authors in November 2018.

Risk of bias

<table>
<thead>
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<th>Bias</th>
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<tr>
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<td>Quote: &quot;Randomisation procedures were automated, using centrally-allocated computer-generated random numbers&quot;.</td>
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<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;Randomisation procedures were automated, using centrally-allocated computer-generated random numbers&quot;.</td>
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</table>
### Ali 2014 (Continued)

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<tr>
<th>Bias</th>
<th>Authors' judgement</th>
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</thead>
<tbody>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk</td>
<td>Quote: &quot;a double-blind, placebo-controlled, randomized trial&quot;</td>
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<tr>
<td>All outcomes</td>
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</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;a double-blind, placebo-controlled, randomized trial&quot;</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Unclear risk</td>
<td>Comment: there was an equal number of dropouts in the two groups as they were lost-to-follow-up, but not clear if these were related to outcomes.</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>Comment: a pre-published protocol was not available, but the important outcomes were reported or obtained by email.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>Comment: no other bias noted</td>
</tr>
</tbody>
</table>

### Amin 2012

#### Methods
- Randomised clinical trial

#### Participants
- Country: Egypt
- Period of recruitment: 2009-2011
- Number randomised: 60
- Post-randomisation dropouts: not stated
- Revised sample size: 60
- Average age (years): not stated
- Females: not stated
- Ascites grade 2: 0 (0.0%)
- Ascites grade 3: 60 (100.0%)
- Refractory or recurrent ascites: not stated
- Alcohol-related cirrhosis: not stated
- Viral-related cirrhosis: not stated
- Autoimmune disease-related cirrhosis: not stated
- Other causes for cirrhosis: not stated
- Prophylactic antibiotics for subacute bacterial peritonitis: not stated

#### Interventions
- Group 1: Systemic vasoconstrictors (n = 30)
  - Further details: Midodrine 2.5 mg TDS for 2 weeks
- Group 2: No active treatment (n = 30)
  - Further details: placebo

#### Outcomes
- None of the outcomes of interest were reported.

#### Notes
- Source of funding: not stated
- Trial name/trial registry number: not stated
- Attempts were made to contact the authors in November 2018.

### Risk of bias

<table>
<thead>
<tr>
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<tr>
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<td>Unclear risk</td>
<td>Comment: this information was not available.</td>
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</table>
Amin 2012 (Continued)

Allocation concealment (selection bias)  Unclear risk  Comment: this information was not available.

Blinding of participants and personnel (performance bias)  Unclear risk  Comment: a placebo was used, but the groups blinded were not reported.

Blinding of outcome assessment (detection bias)  Unclear risk  Comment: a placebo was used, but the groups blinded were not reported.

Incomplete outcome data (attrition bias)  Unclear risk  Comment: this information was not available.

Selective reporting (reporting bias)  Unclear risk  Comment: pre-published protocol was not available.

Other bias  Low risk  Comment: no other bias noted

Appenrodt 2008

Methods  Randomised clinical trial

Participants  Country: Germany
Period of recruitment: 2004-2006
Number randomised: 24
Post-randomisation dropouts: 0 (0.0%)
Revised sample size: 24
Average age (years): 56
Females: 8 (33.3%)
Ascites grade 2: 0 (0.0%)
Ascites grade 3: 24 (100.0%)
Refractory or recurrent ascites: not stated
Alcohol-related cirrhosis: 19 (79.2%)
Viral-related cirrhosis: 3 (12.5%)
Autoimmune disease-related cirrhosis: 0 (0.0%)
Other causes for cirrhosis: 2 (8.3%)
Prophylactic antibiotics for subacute bacterial peritonitis: not stated

Exclusion
1. Renal failure
2. Thrombocytopenia

Interventions  Group 1: Paracentesis plus systemic vasoconstrictors (n = 11)
Further details: Total paracentesis performed under local anaesthesia and aseptic conditions + midodrine 12.5 mg post-paracentesis TDS for 2 days
Group 2: Paracentesis plus fluid replacement (n = 13)
Further details: Total paracentesis performed under local anaesthesia and aseptic conditions + albumin (8 g/L of removed ascites) was infused immediately after the end of paracentesis

Outcomes  None of the outcomes of interest were reported.

Notes  Source of funding (quote): “Authors’ declaration of personal and funding interests: The authors do not have anything to declare”.
Appenrodt 2008 (Continued)

Trial name/trial registry number: not stated
Attempts were made to contact the authors in November 2018.

Risk of bias

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<tr>
<th>Bias</th>
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<th>Support for judgement</th>
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<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Comment: this information was not available.</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Low risk</td>
<td>Quote: &quot;Neither the patient nor the physician was aware of the treatment arm&quot;.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Comment: placebo was used to achieve this.</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Low risk</td>
<td>Quote: &quot;Neither the patient nor the physician was aware of the treatment arm&quot;.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Comment: placebo was used to achieve this.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>Comment: there were no post-randomisation dropouts.</td>
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<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Comment: pre-published protocol was not available.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>Comment: no other bias noted</td>
</tr>
</tbody>
</table>

Bari 2012

Methods

Randomised clinical trial

Participants
Country: USA
Period of recruitment: 2003-2010
Number randomised: 27
Post-randomisation dropouts: 2 (7.4%)
Revised sample size: 25
Reasons for post-randomisation dropouts: had spontaneous bacterial peritonitis on LVP and did not receive the drug
Average age (years): 58
Females: 3 (12.0%)
Ascites grade 2: not stated
Ascites grade 3: not stated
Refractory or recurrent ascites: 25 (100.0%)
Alcohol-related cirrhosis: 13 (52.0%)
Viral-related cirrhosis: 7 (28.0%)
Autoimmune disease-related cirrhosis: 3 (12.0%)
Other causes for cirrhosis: 2 (8.0%)

Prophylactic antibiotics for subacute bacterial peritonitis: not stated

Exclusion
1. Other features of decompensation
2. Cardiac failure
### Bari 2012 (Continued)

#### Interventions

<table>
<thead>
<tr>
<th>Group 1: Paracentesis plus systemic vasoconstrictors (n = 12)</th>
<th>Further details: Large volume paracentesis (details not available) + midodrine 10 mg oral TDS + long-acting octreotide 20 mg/month for 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 2: Paracentesis plus fluid replacement (n = 13)</td>
<td>Further details: Large volume paracentesis (details not available) + albumin 8 g/L of ascites removed once</td>
</tr>
</tbody>
</table>

#### Outcomes

Outcomes reported: mortality at maximal follow-up, any adverse events (number of people), any adverse events (number of events), liver transplantation at maximal follow-up, other features of decompensation at maximal follow-up

Follow-up (months): 10

#### Notes

Source of funding (quote): "Supported by a VA merit review grant and National Institutes of Health grants K-24 DK02727 and P-30DK 034989"

Trial name/trial registry number: NCT00108355

Attempts were made to contact the authors in November 2018.

#### Risk of bias

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<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;The random treatment allocation codes were generated at an independent biostatistical center by the study statistician using SAS version 8.2 (SAS Institute Inc, Cary, NC)&quot;.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;A list with allocation codes was sent to the pharmacy that assigned the participants to interventions based on allocation codes&quot;.</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk</td>
<td>Quote: &quot;double-blind, placebo-controlled trial&quot;</td>
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<td>Blinding of outcome assessment (detection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;double-blind, placebo-controlled trial&quot;</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Unclear risk</td>
<td>Comment: there were 2 post-randomisation dropouts because of SBP, but the diagnosis would have been made only after the intervention was administered and may or may not be related to the intervention.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Comment: pre-published protocol was not available.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
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</table>

#### Bruno 1992

#### Methods

Randomised clinical trial

#### Participants

<table>
<thead>
<tr>
<th>Country: Italy</th>
<th>Period of recruitment: not stated</th>
</tr>
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<tbody>
<tr>
<td>Number randomised: 35</td>
<td>Post-randomisation dropouts: 0 (0.0%)</td>
</tr>
<tr>
<td>Revised sample size: 35</td>
<td>Average age (years): 54</td>
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</table>
**Risk of bias**

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<td>Quote: &quot;patients were randomly assigned by the sealed envelope method on the basis of a computer generated list&quot;.</td>
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<td>Quote: &quot;patients were randomly assigned by the sealed envelope method on the basis of a computer generated list&quot;.</td>
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<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Unclear risk</td>
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<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Comment: this information was not available.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>Comment: there were no post-randomisation dropouts.</td>
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<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
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</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>Comment: no other bias noted</td>
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</tbody>
</table>

Females: 13 (37.1%)
Ascites grade 2: 0 (0.0%)
Ascites grade 3: 35 (100.0%)
Refractory or recurrent ascites: 35 (100.0%)
Alcohol-related cirrhosis: 20 (57.1%)
Viral-related cirrhosis: 7 (20.0%)
Autoimmune disease-related cirrhosis: not stated
Other causes for cirrhosis: not stated

Prophylactic antibiotics for subacute bacterial peritonitis: not stated

Exclusion criteria
1. Other features of decompensation
2. Hepatocellular carcinoma

Interventions
Group 1: Paracentesis plus reinfusion (n = 17)
Further details: Large volume paracentesis + polyanide fibre haemofilter (FH 88, Gambro)
Group 2: Paracentesis plus fluid replacement (n = 18)
Further details: Large volume paracentesis + albumin 4 to 6 g/litre of ascites removed

Outcomes
None of the outcomes of interest were reported.

Notes
Source of funding: not stated
Trial name/trial registry number: not stated
Attempts were made to contact the authors in November 2018.
**Methods**

Randomised clinical trial

**Participants**

Country: France  
Period of recruitment: 2005-2012  
Number randomised: 62  
Post-randomisation dropouts: 0 (0.0%)  
Revised sample size: 62  
Average age (years): 57  
Females: 18 (29.0%)  
Ascites grade 2: 0 (0.0%)  
Ascites grade 3: 62 (100.0%)  
Refractory or recurrent ascites: 62 (100.0%)  
Alcohol-related cirrhosis: 54 (87.1%)  
Viral-related cirrhosis: 4 (6.5%)  
Autoimmune disease-related cirrhosis: not stated  
Other causes for cirrhosis: not stated  
Prophylactic antibiotics for subacute bacterial peritonitis: not stated  

Exclusion criteria  
1. Severe liver failure, other features of decompensation, or expected liver transplantation in the next months  
2. Hepatocellular carcinoma  
3. Cardiac failure  

**Interventions**

Group 1: Transjugular intrahepatic portosystemic shunt (n = 29)  
Further details: Transjugular intrahepatic portosystemic shunt 10 mm covered stent, dilated to 8 mm to 10 mm  
Group 2: Paracentesis plus fluid replacement (n = 33)  
Further details: Large volume paracentesis + albumin 4 to 6 g/litre of ascites removed  

**Outcomes**

Outcomes reported: mortality at maximal follow-up, liver transplantation at maximal follow-up, resolution of ascites at maximal follow-up (by ultrasound), other features of decompensation at maximal follow-up, length of hospital stay (days) (all admissions until maximal follow-up)  
Follow-up (months): 12  

**Notes**

Source of funding (quote): “This work was funded by the French Ministry of Health, by a grant from the Délégation Régionale à la Recherche Clinique des Hôpitaux de Toulouse, and supported by the Gore company”.  
Trial name/trial registry number: NCT00222014  
Attempts were made to contact the authors in November 2018.

**Risk of bias**

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### Bureau 2017c (Continued)

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<tr>
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<td>Other bias</td>
<td>Low risk</td>
<td>Comment: no other bias noted</td>
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</tr>
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</table>

### Caraceni 2018

**Methods**

Randomised clinical trial

**Participants**

Country: Italy

- Period of recruitment: 2011-2015
- Number randomised: 440
- Post-randomisation dropouts: 9 (2.0%)
- Revised sample size: 431
- Reasons for post-randomisation dropouts: withdrew consent, wrong inclusion
- Average age (years): 61
- Females: 135 (31.3%)
- Ascites grade 2: 358 (83.1%)
- Ascites grade 3: 73 (16.9%)
- Refractory or recurrent ascites: not stated
- Alcohol-related cirrhosis: 142 (32.9%)
- Viral-related cirrhosis: 206 (47.8%)
- Autoimmune disease-related cirrhosis: not stated
- Other causes for cirrhosis: 56 (13.0%)

Prophylactic antibiotics for subacute bacterial peritonitis: 83 (19.3%)

**Exclusion criteria**

1. Hepatic portosystemic shunt (transjugular intrahepatic portosystemic shunt)
2. Active hepatocellular carcinoma
3. Liver transplantation
4. Ongoing alcohol abuse
5. Extrahepatic organ failure
6. Albumin use for the treatment of ascites in the month preceding enrolment

**Interventions**

**Group 1:** Aldosterone antagonists plus loop diuretics + albumin (n = 218)

Further details: antialdosterone drug (no further details) ≥ 200 mg/day + furosemide ≥25 mg/day + human albumin 20% 40 gm twice weekly for 2 weeks and then weekly for 18 months

**Group 2:** Aldosterone antagonists plus loop diuretics + paracentesis plus fluid replacement (n = 213)

Further details: antialdosterone drug (no further details) ≥ 200 mg/day + furosemide ≥ 25 mg/day for 18 months

**Outcomes**

Outcomes reported: mortality at maximal follow-up, liver transplantation at maximal follow-up, quality of life (maximal follow-up)

Follow-up (months): 18

**Notes**

Source of funding (quote): "The trial was funded by the competitive peer-reviewed grant FARM6P824B from the Italian Medicine Agency".

Trial name/trial registry number: 2008–000625–19 and NCT01288794

Attempts were made to contact the authors in November 2018.
### Caraceni 2018 (Continued)

**Risk of bias**

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### Chang 1997

**Methods**

<table>
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**Participants**

Country: Taiwan, China  
Period of recruitment: not stated  
Number randomised: 26  
Post-randomisation dropouts: not stated  
Revised sample size: 26  
Average age (years): 59  
Females: 0 (0.0%)  
Ascites grade 2: 0 (0.0%)  
Ascites grade 3: 26 (100.0%)  
Refractory or recurrent ascites: not stated  
Alcohol-related cirrhosis: 0 (0.0%)  
Viral-related cirrhosis: 26 (100.0%)  
Autoimmune disease-related cirrhosis: 0 (0.0%)  
Other causes for cirrhosis: 0 (0.0%)  
Prophylactic antibiotics for subacute bacterial peritonitis: not stated  
Exclusion criteria  
1. Cardiac or respiratory disorders  
2. Other features of decompensated cirrhosis

**Interventions**

Group 1: Aldosterone antagonists plus loop diuretics (n = 13)  
Further details: Spironolactone 100 to 400 mg/day and furosemide 80 to 240 mg/day oral for 4 to 9 days  
Group 2: Paracentesis plus fluid replacement (n = 13)
Further details: Large volume paracentesis + albumin 6 to 8 g/litre of ascites removed

Outcomes None of the outcomes of interest were reported.

Notes Source of funding (quote): "This work was supported by a grant from the National Science Council of the Republic of China (NSC842331-B075-005)". Trial name/trial registry number: not stated. Attempts were made to contact the authors in November 2018.

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### Chesta 1990

Methods Randomised clinical trial

Participants Country: Chile  
Period of recruitment: 1988-1999  
Number randomised: 31  
Post-randomisation dropouts: not stated  
Revised sample size: 31  
Average age (years): 55  
Females: not stated  
Ascites grade 2: 0 (0.0%)  
Ascites grade 3: 31 (100.0%)  
Refractory or recurrent ascites: not stated  
Alcohol-related cirrhosis: 22 (71.0%)  
Viral-related cirrhosis: 0 (0.0%)  
Autoimmune disease-related cirrhosis: 3 (9.7%)  
Other causes for cirrhosis: 6 (19.4%)  
Prophylactic antibiotics for subacute bacterial peritonitis: not stated
Chesta 1990 (Continued)

**Exclusion criteria**

1. Other features of decompensation

**Interventions**

- **Group 1:** Aldosterone antagonists plus loop diuretics (n = 14)
  Further details: Spironolactone 100 mg/day and if no response within a week, furosemide 40 to 80 mg/day + spironolactone 200 mg oral - duration not stated (until hospital discharge)

- **Group 2:** Paracentesis plus fluid replacement (n = 17)
  Further details: Large volume paracentesis + albumin 4 to 6 g/litre of ascites removed (initial patients over 4 to 5 days; later patients in a single session)

**Outcomes**

Outcomes reported: any adverse events (number of people), any adverse events (number of events), resolution of ascites at maximal follow-up (by ultrasound), other features of decompensation at maximal follow-up, length of hospital stay (days) (all admissions until maximal follow-up)

Follow-up (months): 18

**Notes**

Source of funding: not stated

Trial name/trial registry number: not stated

Attempts were made to contact the authors in November 2018.

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Descos 1983

**Methods**

Randomised clinical trial

**Participants**

Country: France
Period of recruitment: not stated
Number randomised: 131
Post-randomisation dropouts: not stated
Revised sample size: 131
Average age (years): 57
Females: 46 (35.1%)
Ascites grade 2: 0 (0.0%)
Ascites grade 3: 131 (100.0%)
Refractory or recurrent ascites: not stated
Alcohol-related cirrhosis: not stated
Viral-related cirrhosis: not stated
Autoimmune disease-related cirrhosis: not stated
Other causes for cirrhosis: not stated

Prophylactic antibiotics for subacute bacterial peritonitis: not stated

Exclusion criteria
1. Other features of decompensation

Interventions

Group 1: Aldosterone antagonists (n = 72)
Further details: Spironolactone 100 mg to 200 mg/day for 4 weeks
Group 2: Paracentesis plus reinfusion (n = 59)
Further details: Large volume paracentesis with reinfusion or concentrated ascites or unconcentrated ascites

Outcomes

Outcomes reported: mortality at maximal follow-up, resolution of ascites at maximal follow-up (by ultrasound), length of hospital stay (days) (all admissions until maximal follow-up)
Follow-up (months): 1.2

Notes

Source of funding: not stated
Trial name/trial registry number: ENTAC
Attempts were made to contact the authors in November 2018.

Risk of bias

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### Fernandez-Esparrach 1997

#### Methods
- **Randomised clinical trial**

#### Participants
- **Country:** Spain
- **Period of recruitment:** not stated
- **Number randomised:** 36
- **Post-randomisation dropouts:** 0 (0.0%)
- **Revised sample size:** 36
- **Average age (years):** 57
- **Females:** 9 (25.0%)
- **Ascites grade 2:** 0 (0.0%)
- **Ascites grade 3:** 36 (100.0%)
- **Refractory or recurrent ascites:** not stated
- **Alcohol-related cirrhosis:** 24 (66.7%)
- **Viral-related cirrhosis:** not stated
- **Autoimmune disease-related cirrhosis:** not stated
- **Other causes for cirrhosis:** not stated
- **Prophylactic antibiotics for subacute bacterial peritonitis:** not stated

#### Exclusion criteria
1. Other features of decompensation
2. Cardiac or kidney disease

#### Interventions
- **Group 1:** Aldosterone antagonists plus paracentesis plus fluid replacement (n = 19)
  - Further details: Spironolactone 75 mg TDS for 4 weeks + total paracentesis with IV albumin infusion (8 g per litre of ascitic fluid removed)
- **Group 2:** Paracentesis plus fluid replacement (n = 17)
  - Further details: total paracentesis with IV albumin infusion (8 g per litre of ascitic fluid removed)

#### Outcomes
- **Outcomes reported:** resolution of ascites at maximal follow-up (by ultrasound)
- **Follow-up (months):** 1

#### Notes
- **Source of funding (quote):** "This study was supported by a grant from SEARLE."
- **Trial name/trial registry number:** not stated
- **Attempts were made to contact the authors in November 2018.**

### Risk of bias

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### Fernandez-Esparrach 1997 (Continued)

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### Fogel 1981

#### Methods
Randomised clinical trial

#### Participants
- **Country:** USA  
  - **Period of recruitment:** not stated  
  - **Number randomised:** 90  
  - **Post-randomisation dropouts:** 0 (0.0%)  
  - **Revised sample size:** 90  
  - **Average age (years):** 52  
  - **Females:** 17 (18.9%)  
  - **Ascites grade 2:** not stated  
  - **Ascites grade 3:** not stated  
  - **Refractory or recurrent ascites:** not stated  
  - **Alcohol-related cirrhosis:** not stated  
  - **Viral-related cirrhosis:** not stated  
  - **Autoimmune disease-related cirrhosis:** not stated  
  - **Other causes for cirrhosis:** 6 (6.7%)  
  - **Prophylactic antibiotics for subacute bacterial peritonitis:** not stated

#### Interventions
- **Group 1:** Loop diuretics (n = 29)  
  - **Further details:** Furosemide 40 mg to 400 mg/day for 6 weeks orally  
- **Group 2:** Aldosterone antagonists plus loop diuretics (n = 61)  
  - **Further details:** Sequential or combination of spironolactone 100 mg/day + furosemide 40 mg to 120 mg/day oral for 6 weeks

#### Outcomes
- **Outcomes reported:** mortality at maximal follow-up, liver transplantation at maximal follow-up, other features of decompensation at maximal follow-up, length of hospital stay (days) (all admissions until maximal follow-up)  
  - **Follow-up (months):** 1.5

#### Notes
- **Source of funding (quote):** "Sponsored in part by a research grant (#76273) from the John A Hartford Foundation"  
- **Trial name/trial registry number:** not stated  
- **Attempts were made to contact the authors in November 2018.**

### Risk of bias

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### Gentilini 1999a

#### Methods
- Randomised clinical trial

#### Participants
- Country: Italy
- Period of recruitment: 1993-1996
- Number randomised: 126
- Post-randomisation dropouts: 0 (0.0%)
- Revised sample size: 126
- Average age (years): 62
- Females: 59 (46.8%)
- Ascites grade 2: not stated
- Ascites grade 3: not stated
- Refractory or recurrent ascites: not stated
- Alcohol-related cirrhosis: 16 (12.7%)
- Viral-related cirrhosis: 104 (82.5%)
- Autoimmune disease-related cirrhosis: 0 (0.0%)
- Other causes for cirrhosis: not stated
- Prophylactic antibiotics for subacute bacterial peritonitis: not stated

#### Exclusion criteria
1. Other features of decompensation
2. Cardiac or kidney disease
3. Hepatocellular carcinoma

#### Interventions
- Group 1: Aldosterone antagonists plus loop diuretics + albumin (n = 63)
  - Further details: Albumin 12.5 mg/day IV weekly + potassium canrenone 200 mg to 400 mg/day and furosemide 40 mg to 160 mg/day for 3 years
- Group 2: Aldosterone antagonists plus loop diuretics (n = 63)
  - Further details: Potassium canrenone 200 mg to 400 mg/day and furosemide 40 mg to 160 mg/day for 3 years

#### Outcomes
- Outcomes reported: mortality at maximal follow-up, resolution of ascites at maximal follow-up (by ultrasound), other features of decompensation at maximal follow-up, length of hospital stay (days) (all admissions until maximal follow-up)
- Follow-up (months): 20

#### Notes
- Source of funding (quote): "Supported by grants from the Consiglio Nazionale delle Ricerche, Rome, Ministero Italiano dell’universita e della Ricerca Scientifica e Tecnologica (Progetto Nazionale Epatiti Virali e Cirrosi Epatiche), Rome, and the Italian Liver Foundation, Florence, Italy"
### Gentilini 1999a (Continued)

#### Risk of bias

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#### Gines 1987

**Methods**

Randomised clinical trial

**Participants**

Country: Spain  
Period of recruitment: 1983-1985  
Number randomised: 117  
Post-randomisation dropouts: not stated  
Revised sample size: 117  
Average age (years): 57  
Females: 40 (34.2%)  
Ascites grade 2: 0 (0.0%)  
Ascites grade 3: 117 (100.0%)  
Refractory or recurrent ascites: not stated  
Alcohol-related cirrhosis: 83 (70.9%)  
Viral-related cirrhosis: 7 (6.0%)  
Autoimmune disease-related cirrhosis: not stated  
Other causes for cirrhosis: 27 (23.1%)  
Prophylactic antibiotics for subacute bacterial peritonitis: not stated

Exclusion criteria  
1. Other features of decompensation  
2. Hepatocellular carcinoma

**Interventions**

Group 1: Aldosterone antagonists plus loop diuretics (n = 59)  
Further details: Spironolactone 200 to 400 mg/day and furosemide 40 to 240 mg/day oral duration not stated, probably until follow-up  
Group 2: Paracentesis plus fluid replacement (n = 58)
Gines 1987 (Continued)

Further details: Repeated paracentesis removing 4 to 6 litres per day + 40 g albumin after each paracentesis

Outcomes

Outcomes reported: mortality at maximal follow-up, other features of decompensation at maximal follow-up, length of hospital stay (days) (all admissions until maximal follow-up)

Follow-up (months): 11

Notes

Source of funding (quote): “This work was supported by grants from Comision Asesora de Investigacion Cientifico y Tecnica (CAICYT 2643-83 and 2114-81) and from Fondo de Investigaciones Sanitarias do la Seguridad Social (FISS, 82-410)”. Trial name/trial registry number: not stated

Attempts were made to contact the authors in November 2018.

Risk of bias

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Ginès 1991

Methods

Randomised clinical trial

Participants

Country: Spain
Period of recruitment: not stated
Number randomised: 89
Post-randomisation dropouts: not stated
Revised sample size: 89
Average age (years): 56
Females: 25 (28.1%)
Ascites grade 2: not stated
Ascites grade 3: not stated
Refractory or recurrent ascites: 89 (100.0%)
Alcohol-related cirrhosis: 65 (73.0%)
Viral-related cirrhosis: 5 (5.6%)
Ginès 1991
(Continued)

Autoimmune disease-related cirrhosis: 0 (0.0%)
Other causes for cirrhosis: 19 (21.3%)

Prophylactic antibiotics for subacute bacterial peritonitis: not stated

Exclusion criteria
1. Other features of decompensation

Interventions

Group 1: Aldosterone antagonists plus loop diuretics + peritoneovenous shunt (n = 48)
Further details: Le Veen shunt + spironolactone 200 mg/day + furosemide 80 mg/day

Group 2: Aldosterone antagonists plus loop diuretics + paracentesis plus fluid replacement (n = 41)
Further details: Repeated paracentesis removing 4 to 6 litres per day + 200 mL of 20% albumin for each paracentesis + spironolactone 200 mg/day + furosemide 80 mg/day

Outcomes

Outcomes reported: mortality at maximal follow-up, other features of decompensation at maximal follow-up, length of hospital stay (days) (all admissions until maximal follow-up)
Follow-up (months): 14

Notes

Source of funding (quote): "Supported by a grant (2018/84) from the Fondo de Investigaciones Sanitarias de la Seguridad Social and by the Fundació Catalana per a l’Estudi de les Malalties del Fetge"
Trial name/trial registry number: not stated
Attempts were made to contact the authors in November 2018.

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Ginès 1995

Methods
Randomised clinical trial

Participants
Country: Multiple
Period of recruitment: not stated  
Number randomised: 81  
Post-randomisation dropouts: not stated  
Revised sample size: 81  
Average age (years): 61  
Females: 36 (44.4%)  
Ascites grade 2: not stated  
Ascites grade 3: not stated  
Refractory or recurrent ascites: 81 (100.0%)  
Alcohol-related cirrhosis: 41 (50.6%)  
Viral-related cirrhosis: 32 (39.5%)  
Autoimmune disease-related cirrhosis: 0 (0.0%)  
Other causes for cirrhosis: 8 (9.9%)  

Propylactic antibiotics for subacute bacterial peritonitis: stated only for surgical group  
Exclusion criteria  
1. Other features of decompensation

| Interventions | Group 1: Aldosterone antagonists plus loop diuretics + peritoneovenous shunt (n = 39)  
Further details: Le Veen shunt + spironolactone 200 mg/day + furosemide 80 mg/day  
Group 2: Aldosterone antagonists plus loop diuretics + paracentesis plus fluid replacement (n = 42)  
Further details: Repeated paracentesis removing 4 to 6 litres per day + 200 mL of 20% albumin for each paracentesis + spironolactone 200 mg/day + furosemide 80 mg/day  

| Outcomes | Outcomes reported: mortality at maximal follow-up, other features of decompensation at maximal follow-up, length of hospital stay (days) (all admissions until maximal follow-up)  
Follow-up (months): 10

| Notes | Source of funding (quote): “Supported by grants from Fondo de Investigaciones Sanitarias de la Seguridad Social (FISS 93/0610) and Direccion General de Investigacion Cientifica y Tecnica (DGICYT PM 91-0216). A. Gin,s and J. Sal5 were granted by FISS (91/5549 and 93/0610, respectively)”.  
Trial name/trial registry number: not stated  
Attempts were made to contact the authors in November 2018.

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Other bias Low risk Comment: no other bias noted

**Ginès 2002**

**Methods**
Randomised clinical trial

**Participants**
Country: Multiple  
Period of recruitment: 1996-2000  
Number randomised: 70  
Post-randomisation dropouts: 0 (0.0%)  
Revised sample size: 70  
Average age (years): 58  
Females: 20 (28.6%)  
Ascites grade 2: not stated  
Ascites grade 3: not stated  
Refractory or recurrent ascites: 70 (100.0%)  
Alcohol-related cirrhosis: 39 (55.7%)  
Viral-related cirrhosis: not stated  
Autoimmune disease-related cirrhosis: not stated  
Other causes for cirrhosis: not stated  
Prophylactic antibiotics for subacute bacterial peritonitis: not stated

Exclusion criteria  
1. Other features of decompensation  
2. Cardiac or kidney disease  
3. Hepatocellular carcinoma

**Interventions**
Group 1: Transjugular intrahepatic portosystemic shunt (n = 35)  
Further details: Transjugular intrahepatic portosystemic shunt, dilated to 8 mm to 10 mm  
Group 2: Paracentesis plus fluid replacement (n = 35)  
Further details: total paracentesis + albumin 8 g/litre of ascites removed

**Outcomes**
Outcomes reported: mortality at maximal follow-up, serious adverse events (number of events), liver transplantation at maximal follow-up, resolution of ascites at maximal follow-up (by ultrasound), other features of decompensation at maximal follow-up  
Follow-up (months): 10

**Notes**
Source of funding (quote): "Supported by grants from the Fondo de Investigación Sanitaria (Spain) (FIS 97/2073 and 00/0616) and the Veterans Administration Merit Review and NIH-K24-DK 02727 (USA)"

Trial name/trial registry number: not stated  
Attempts were made to contact the authors in November 2018.

**Risk of bias**

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Ginès 2002 (Continued)

All outcomes

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Graziotto 1997

Methods
Randomised clinical trial

Participants
Country: Multiple
Period of recruitment: 1990-1992
Number randomised: 24
Post-randomisation dropouts: 0 (0.0%)
Revised sample size: 24
Average age (years): 57
Females: 7 (29.2%)
Ascites grade 2: 0 (0.0%)
Ascites grade 3: 24 (100.0%)
Refractory or recurrent ascites: not stated
Alcohol-related cirrhosis: not stated
Viral-related cirrhosis: not stated
Autoimmune disease-related cirrhosis: not stated
Other causes for cirrhosis: not stated
Prophylactic antibiotics for subacute bacterial peritonitis: not stated
Exclusion criteria
1. Other features of decompensation

Interventions
Group 1: Paracentesis plus reinfusion (n = 12)
Further details: Large volume paracentesis + apheresis and reinfusion of concentrated ascites (Albusave BT 902 or Hemofilter Pan 15)
Group 2: Paracentesis plus fluid replacement (n = 12)
Further details: Large volume paracentesis + albumin 6 g/litre of ascites removed

Outcomes
Outcomes reported: mortality at maximal follow-up, liver transplantation at maximal follow-up, resolution of ascites at maximal follow-up (by ultrasound)
Follow-up (months): 20

Notes
Source of funding (quote): "We would like to thank Mr. Libero Barbieri and Dr. Leonardo Bigi from DiDecco Co., Mirandola, Modena, Italy, for their expert technical assistance".
Trial name/trial registry number: not stated
Attempts were made to contact the authors in November 2018.
### Graziotto 1997 (Continued)

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### Gregory 1977

#### Methods
- Randomised clinical trial

#### Participants
- Country: USA
- Period of recruitment: not stated
- Number randomised: 43
- Post-randomisation dropouts: 0 (0.0%)
- Revised sample size: 43
- Average age (years): 48
- Females: 9 (20.9%)
- Ascites grade 2: not stated
- Ascites grade 3: not stated
- Refractory or recurrent ascites: not stated
- Alcohol-related cirrhosis: 43 (100.0%)
- Viral-related cirrhosis: 0 (0.0%)
- Autoimmune disease-related cirrhosis: 0 (0.0%)
- Other causes for cirrhosis: 0 (0.0%)
- Prophylactic antibiotics for subacute bacterial peritonitis: not stated

#### Interventions
- Group 1: No active treatment (n = 21)
  - Further details: placebo
- Group 2: Aldosterone antagonists plus loop diuretics (n = 22)
  - Further details: Spironolactone 100 to 400 mg/day and furosemide 40 mg/day oral and then increased in incremental steps of 40 mg (maximum dose not stated), duration not stated - probably until follow-up

#### Outcomes
- Outcomes reported: mortality at maximal follow-up, resolution of ascites at maximal follow-up (by ultrasound), other features of decompensation at maximal follow-up
- Follow-up (months): 2

#### Notes
- Source of funding: not stated
**Gregory 1977** (Continued)

Trial name/trial registry number: not stated
Attempts were made to contact the authors in November 2018.

### Risk of bias

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**Hagege 1992**

**Methods**

Randomised clinical trial

**Participants**

Country: France

Period of recruitment: not stated

Number randomised: 53

Post-randomisation dropouts: not stated

Revised sample size: 53

Average age (years): 56

Females: 16 (30.2%)

Ascites grade 2: not stated

Ascites grade 3: not stated

Refractory or recurrent ascites: not stated

Alcohol-related cirrhosis: 48 (90.6%)

Viral-related cirrhosis: not stated

Autoimmune disease-related cirrhosis: not stated

Other causes for cirrhosis: not stated

Prophylactic antibiotics for subacute bacterial peritonitis: not stated

**Exclusion criteria**

1. Other features of decompensation

2. Hepatocellular carcinoma

**Interventions**

Group 1: Aldosterone antagonists plus loop diuretics (n = 27)
Further details: Spironolactone 225 to 300 mg/day and furosemide 40 mg to 80/day oral, duration not stated - probably until follow-up
Group 2: Paracentesis plus fluid replacement (n = 26)
Further details: paracentesis up to 4 litres/day + albumin 10 g/litre of ascites removed

Outcomes
Outcomes reported: mortality at maximal follow-up, serious adverse events (number of people), any adverse events (number of people), liver transplantation at maximal follow-up, resolution of ascites at maximal follow-up (by ultrasound), other features of decompensation at maximal follow-up, length of hospital stay (days) (all admissions until maximal follow-up)
Follow-up (months): 3

Notes
Source of funding: not stated
Trial name/trial registry number: not stated
Attempts were made to contact the authors in November 2018.

Risk of bias

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Hamdy 2014

Methods
Randomised clinical trial

Participants
Country: Egypt
Period of recruitment: 2010-2012
Number randomised: 50
Post-randomisation dropouts: not stated
Revised sample size: 50
Average age (years): 57
Females: 12 (24.0%)
Ascites grade 2: 0 (0.0%)
Ascites grade 3: 50 (100.0%)
Refractory or recurrent ascites: 50 (100.0%)
Hamdy 2014 (Continued)

Alcohol-related cirrhosis: not stated
Viral-related cirrhosis: not stated
Autoimmune disease-related cirrhosis: not stated
Other causes for cirrhosis: not stated
Prophylactic antibiotics for subacute bacterial peritonitis: not stated

Exclusion criteria
1. Other features of decompensation
2. Cardiac or respiratory disease

Interventions
Group 1: Paracentesis plus systemic vasoconstrictors (n = 25)
Further details: Large volume paracentesis + midodrine 12.5 mg TDS for 3 days
Group 2: Paracentesis plus fluid replacement (n = 25)
Further details: Large volume paracentesis + albumin 8 g/litre of ascites removed

Outcomes
Outcomes reported: treatment costs
Follow-up (months): 0.25

Notes
Source of funding (quote): "The authors declare that they have nothing to disclose".
Trial name/trial registry number: not stated
Attempts were made to contact the authors in November 2018.

Risk of bias

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Lata 2007

Methods
Randomised clinical trial

Participants
Country: Czech Republic
Period of recruitment: 2002-2004
Number randomised: 49
Post-randomisation dropouts: not stated
Revised sample size: 49
Average age (years): 57
Females: 15 (30.6%)
Ascites grade 2: 0 (0.0%)
Ascites grade 3: 49 (100.0%)
Refractory or recurrent ascites: not stated
Alcohol-related cirrhosis: 29 (59.2%)
Viral-related cirrhosis: not stated
Autoimmune disease-related cirrhosis: not stated
Other causes for cirrhosis: not stated
Prophylactic antibiotics for subacute bacterial peritonitis: not stated
Exclusion criteria
1. Other features of decompensation
2. Ischaemic heart disease

Interventions
Group 1: Paracentesis plus systemic vasoconstrictors (n = 24)
Further details: Large volume paracentesis + terlipressin 1 mg every 4 hours for 2 days
Group 2: Paracentesis plus fluid replacement (n = 25)
Further details: Large volume paracentesis + albumin 8 g/litre of ascites removed

Outcomes
Outcomes reported: serious adverse events (number of people), other features of decompensation at maximal follow-up
Follow-up (months): 0.25

Notes
Source of funding: not stated
Trial name/trial registry number: not stated
Attempts were made to contact the authors in November 2018.

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Lata 2007 (Continued)
### Lebrec 1996

**Methods**

Randomised clinical trial

**Participants**

Country: France  
Period of recruitment: 1992-1994  
Number randomised: 25  
Post-randomisation dropouts: not stated  
Revised sample size: 25  
Average age (years): 51  
Females: 7 (28.0%)  
Ascites grade 2: not stated  
Ascites grade 3: not stated  
Refractory or recurrent ascites: 25 (100.0%)  
Alcohol-related cirrhosis: 20 (80.0%)  
Viral-related cirrhosis: 5 (20.0%)  
Autoimmune disease-related cirrhosis: 0 (0.0%)  
Other causes for cirrhosis: 0 (0.0%)  
Prophylactic antibiotics for subacute bacterial peritonitis: not stated  
Exclusion criteria
1. Other features of decompensation  
2. Heart disease  
3. Hepatocellular carcinoma

**Interventions**

Group 1: Transjugular intrahepatic portosystemic shunt (n = 13)  
Further details: Transjugular intrahepatic portosystemic shunt (performed after paracentesis), expanded to a diameter of 10 mm  
Group 2: Paracentesis plus fluid replacement (n = 12)  
Further details: Large volume paracentesis + albumin, no further details

**Outcomes**

Outcomes reported: mortality at maximal follow-up, resolution of ascites at maximal follow-up (by ultrasound), other features of decompensation at maximal follow-up  
Follow-up (months): 12

**Notes**

Source of funding: not stated  
Trial name/trial registry number: not stated  
Attempts were made to contact the authors in November 2018.

**Risk of bias**

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Lebrec 1996 (Continued)

Incomplete outcome data
(attrition bias)
All outcomes
Unclear risk
Comment: this information was not available.

Selective reporting (reporting bias)
Unclear risk
Comment: pre-published protocol was not available.

Other bias
Low risk
Comment: no other bias noted

Licata 2009

Methods
Randomised clinical trial

Participants
Country: Italy
Period of recruitment: 2002-2007
Number randomised: 84
Post-randomisation dropouts: 0 (0.0%)
Revised sample size: 84
Average age (years): 64
Females: 31 (36.9%)
Ascites grade 2: not stated
Ascites grade 3: not stated
Refractory or recurrent ascites: 84 (100.0%)
Alcohol-related cirrhosis: 13 (15.5%)
Viral-related cirrhosis: 70 (83.3%)
Autoimmune disease-related cirrhosis: 0 (0.0%)
Other causes for cirrhosis: 1 (1.2%)
Prophylactic antibiotics for subacute bacterial peritonitis: not stated

Exclusion criteria
1. Other features of decompensation
2. Heart failure
3. Hepatocellular carcinoma

Interventions
Group 1: Loop diuretics (n = 60)
Further details: High dose furosemide 250 mg to 1000 mg BD until 3 days before discharge along with hypertonic saline infusion
Group 2: Aldosterone antagonists plus loop diuretics + paracetamol+ plus fluid replacement (n = 24)
Further details: Repeated paracentesis removing 4 to 6 litres per day + albumin 5 to 8 g/litre removed + spironolactone 400 mg/day + furosemide up to 160 mg/day until 3 days before discharge

Outcomes
Outcomes reported: mortality at maximal follow-up, resolution of ascites at maximal follow-up (by ultrasound), other features of decompensation at maximal follow-up, length of hospital stay (days) (all admissions until maximal follow-up)
Follow-up (months): 0.3

Notes
Source of funding (quote): "Declaration of personal and funding interests: None"
Trial name/trial registry number: not stated
Attempts were made to contact the authors in November 2018.

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### Ljubici 1994

#### Methods
- Randomised clinical trial

#### Participants
- Country: Croatia
- Period of recruitment: 1990-1992
- Number randomised: 21
- Post-randomisation dropouts: not stated
- Revised sample size: 21
- Average age (years): 56
- Females: 10 (47.6%)
- Ascites grade 2: 0 (0.0%)
- Ascites grade 3: 21 (100.0%)
- Refractory or recurrent ascites: not stated
- Alcohol-related cirrhosis: 21 (100.0%)
- Viral-related cirrhosis: 0 (0.0%)
- Autoimmune disease-related cirrhosis: 0 (0.0%)
- Other causes for cirrhosis: not stated
- Prophylactic antibiotics for subacute bacterial peritonitis: not stated

#### Interventions
- Group 1: Aldosterone antagonists plus loop diuretics + paracentesis plus fluid replacement ($n = 10$)
  Further details: Large volume paracentesis removing 5 to 6 litres + albumin 6 to 8 g/litre removed + spironolactone 200 mg/day + furosemide up to 40 to 80 mg/day stepped treatment duration not reported probably for the follow-up period
- Group 2: Aldosterone antagonists plus loop diuretics ($n = 11$)
  Further details: Spironolactone 200 mg/day + furosemide up to 40 to 80 mg/day stepped treatment duration not reported probably for the follow-up period

#### Outcomes
- Outcomes reported: mortality at maximal follow-up, serious adverse events (number of people)
### Ljubicic 1994 (Continued)

- **Follow-up (months):** 3

**Notes**
- **Source of funding:** not stated
- **Trial name/trial registry number:** not stated
- **Attempts were made to contact the authors in November 2018.**

### Risk of bias

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### Mchutchison 1989

**Methods**
- **Randomised clinical trial**

**Participants**
- **Country:** USA
- **Period of recruitment:** not stated
- **Number randomised:** 21
- **Post-randomisation dropouts:** not stated
- **Revised sample size:** 21
- **Average age (years):** not stated
- **Females:** not stated
- **Ascites grade 2:** not stated
- **Ascites grade 3:** not stated
- **Refractory or recurrent ascites:** not stated
- **Alcohol-related cirrhosis:** not stated
- **Viral-related cirrhosis:** not stated
- **Autoimmune disease-related cirrhosis:** not stated
- **Other causes for cirrhosis:** not stated
- **Prophylactic antibiotics for subacute bacterial peritonitis:** not stated

**Interventions**
- **Group 1:** Thiazide diuretics (n = 11)
- **Further details:** hydrochlorothiazide 50 mg oral daily for 3 days
Mchutchison 1989

Group 2: Loop diuretics (n = 10)
Further details: furosemide 240 mg oral daily for 3 days
Additional details: The intervention and control numbers were not reported.

Outcomes
None of the outcomes of interest were reported.

Notes
Source of funding: not stated
Trial name/trial registry number: not stated
Attempts were made to contact the authors in November 2018.

Risk of bias

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Mehta 1998

Methods
Randomised clinical trial

Participants
Country: India
Period of recruitment: not stated
Number randomised: 20
Post-randomisation dropouts: not stated
Revised sample size: 20
Average age (years): 52
Females: 4 (20.0%)
Ascites grade 2: not stated
Ascites grade 3: not stated
Refractory or recurrent ascites: not stated
Alcohol-related cirrhosis: 13 (65.0%)
Viral-related cirrhosis: not stated
Autoimmune disease-related cirrhosis: not stated
Other causes for cirrhosis: not stated
Mehta 1998 (Continued)

Prophylactic antibiotics for subacute bacterial peritonitis: not stated

Exclusion criteria
1. Other features of decompensation
2. Malignancy
3. Pregnancy

Interventions

Group 1: Paracentesis plus reinfusion (n = 10)
Further details: Large volume paracentesis + haemodialysis and reinfusion

Group 2: Paracentesis plus fluid replacement (n = 10)
Further details: Large volume paracentesis + polymerised gelatin haemaccel 150 mL/litre of ascites removed

Outcomes

Outcomes reported: treatment costs
Follow-up (months): 3

Notes

Source of funding: not stated
Trial name/trial registry number: not stated
Attempts were made to contact the authors in November 2018.

Risk of bias

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Moreau 2002

Methods

Randomised clinical trial

Participants

Country: France
Period of recruitment: 1998-2000
Number randomised: 24
Post-randomisation dropouts: 4 (16.7%)
Revised sample size: 20
Reasons for post-randomisation dropouts: did not receive paracentesis (3) and had high plasma renin level (1)
Average age (years): 54
Females: 4 (20.0%)
Ascites grade 2: 0 (0.0%)
Ascites grade 3: 20 (100.0%)
Refractory or recurrent ascites: not stated
Alcohol-related cirrhosis: 17 (85.0%)
Viral-related cirrhosis: 3 (15.0%)
Autoimmune disease-related cirrhosis: 0 (0.0%)
Other causes for cirrhosis: 0 (0.0%)
Prophylactic antibiotics for subacute bacterial peritonitis: not stated

Exclusion criteria
1. Other features of decompensation
2. Cardiac or respiratory disease

Interventions
Group 1: Paracentesis plus systemic vasoconstrictors (n = 10)
Further details: Total paracentesis + terlipressin 1 mg three doses at paracentesis, 8 hours, and 16 hours
Group 2: Paracentesis plus fluid replacement (n = 10)
Further details: Total paracentesis + albumin (8 g/L of removed ascites) was infused immediately after the end of paracentesis.

Outcomes
Outcomes reported: mortality at maximal follow-up, length of hospital stay (days) (all admissions until maximal follow-up)
Follow-up (months): 3

Notes
Source of funding: not stated
Trial name/trial registry number: not stated
Attempts were made to contact the authors in November 2018.

Risk of bias

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**Methods**

**Participants**
- Country: Japan
- Period of recruitment: 2000-2007
- Number randomised: 60
- Post-randomisation dropouts: 0 (0.0%)
- Revised sample size: 60
- Average age (years): 60
- Females: 16 (26.7%)
- Ascites grade 2: not stated
- Ascites grade 3: not stated
- Refractory or recurrent ascites: 60 (100.0%)
- Alcohol-related cirrhosis: 21 (35.0%)
- Viral-related cirrhosis: 33 (55.0%)
- Autoimmune disease-related cirrhosis: not stated
- Other causes for cirrhosis: not stated
- Prophylactic antibiotics for subacute bacterial peritonitis: not stated

**Interventions**
- Group 1: Transjugular intrahepatic portosystemic shunt (n = 30)
  - Further details: Transjugular intrahepatic portosystemic shunt (expandable stent) - initially dilated to 6 to 8 mm and further dilated to 8 mm to 10 mm depending upon portosystemic pressure gradient
- Group 2: Paracentesis plus fluid replacement (n = 30)
  - Further details: Large volume paracentesis + albumin 6 g/litre of ascites removed

**Outcomes**
- Outcomes reported: mortality at maximal follow-up, serious adverse events (number of people), any adverse events (number of people), liver transplantation at maximal follow-up, resolution of ascites at maximal follow-up (by ultrasound), other features of decompensation at maximal follow-up
- Follow-up (months): 20

**Notes**
- Source of funding: not stated
- Trial name/trial registry number: not stated
- Attempts were made to contact the authors in November 2018.

**Risk of bias**

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Narahara 2011 (Continued)

All outcomes

| Blinding of outcome assessment (detection bias) | Unclear risk | Comment: this information was not available. |
| Incomplete outcome data (attrition bias) | Low risk | Comment: there were no post-randomisation dropouts. |
| Selective reporting (reporting bias) | Unclear risk | Comment: pre-published protocol was not available. |
| Other bias | Low risk | Comment: no other bias noted |

Rai 2017

Methods Randomised clinical trial

Participants Country: India
Period of recruitment: 2013-2015
Number randomised: 25
Post-randomisation dropouts: 0 (0.0%)
Revised sample size: 25
Average age (years): 48
Females: 6 (24.0%)
Ascites grade 2: not stated
Ascites grade 3: not stated
Refractory or recurrent ascites: 25 (100.0%)
Alcohol-related cirrhosis: 16 (64.0%)
Viral-related cirrhosis: 6 (24.0%)
Autoimmune disease-related cirrhosis: 0 (0.0%)
Other causes for cirrhosis: 3 (12.0%)
Prophylactic antibiotics for subacute bacterial peritonitis: not stated

Exclusion criteria
1. Other features of decompensation
2. Cardiac disease
3. Hepatocellular carcinoma

Interventions Group 1: Aldosterone antagonists plus loop diuretics + systemic vasoconstrictors + paracentesis plus fluid replacement (n = 13)
Further details: Spironolactone 100 to 400 mg/day + furosemide 40 to 160 mg/day + midodrine 7.5 mg TDS for 3 months + large volume paracentesis + albumin 8 g/litre of ascites removed
Group 2: Aldosterone antagonists plus loop diuretics + paracentesis plus fluid replacement (n = 12)
Further details: Spironolactone 100 to 400 mg/day + furosemide 40 to 160 mg/day + large volume paracentesis + albumin 8 g/litre of ascites removed

Outcomes Outcomes reported: mortality at maximal follow-up, serious adverse events (number of people), any adverse events (number of events), liver transplantation at maximal follow-up, resolution of ascites at maximal follow-up (by ultrasound), other features of decompensation at maximal follow-up
Follow-up (months): 3

Notes Source of funding (quote): "Funding information: None"
Trial name/trial registry number: NCT02173288
Attempts were made to contact the authors in November 2018.
### Rai 2017 (Continued)

#### Risk of bias

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#### Methods

**Randomised clinical trial**

**Participants**
- Country: Pakistan
- Period of recruitment: 2009-2010
- Number randomised: 60
- Post-randomisation dropouts: not stated
- Revised sample size: 60
- Average age (years): 51
- Females: 27 (45.0%)
- Ascites grade 2: not stated
- Ascites grade 3: not stated
- Refractory or recurrent ascites: 60 (100.0%)
- Alcohol-related cirrhosis: 0 (0.0%)
- Viral-related cirrhosis: 57 (95.0%)
- Autoimmune disease-related cirrhosis: 0 (0.0%)
- Other causes for cirrhosis: 3 (5.0%)
- Prophylactic antibiotics for subacute bacterial peritonitis: not stated

**Exclusion criteria**
1. Other features of decompensation
2. Hepatocellular carcinoma

**Interventions**
- Group 1: Osmotic diuretics (n = 30)
  - Further details: Mannitol 30 g IV - number of doses and duration not clear, but appeared to be a single dose
- Group 2: No active treatment (n = 30)
### Raza 2011 (Continued)

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### Romanelli 2006

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<td>Average age (years): 63</td>
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<td>Females: 38 (38.0%)</td>
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<td>Ascites grade 2: 65 (65.0%)</td>
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<td>Ascites grade 3: 35 (35.0%)</td>
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<td>Refractory or recurrent ascites: not stated</td>
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<tr>
<td>Alcohol-related cirrhosis: 2 (2.0%)</td>
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<tr>
<td>Viral-related cirrhosis: 79 (79.0%)</td>
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<tr>
<td>Autoimmune disease-related cirrhosis: 0 (0.0%)</td>
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</tr>
<tr>
<td>Other causes for cirrhosis: 19 (19.0%)</td>
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</table>
### Romanelli 2006 (Continued)

**Prophylactic antibiotics for subacute bacterial peritonitis: not stated**

**Interventions**
- **Group 1: Aldosterone antagonists plus loop diuretics + albumin (n = 54)**
  - Further details: Albumin 25 mg/day IV for first year and after that, the same once every 2 weeks + spironolactone 100 mg to 400 mg/day and furosemide 25 mg to 150 mg/day for duration of follow-up
- **Group 2: Aldosterone antagonists plus loop diuretics (n = 46)**
  - Further details: Spironolactone 100 mg to 400 mg/day and furosemide 25 mg to 150 mg/day for duration of follow-up

**Outcomes**
- Outcomes reported: mortality at maximal follow-up, liver transplantation at maximal follow-up, resolution of ascites at maximal follow-up (by ultrasound), other features of decompensation at maximal follow-up
- Follow-up (months): 84

**Notes**
- Source of funding (quote): "Supported by grants from the Italian Ministry of Education, University and Research and the University of Florence, Italy"
- Trial name/trial registry number: not stated
- Attempts were made to contact the authors in November 2018.

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### Rossle 2000

**Methods**
- Randomised clinical trial

**Participants**
- Country: Germany
- Period of recruitment: 1993-1997
- Number randomised: 60
- Post-randomisation dropouts: 0 (0.0%)
- Revised sample size: 60
- Average age (years): 60
Rossle 2000 (Continued)

Females: 18 (30.0%)
Ascites grade 2: 0 (0.0%)
Ascites grade 3: 60 (100.0%)
Refractory or recurrent ascites: 60 (100.0%)
Alcohol-related cirrhosis: 47 (78.3%)
Viral-related cirrhosis: not stated
Autoimmune disease-related cirrhosis: not stated
Other causes for cirrhosis: not stated
Prophylactic antibiotics for subacute bacterial peritonitis: not stated

Exclusion criteria
1. Other features of decompensation
2. Advanced cancer

Interventions
Group 1: Transjugular intrahepatic portosystemic shunt (n = 29)
Further details: Transjugular intrahepatic portosystemic shunt (expandable stent: Palmaz–Schatz stent or a self-expandable nitinol stent (Memotherm))
Group 2: Paracentesis plus fluid replacement (n = 31)
Further details: Large volume paracentesis + albumin 8 g/litre of ascites removed

Outcomes
Outcomes reported: mortality at maximal follow-up, liver transplantation at maximal follow-up, other features of decompensation at maximal follow-up, length of hospital stay (days) (all admissions until maximal follow-up)
Follow-up (months): 44.5

Notes
Source of funding: not stated
Trial name/trial registry number: not stated
Attempts were made to contact the authors in November 2018.

Risk of bias

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### Methods
Randomised clinical trial

### Participants
Country: Italy  
Period of recruitment: 1985-1986  
Number randomised: 41  
Post-randomisation dropouts: 0 (0.0%)  
Revised sample size: 41  
Average age (years): 55  
Females: 9 (22.0%)  
Ascites grade 2: 0 (0.0%)  
Ascites grade 3: 41 (100.0%)  
Refractory or recurrent ascites: not stated  
Alcohol-related cirrhosis: 20 (48.8%)  
Viral-related cirrhosis: 7 (17.1%)  
Autoimmune disease-related cirrhosis: 0 (0.0%)  
Other causes for cirrhosis: 9 (22.0%)  
Prophylactic antibiotics for subacute bacterial peritonitis: not stated  
Exclusion criteria  
1. Other features of decompensation  
2. Cancer

### Interventions
Group 1: Aldosterone antagonists plus loop diuretics (n = 21)  
Further details: Spironolactone 200 to 400 mg/day and furosemide 50 mg/day oral added as necessary, duration not stated - probably until follow-up  
Group 2: Paracentesis plus fluid replacement (n = 20)  
Further details: paracentesis up to 4 litres/day + albumin 20 g to 60 g depending on ascites removed each day

### Outcomes
Outcomes reported: mortality at maximal follow-up, serious adverse events (number of events), resolution of ascites at maximal follow-up (by ultrasound), other features of decompensation at maximal follow-up  
Follow-up (months): 4

### Notes
Source of funding: not stated  
Trial name/trial registry number: not stated  
Attempts were made to contact the authors in November 2018.

### Risk of bias

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Unclear risk  
Comment: pre-published protocol was not available.

Other bias  
Low risk  
Comment: no other bias noted

Salerno 2004

Methods  
Randomised clinical trial

Participants  
Country: Italy  
Period of recruitment: 1996-2002  
Number randomised: 66  
Post-randomisation dropouts: 0 (0.0%)  
Revised sample size: 66  
Average age (years): 59  
Females: 17 (25.8%)  
Ascites grade 2: not stated  
Ascites grade 3: not stated  
Refractory or recurrent ascites: 66 (100.0%)  
Alcohol-related cirrhosis: 28 (42.4%)  
Viral-related cirrhosis: 31 (47.0%)  
Autoimmune disease-related cirrhosis: not stated  
Other causes for cirrhosis: not stated  
Prophylactic antibiotics for subacute bacterial peritonitis: not stated  
Exclusion criteria  
1. Other features of decompensation  
2. Cancer

Interventions  
Group 1: Transjugular intrahepatic portosystemic shunt (n = 33)  
Further details: Transjugular intrahepatic portosystemic shunt dilated to obtain a portal pressure gradient of 12 mmHg  
Group 2: Paracentesis plus fluid replacement (n = 33)  
Further details: Large volume paracentesis + albumin 8 g/litre of ascites removed

Outcomes  
Outcomes reported: mortality at maximal follow-up, liver transplantation at maximal follow-up, resolution of ascites at maximal follow-up (by ultrasound), other features of decompensation at maximal follow-up, length of hospital stay (days) (all admissions until maximal follow-up)  
Follow-up (months): 18

Notes  
Source of funding (quote): "Supported by grants of the Ministero dell’Universita ` Italiana and of the Ospedale Maggiore Policlinico Instituto di Ricovero e Cura a Carattere Scientifico (IRCCS) of Milan"  
Trial name/trial registry number: not stated  
Attempts were made to contact the authors in November 2018.

Risk of bias

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Salerno 2004

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Sanyal 2003

Methods
Randomised clinical trial

Participants
Country: USA
Period of recruitment: 1997-2000
Number randomised: 109
Post-randomisation dropouts: 0 (0.0%)
Revised sample size: 109
Average age (years): 54
Females: 37 (33.9%)
Ascites grade 2: not stated
Ascites grade 3: not stated
Refractory or recurrent ascites: 109 (100.0%)
Alcohol-related cirrhosis: 65 (59.6%)
Viral-related cirrhosis: 27 (24.8%)
Autoimmune disease-related cirrhosis: not stated
Other causes for cirrhosis: not stated
Prophylactic antibiotics for subacute bacterial peritonitis: not stated

Exclusion criteria
1. Conditions likely to limit life expectancy to < 1 year
2. Acute renal failure or renal diseases
3. Cardiac failure

Interventions
| Group 1: Transjugular intrahepatic portosystemic shunt (n = 52) |
| Further details: Transjugular intrahepatic portosystemic shunt (no further details) was performed after large volume paracentesis. |
| Group 2: Paracentesis plus fluid replacement (n = 57) |
| Further details: Large volume paracentesis + albumin 6 to 8 g/litre of ascites removed |

Outcomes
Outcomes reported: mortality at maximal follow-up, liver transplantation at maximal follow-up, resolution of ascites at maximal follow-up (by ultrasound), other features of decompensation at maximal follow-up
Follow-up (months): 12

Notes
Source of funding (quote): "Supported by grant RO1 DK 51523 from the National Institutes of Health (to A.J.S.) and MO1-RR-00065"
Trial name/trial registry number: NASTRA
Attempts were made to contact the authors in November 2018.

Risk of bias

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Schaub 1995

Methods
Randomised clinical trial

Participants
Country: Switzerland
Period of recruitment: not stated
Number randomised: 20
Post-randomisation dropouts: 3 (15.0%)
Revised sample size: 17
Reasons for post-randomisation dropouts: not stated
Average age (years): not stated
Females: not stated
Ascites grade 2: not stated
Ascites grade 3: not stated
Refractory or recurrent ascites: not stated
Alcohol-related cirrhosis: 18 (105.9%)
Viral-related cirrhosis: 2 (11.8%)
Autoimmune disease-related cirrhosis: not stated
Other causes for cirrhosis: not stated
**Schaub 1995** (Continued)

Prophylactic antibiotics for subacute bacterial peritonitis: not stated

| Interventions | Group 1: Aldosterone antagonists plus loop diuretics (n = 9) Further details: Spironolactone 200 mg/day + furosemide 40 mg/day, duration not stated Group 2: Paracentesis plus fluid replacement (n = 8) Further details: Large volume paracentesis over 2 days + albumin 60 g for each puncture |
| Notes | Source of funding: not stated Trial name/trial registry number: not stated Attempts were made to contact the authors in November 2018. |

**Risk of bias**

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**Singh 2006a**

Methods Randomised clinical trial

| Participants | Country: India Period of recruitment: 2004-2005 Number randomised: 40 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 40 Average age (years): 48 Females: 8 (20.0%) Ascites grade 2: 0 (0.0%) Ascites grade 3: 40 (100.0%) Refractory or recurrent ascites: not stated Alcohol-related cirrhosis: 26 (65.0%) |
Singh 2006a (Continued)

Viral-related cirrhosis: 6 (15.0%)
Autoimmune disease-related cirrhosis: 1 (2.5%)
Other causes for cirrhosis: 7 (17.5%)

Prophylactic antibiotics for subacute bacterial peritonitis: not stated

Exclusion criteria
1. Other features of decompensation
2. Cardiac or respiratory disease

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Group 1: Paracentesis plus systemic vasoconstrictors (n = 20)</th>
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<tbody>
<tr>
<td>Further details: Total paracentesis + noradrenaline 0.5 mg/hr titrated to maintain mean arterial pressure about 10 mmHg above baseline for 72 hours</td>
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<tr>
<th>Group 2: Paracentesis plus fluid replacement (n = 20)</th>
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<tr>
<td>Further details: Total paracentesis + albumin (8 g/L of removed ascites)</td>
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**Risk of bias**

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Singh 2006b

Methods
Randomised clinical trial
### Participants

- **Country:** India  
- **Period of recruitment:** 2002-2003  
- **Number randomised:** 43  
- **Post-randomisation dropouts:** 3 (7.0%)  
- **Revised sample size:** 40  
- **Reasons for post-randomisation dropouts:** GI bleed, abdominal tuberculosis  
- **Average age (years):** 47  
- **Females:** 4 (10.0%)  
- **Ascites grade 2:** 0 (0.0%)  
- **Ascites grade 3:** 40 (100.0%)  
- **Refractory or recurrent ascites: not stated**  
- **Alcohol-related cirrhosis:** 28 (70.0%)  
- **Viral-related cirrhosis:** 8 (20.0%)  
- **Autoimmune disease-related cirrhosis:** 0 (0.0%)  
- **Prophylactic antibiotics for subacute bacterial peritonitis: not stated**  
- **Other causes for cirrhosis:** 4 (10.0%)  

### Exclusion criteria

1. Other features of decompensation  
2. Cardiac or respiratory disease

### Interventions

- **Group 1:** Paracentesis plus systemic vasoconstrictors (n = 20)  
  - Further details: Total paracentesis + terlipressin 1 mg at 0, 8, and 16 hours of paracentesis  
- **Group 2:** Paracentesis plus fluid replacement (n = 20)  
  - Further details: Total paracentesis + albumin (8 g/L of removed ascites)

### Outcomes

- **Outcomes reported:** mortality at maximal follow-up, serious adverse events (number of people), any adverse events (number of people), liver transplantation at maximal follow-up  
- **Follow-up (months):** 0.25

### Notes

- **Source of funding (quote):** "No major funding. If patients were unable to purchase medications, we assisted them and they were provided medications (author replies)."  
- **Trial name/trial registry number:** not stated  
- **Attempts were made to contact the authors in November 2018.**

### Risk of bias

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Singh 2006b (Continued)

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Singh 2008

Methods
Randomised clinical trial

Participants
Country: India
Period of recruitment: 2005-2006
Number randomised: 40
Post-randomisation dropouts: 0 (0.0%)
Revised sample size: 40
Average age (years): 47
Females: 5 (12.5%)
Ascites grade 2: 0 (0.0%)
Ascites grade 3: 40 (100.0%)
Refractory or recurrent ascites: not stated
Alcohol-related cirrhosis: 26 (65.0%)
Viral-related cirrhosis: 9 (22.5%)
Autoimmune disease-related cirrhosis: 1 (2.5%)
Other causes for cirrhosis: 4 (10.0%) prophylactic antibiotics for subacute bacterial peritonitis: not stated
Exclusion criteria
1. Other features of decompensation
2. Cardiac or respiratory disease

Interventions
Group 1: Paracentesis plus systemic vasoconstrictors (n = 20)
Further details: Total paracentesis + midodrine 5 to 10 mg TDS for 72 hours
Group 2: Paracentesis plus fluid replacement (n = 20)
Further details: Total paracentesis + albumin (8 g/L of removed ascites)

Outcomes
Outcomes reported: mortality at maximal follow-up, serious adverse events (number of people), any adverse events (number of people), liver transplantation at maximal follow-up, other features of decompensation at maximal follow-up, treatment costs
Follow-up (months): 2

Notes
Source of funding (quote): "Financial support: None"
Trial name/trial registry number: not stated
Attempts were made to contact the authors in November 2018.

Risk of bias

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| Allocation concealment (selection bias) | Low risk | Quote: "opaque sealed envelopes (author replies)"
| Blinding of participants and personnel (performance bias) | High risk | Quote: "No blinding (author replies)"
### Singh 2008 (Continued)

#### All outcomes

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### Singh 2012a

#### Methods

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#### Participants

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<td>Average age (years): 47</td>
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<td>Females: 3 (7.5%)</td>
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<td>Alcohol-related cirrhosis: 29 (72.5%)</td>
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<td>Autoimmune disease-related cirrhosis: 1 (2.5%)</td>
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<td>Other causes for cirrhosis: 0 (0.0%)</td>
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<td>Prophylactic antibiotics for subacute bacterial peritonitis: not stated</td>
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#### Exclusion criteria

1. Other features of decompensation

#### Years of recruitment: 2007-2009

#### Interventions

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<td>Group 1: Aldosterone antagonists plus loop diuretics + systemic vasoconstrictors (n = 20)</td>
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<td>Further details: Spironolactone 100 to 400 mg/day + furosemide 40 to 160 mg/day + midodrine 7.5 mg TDS oral for a mean of 2 months</td>
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<tr>
<td>Group 2: Aldosterone antagonists plus loop diuretics (n = 20)</td>
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<td>Further details: Spironolactone 100 to 400 mg/day + furosemide 40 to 160 mg/day, duration not stated</td>
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#### Outcomes

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<tbody>
<tr>
<td>Outcomes reported: mortality at maximal follow-up, serious adverse events (number of people), liver transplantation at maximal follow-up, resolution of ascites at maximal follow-up (by ultrasound)</td>
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<td>Follow-up (months): 6</td>
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#### Notes

<table>
<thead>
<tr>
<th>Details</th>
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<tbody>
<tr>
<td>Source of funding (quote): &quot;The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript&quot;.</td>
</tr>
<tr>
<td>Trial name/trial registry number: not stated</td>
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<tr>
<td>Attempts were made to contact the authors in November 2018.</td>
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</table>

### Risk of bias

---

**Treatment for ascites in adults with decompensated liver cirrhosis: a network meta-analysis**

Copyright © 2020 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
### Singh 2012a (Continued)

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
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<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;A computer made randomization code&quot;</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;opaque sealed envelopes (author replies)&quot;</td>
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<td>Blinding of participants and personnel (performance bias)</td>
<td>Unclear risk</td>
<td>Quote: &quot;Patients and investigators were blinded to the treatment assignments&quot;. Comment: it was not clear how they were blinded.</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>Quote: &quot;Patients and investigators were blinded to the treatment assignments&quot;. Comment: it was not clear how they were blinded.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>Comment: there were no post-randomisation dropouts.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>Comment: a pre-published protocol was not available, but the important outcomes were reported or obtained by email.</td>
</tr>
<tr>
<td>Other bias</td>
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<td>Comment: no other bias noted</td>
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</table>

### Singh 2013

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised clinical trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td></td>
</tr>
<tr>
<td>Country: India</td>
<td></td>
</tr>
<tr>
<td>Period of recruitment: 2010-2011</td>
<td></td>
</tr>
<tr>
<td>Number randomised: 60</td>
<td></td>
</tr>
<tr>
<td>Post-randomisation dropouts: 0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>Revised sample size: 60</td>
<td></td>
</tr>
<tr>
<td>Average age (years): 53</td>
<td></td>
</tr>
<tr>
<td>Females: 4 (6.7%)</td>
<td></td>
</tr>
<tr>
<td>Ascites grade 2: not stated</td>
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</tr>
<tr>
<td>Ascites grade 3: not stated</td>
<td></td>
</tr>
<tr>
<td>Refractory or recurrent ascites: 60 (100.0%)</td>
<td></td>
</tr>
<tr>
<td>Alcohol-related cirrhosis: 49 (81.7%)</td>
<td></td>
</tr>
<tr>
<td>Viral-related cirrhosis: 7 (11.7%)</td>
<td></td>
</tr>
<tr>
<td>Autoimmune disease-related cirrhosis: 0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>Other causes for cirrhosis: 5 (8.3%)</td>
<td></td>
</tr>
<tr>
<td>Prophylactic antibiotics for subacute bacterial peritonitis: not stated</td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria</td>
<td></td>
</tr>
<tr>
<td>1. Other features of decompensation</td>
<td></td>
</tr>
</tbody>
</table>

| Interventions                                 |                           |
| Group 1: Aldosterone antagonists plus loop diuretics + systemic vasoconstrictors + systemic vasodilator (n = 15) |                           |
| Further details: Spironolactone 100 to 400 mg/day + furosemide 40 to 160 mg/day + midodrine 7.5 mg |                           |
| TDS oral + clonidine 0.1 mg BD or both until endpoints were reached - probably 1 month |                           |
| Group 2: Aldosterone antagonists plus loop diuretics + systemic vasoconstrictors (n = 15) |                           |
| Further details: Spironolactone 100 to 400 mg/day + furosemide 40 to 160 mg/day + midodrine 7.5 mg |                           |
| TDS oral until endpoints were reached - probably 1 month |                           |
Cochrane Database of Systematic Reviews

Singh 2013 (Continued)

Group 3: Aldosterone antagonists plus loop diuretics + systemic vasodilator (n = 15)
Further details: Spironolactone 100 to 400 mg/day + furosemide 40 to 160 mg/day + clonidine 0.1 mg
BD until endpoints were reached - probably 1 month
Group 4: Aldosterone antagonists plus loop diuretics (n = 15)
Further details: Spironolactone 100 to 400 mg/day + furosemide 40 to 160 mg/day duration until end-
points were reached - probably 1 month

Outcomes
Outcomes reported: mortality at maximal follow-up, serious adverse events (number of people), any
adverse events (number of events), liver transplantation at maximal follow-up, resolution of ascites at
maximal follow-up (by ultrasound), other features of decompensation at maximal follow-up
Follow-up (months): 1

Notes
Source of funding (quote): "Financial support: None"
Trial name/trial registry number: not stated
Attempts were made to contact the authors in November 2018.

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;A computer made the randomization code with 60 envelopes, with 15 patients in each group&quot;.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;A computer made the randomization code with 60 envelopes, with 15 patients in each group&quot;.</td>
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<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>High risk</td>
<td>Quote: &quot;Patients and investigators were not blinded to the treatment assignments&quot;.</td>
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<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>High risk</td>
<td>Quote: &quot;Patients and investigators were not blinded to the treatment assignments&quot;.</td>
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<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>Comment: there were no post-randomisation dropouts.</td>
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<tr>
<td>Selective reporting (reporting bias)</td>
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<td>Comment: a pre-published protocol was not available, but the important outcomes were reported or obtained by email.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>Comment: no other bias noted</td>
</tr>
</tbody>
</table>

Sola 1994

Methods
Randomised clinical trial

Participants
Country: Spain
Period of recruitment: not stated
Number randomised: 80
Post-randomisation dropouts: 9 (11.3%)
Revised sample size: 71
Reasons for post-randomisation dropouts: cross-over or lost to follow-up
Average age (years): 59
Females: 22 (31.0%)
Ascites grade 2: 0 (0.0%)
### Sola 1994 (Continued)

<table>
<thead>
<tr>
<th>Ascites grade: 71 (100.0%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory or recurrent ascites: not stated</td>
</tr>
<tr>
<td>Alcohol-related cirrhosis: 63 (88.7%)</td>
</tr>
<tr>
<td>Viral-related cirrhosis: not stated</td>
</tr>
<tr>
<td>Autoimmune disease-related cirrhosis: not stated</td>
</tr>
<tr>
<td>Other causes for cirrhosis: not stated</td>
</tr>
<tr>
<td>Prophylactic antibiotics for subacute bacterial peritonitis: not stated</td>
</tr>
</tbody>
</table>

**Interventions**

<table>
<thead>
<tr>
<th>Group 1: Aldosterone antagonists plus loop diuretics + paracentesis plus fluid replacement (n = 38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Further details: Total paracentesis + dextran-40 (8 g/L of removed ascites) + spironolactone 100 to 400 mg/day + furosemide 40 to 240 mg/day; duration not reported, probably end of follow-up</td>
</tr>
<tr>
<td>Group 2: Aldosterone antagonists plus loop diuretics (n = 33)</td>
</tr>
<tr>
<td>Further details: Spironolactone 100 to 400 mg/day + furosemide 40 to 240 mg/day; duration not reported, probably end of follow-up</td>
</tr>
</tbody>
</table>

**Outcomes**

| Outcomes reported: mortality at maximal follow-up, other features of decompensation at maximal follow-up |
| Follow-up (months): 13 |

**Notes**

Source of funding (quote): "This work was supported by a grant from the Institut Municipal d’Investigació Médica (IMIM) IM 876413601."

Trial name/trial registry number: not stated

Attempts were made to contact the authors in November 2018.

### Risk of bias

<table>
<thead>
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<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Quote: “random number table”</td>
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<td>Allocation concealment (selection bias)</td>
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<td>Comment: this information was not available.</td>
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<td>Comment: this information was not available.</td>
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<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Unclear risk</td>
<td>Comment: there were post-randomisation dropouts, but it is not clear whether this could have led to biased treatment effects.</td>
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<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Comment: pre-published protocol was not available.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>Comment: no other bias noted</td>
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</table>

### Sola 2018

**Methods**

Randomised clinical trial
Sola 2018 (Continued)

Participants

<table>
<thead>
<tr>
<th>Country: Spain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Period of recruitment: 2008-2015</td>
</tr>
<tr>
<td>Number randomised: 196</td>
</tr>
<tr>
<td>Post-randomisation dropouts: 23 (11.7%)</td>
</tr>
<tr>
<td>Revised sample size: 173</td>
</tr>
<tr>
<td>Reasons for post-randomisation dropouts: liver transplantation, death, incorrect randomisation, withdrawal of consent</td>
</tr>
<tr>
<td>Average age (years): 55</td>
</tr>
<tr>
<td>Females: 36 (20.8%)</td>
</tr>
<tr>
<td>Ascites grade 2: not stated</td>
</tr>
<tr>
<td>Ascites grade 3: not stated</td>
</tr>
<tr>
<td>Refractory or recurrent ascites: not stated</td>
</tr>
<tr>
<td>Alcohol-related cirrhosis: 72 (41.6%)</td>
</tr>
<tr>
<td>Viral-related cirrhosis: 80 (46.2%)</td>
</tr>
<tr>
<td>Autoimmune disease-related cirrhosis: not stated</td>
</tr>
<tr>
<td>Other causes for cirrhosis: not stated</td>
</tr>
<tr>
<td>Prophylactic antibiotics for subacute bacterial peritonitis: both</td>
</tr>
<tr>
<td>Other inclusion criteria</td>
</tr>
<tr>
<td>1. Patients awaiting liver transplantation</td>
</tr>
</tbody>
</table>

Interventions

| Group 1: Systemic vasoconstrictors + albumin (n = 87) |
| Further details: Midodrine 5 mg TDS orally (increased up to 30 mg daily) + albumin IV 40 mg every 15 days for 1 year |
| Group 2: No active treatment (n = 86) |
| Further details: placebo |

Outcomes

| Outcomes reported: mortality at maximal follow-up, serious adverse events (number of people), any adverse events (number of people), any adverse events (number of events), liver transplantation at maximal follow-up, other features of decompensation at maximal follow-up |
| Follow-up (months): 11 |

Notes

| Source of funding (quote): "No economic support was provided by the companies, except that Grifols S.A. (Spain) gave a donation to support the transport costs incurred by patients participating in the study". |
| Trial name/trial registry number: NCT00839358 |
| Attempts were made to contact the authors in November 2018. |

Risk of bias

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<tbody>
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<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;A computer-generated…&quot;</td>
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<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;Randomization was performed at the CTU of the Hospital Clinic of Barcelona&quot;.</td>
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<tr>
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<td>Quote: &quot;All investigators and patients were blinded to treatment assignment…placebo&quot;.</td>
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### Sola 2018 (Continued)

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<tr>
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<td>High risk</td>
<td>Comment: there were post-randomisation dropouts, which were probably related to intervention and outcomes.</td>
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<tr>
<td>(attrition bias)</td>
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</tr>
<tr>
<td>All outcomes</td>
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<tr>
<td>Selective reporting</td>
<td>Low risk</td>
<td>Comment: a pre-published protocol was not available, but the important outcomes were reported.</td>
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<tr>
<td>(reporting bias)</td>
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<td></td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>Comment: no other bias noted</td>
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</tbody>
</table>

### Stanley 1989b

#### Methods
Randomised clinical trial

#### Participants
- Country: USA
- Period of recruitment: not stated
- Number randomised: 299
- Post-randomisation dropouts: 0 (0.0%)
- Revised sample size: 299
- Average age (years): not stated
- Females: not stated
- Ascites grade 2: not stated
- Ascites grade 3: not stated
- Refractory or recurrent ascites: not stated
- Alcohol-related cirrhosis: 299 (100.0%)
- Viral-related cirrhosis: not stated
- Autoimmune disease-related cirrhosis: not stated
- Other causes for cirrhosis: not stated
- Prophylactic antibiotics for subacute bacterial peritonitis: not stated

#### Interventions
- Group 1: Peritoneovenous shunt (n = 146)
  - Further details: Le Veen shunt
- Group 2: Aldosterone antagonists plus loop diuretics (n = 153)
  - Further details: spironolactone 100 to 400 mg/day + furosemide 40 to 320 mg/day

#### Outcomes
None of the outcomes of interest were reported.

#### Notes
- Source of funding (quote): "We are indebted to Becton Dickinson (Rutherford, N.J.) for its donation of the LeVeen shunts."
- Trial name/trial registry number: not stated
- Attempts were made to contact the authors in November 2018.

### Risk of bias

<table>
<thead>
<tr>
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<tr>
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<td>Comment: this information was not available.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;Each patient who consented to participate was assigned to a treatment group by telephone by the Cooperative Studies Program Coordinating Center after his eligibility had been verified&quot;.</td>
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### Stanley 1989b (Continued)

**All outcomes**

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<td>Low risk</td>
<td>Comment: this information was not available.</td>
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<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Unclear risk</td>
<td>Comment: there were no post-randomisation dropouts.</td>
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<tr>
<td>Selective reporting (reporting bias) All outcomes</td>
<td>Unclear risk</td>
<td>Comment: pre-published protocol was not available.</td>
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**Other bias**

<table>
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<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>Comment: no other bias noted</td>
</tr>
</tbody>
</table>

### Strauss 1991

**Methods**

Randomised clinical trial

**Participants**

Country: Brazil  
Period of recruitment: 1995-1990  
Number randomised: 33  
Post-randomisation dropouts: 2 (6.1%)  
Revised sample size: 31  
Reasons for post-randomisation dropouts: death before starting treatment and diagnosed with HRS  
Average age (years): 52  
Females: 7 (22.6%)  
Ascites grade 2: not stated  
Ascites grade 3: not stated  
Refractory or recurrent ascites: 31 (100.0%)  
Alcohol-related cirrhosis: 19 (61.3%)  
Viral-related cirrhosis: 6 (19.4%)  
Autoimmune disease-related cirrhosis: not stated  
Other causes for cirrhosis: not stated  
Prophylactic antibiotics for subacute bacterial peritonitis: not stated  

Exclusion criteria  
1. Other features of decompensation  
2. Cardiac or renal disease

**Interventions**

Group 1: Aldosterone antagonists plus loop diuretics + paracentesis + albumin (20 g paracentesis) + spironolactone 150 to 300 mg/day + furosemide 40 to 80 mg/day; duration not reported, probably end of follow-up  
Group 2: Aldosterone antagonists plus loop diuretics (n = 15)  
Further details: Spironolactone 150 to 300 mg/day + furosemide 40 to 80 mg/day; duration not reported, probably end of follow-up

**Outcomes**

Outcomes reported: resolution of ascites at maximal follow-up (by ultrasound), other features of decompensation at maximal follow-up  
Follow-up (months): 0.5

**Notes**

Source of funding: not stated  
Trial name/trial registry number: not stated  
Attempts were made to contact the authors in November 2018.
**Strauss 1991 (Continued)**

<table>
<thead>
<tr>
<th>Bias</th>
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<th>Support for judgement</th>
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<tbody>
<tr>
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<td>Low risk</td>
<td>Quote: &quot;statistical table of random numbers&quot;</td>
</tr>
<tr>
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<td>Low risk</td>
<td>Quote: &quot;system of sealed envelopes, numbered successively, after the selection of each patient for the study, the doctor made the opening of the next envelope&quot;</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Unclear risk</td>
<td>Comment: this information was not available.</td>
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<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Comment: this information was not available.</td>
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<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Unclear risk</td>
<td>Comment: there were post-randomisation dropouts, but it was not clear whether this could be related to intervention or could have affected the treatment effect.</td>
</tr>
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<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Comment: pre-published protocol was not available.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>Comment: no other bias noted</td>
</tr>
</tbody>
</table>

**Tuttolomondo 2016**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised clinical trial</th>
</tr>
</thead>
</table>
| Participants | Country: Italy  
Period of recruitment: 2013-2015  
Number randomised: 59  
Post-randomisation dropouts: 0 (0.0%)  
Revised sample size: 59  
Average age (years): 64  
Females: 23 (39.0%)  
Ascites grade 2: not stated  
Ascites grade 3: not stated  
Refractory or recurrent ascites: 59 (100.0%)  
Alcohol-related cirrhosis: 11 (18.6%)  
Viral-related cirrhosis: 48 (81.4%)  
Autoimmune disease-related cirrhosis: 0 (0.0%)  
Other causes for cirrhosis: not stated  
Prophylactic antibiotics for subacute bacterial peritonitis: not stated |
| Exclusion criteria | 1. Other features of decompensation  
2. Heart failure  
3. Hepatocellular carcinoma |
| Interventions | Group 1: Loop diuretics (n = 31)  
Further details: High dose furosemide 125 mg to 250 mg BD until 3 days before discharge along with hypertonic saline infusion  
Group 2: Paracentesis plus fluid replacement (n = 28) |
Further details: Repeated paracentesis removing 4 to 6 litres per day + albumin 5 to 8 g/litre removed

Outcomes reported: length of hospital stay (days) (all admissions until maximal follow-up)
Follow-up (months): 0.3

Notes
Source of funding (quote): "Author(s) received no specific funding for this work".
Trial name/trial registry number: NCT02821377
Attempts were made to contact the authors in November 2018.

Risk of bias

<table>
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<tr>
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<td>Comment: there were no post-randomisation dropouts.</td>
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</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>Comment: no other bias noted</td>
</tr>
</tbody>
</table>

BD: twice daily
HCC: hepatocellular carcinoma
HES: hydroxy-ethyl start
HRS: hepatorenal syndrome
IV: intravenous
LVP: large volume paracentesis
SBP: spontaneous bacterial peritonitis
TDS: thrice daily
TP: therapeutic paracentesis

Characteristics of excluded studies [ordered by study ID]

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdel-Khalek 2010b</td>
<td>Comparison of variations in treatment</td>
</tr>
<tr>
<td>Altman 1998</td>
<td>Comparison of variations in treatment</td>
</tr>
<tr>
<td>Angeli 1994</td>
<td>Comparison of variations in treatment</td>
</tr>
<tr>
<td>Study</td>
<td>Reason for exclusion</td>
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<tr>
<td>--------------------</td>
<td>--------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Antillon 1993</td>
<td>Not a randomised clinical trial</td>
</tr>
<tr>
<td>Applefeld 1994</td>
<td>In this cross-over randomised clinical trial, the cross-over took place after 12 days of treatment with just 2 days between the cross-over; this short duration of treatment and cross-over period is insufficient time to determine the objectives of this review.</td>
</tr>
<tr>
<td>Arrigoni 1988</td>
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<tr>
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<td>The diuretics used in the control group was variable - these may or may not have been used; therefore it is not possible to define the control group.</td>
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<tr>
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<td>There were several differences between the intervention and control group: the antibiotic prophylaxis was given only to intervention group, the diuretics were stopped in the intervention but not in the control group and this was variable; therefore, it was not possible to define the control group.</td>
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<tr>
<td>Cadranel 1992a</td>
<td>The unit of randomisation was the procedure (i.e. each patient underwent both procedures).</td>
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<td>Large volume paracentesis without fluid replacement or systemic vasoconstrictors was not one of the treatments included in this review.</td>
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<td>No details of the diuretic regimen were available; so, it was not entirely clear if the drugs in the diuretic regimen were similar in the two groups.</td>
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<td>In the control group, the diuretic regimen was variable.</td>
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<td>Wapnick 1979</td>
<td>Appeared to be a quasi-randomised study or a nonrandomised study: authors stated &quot;Patients in the medical group were matched with those in the surgical group according to the subgroups listed in Table I and sequentially according to the date of entry into the study&quot;.</td>
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<td>Although authors called this a randomised study, the authors also stated that the patients were studied retrospectively. An adequate method of randomisation was also not reported.</td>
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**Characteristics of ongoing studies [ordered by study ID]**

**EUCTR 2018**

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<td>2. Overall survival</td>
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<td>3. Non-resolution of ascites</td>
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<tr>
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</tr>
<tr>
<td>Contact information</td>
<td>Instituto Grifols S.A. (<a href="mailto:IGregulatory.affairs@grifols.com">IGregulatory.affairs@grifols.com</a>)</td>
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**Macken 2018**

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<td>Interventions</td>
<td>Tunnelled peritoneal catheter versus paracentesis plus fluid replacement</td>
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<td>3. Health resource utilisation and quality of life</td>
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<tr>
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<tr>
<td>Contact information</td>
<td>Lucia Macken (<a href="mailto:lucia.macken@bsuh.nhs.uk">lucia.macken@bsuh.nhs.uk</a>)</td>
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<td>Interventions</td>
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| Outcomes            | 1. Non-resolution of ascites  
  2. Adverse events |
| Starting date       | 20 January 2017 |
| Contact information | Gastro Unit, Medical Division, University Hospital Hvidovre, Hvidovre, Denmark, 2650 |
| Notes               | NCT03027635; Study terminated |

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</tr>
<tr>
<td>Interventions</td>
<td>Transjugular intrahepatic portosystemic shunt versus paracentesis plus albumin</td>
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| Outcomes            | 1. Transplant-free survival  
  2. Hepatic decompensation  
  3. Quality of life  
  4. Adverse events |
| Starting date       | 29 June 2017 |
| Contact information | Guohong Han (hangh@fmmu.edu.cn) |
| Notes               | NCT03172273 |

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<td>Interventions</td>
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Treatment for ascites in adults with decompensated liver cirrhosis: a network meta-analysis (Review)
NCT03202524 (Continued)

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<th>Outcomes</th>
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<tr>
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NCT03451292

| Trial name or title                          | ARIAPUMP                                                 |
| Methods                                      | Randomised clinical trial                                |
| Participants                                 | Refractory ascites and cirrhosis                         |
| Interventions                                | Alfapump versus paracentesis plus albumin                |
| Outcomes                                     | 1. Treatment costs                                       |
|                                              | 2. Non-resolution of ascites                             |
|                                              | 3. Hepatic decompensation                                |
|                                              | 4. Adverse events                                         |
| Starting date                                | 17 July 2018                                             |
| Contact information                         | Sandra David-Tchouda (sdavidtchouda@chu-grenoble.fr)      |
| Notes                                        | NCT03506893                                              |

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.
This table is too wide to be displayed in RevMan. This table can be found at: https://doi.org/10.5281/zenodo.3604600.
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### Table 3. Risk of bias (Continued)

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### Table 4. Model fit

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<th>Outcome</th>
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<td><strong>Mortality at maximal follow-up</strong></td>
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<td>pD</td>
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<td><strong>Any adverse events (number of people)</strong></td>
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<td><strong>Other features of decompensation at maximal follow-up</strong></td>
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<td><strong>Length of hospital stay (days) (all admissions until maximal follow-up)</strong></td>
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<td>pD</td>
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Table 4. Model fit (Continued)

<table>
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<th>Treatment costs</th>
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Dbar = posterior mean of deviance  
DIC = deviance information criteria  
pD = effective number of parameters or leverage

Table 5. Effect estimates (network meta-analysis)

This table is too wide to be displayed in RevMan. This table can be found at: https://doi.org/10.5281/zenodo.3604602

The table provides the effect estimates of each pairwise comparison for the different outcomes. The top half of the table indicates the effect estimates from the direct comparisons. The bottom half of the table indicates the effect estimates from the network meta-analysis. For network meta-analysis, to identify the effect estimate of a comparison, say A versus B, look at the cell that occupies the row corresponding to intervention A and the column corresponding to intervention B for the direct effect estimate. If that cell is empty (indicated by a ‘-‘), look at the row corresponding to intervention B and the column corresponding to intervention A. Take the inverse of this number (i.e. 1/number) to arrive at the treatment effect of A versus B. For direct comparisons, this is exactly the opposite; look at the cell that occupies the column corresponding to intervention A and the row corresponding to intervention B for the direct effect estimate. If that cell is empty, look at the column corresponding to intervention B and the row corresponding to intervention A. Take the inverse of this number to arrive at the treatment effect of A versus B. If the cell corresponding to B versus A is also missing in direct comparisons, this means that there was no direct comparison.

Statistically significant results are shown in italics.
<table>
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<tr>
<th>Study name</th>
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<th>Mean in intervention group</th>
<th>Standard deviation in intervention group</th>
<th>Number of participants in intervention group</th>
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<th>Standard deviation in control group</th>
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<th>Mean difference and 95% confidence intervals (according to Review Manager formula)</th>
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<td>10.5 USD</td>
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<td>1629.0 USD</td>
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<td>-1739.00 (95% CI -1788.37 to -1689.63)</td>
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<td>295 USD</td>
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Abbreviations:
USD = United States Dollar
CI = confidence intervals
Table 7. Effect estimates (Subgroup: grade 3 ascites only)

This table is too wide to be displayed in RevMan. This table can be found at: https://doi.org/10.5281/zenodo.3604780.

The table provides the network meta-analysis effect estimates for the subgroup of grade 3 ascites only of each pairwise comparison for the different outcomes. To identify the effect estimate of a comparison, say A versus B, look at the cell that occupies the row corresponding to intervention A and the column corresponding to intervention B for the direct effect estimate. If that cell is empty (indicated by a ‘-’), look at the row corresponding to intervention B and the column corresponding to intervention A. Take the inverse of this number (i.e. 1/number) to arrive at the treatment effect of A versus B.
Statistically significant results are shown in italics.

**Abbreviations:**

HR = hazard ratio; OR = odds ratio

Table 8. Effect estimates (Subgroup: refractory or recurrent ascites only)

This table is too wide to be displayed in RevMan. This table can be found at: https://doi.org/10.5281/zenodo.3604784.

The table provides the network meta-analysis effect estimates for the subgroup of refractory or recurrent ascites only of each pairwise comparison for the different outcomes. To identify the effect estimate of a comparison, say A versus B, look at the cell that occupies the row corresponding to intervention A and the column corresponding to intervention B for the direct effect estimate. If that cell is empty (indicated by a ‘-’), look at the row corresponding to intervention B and the column corresponding to intervention A. Take the inverse of this number (i.e. 1/number) to arrive at the treatment effect of A versus B.
Statistically significant results are shown in italics.

**Abbreviations:**

HR = hazard ratio
OR = odds ratio

**APPENDICES**

Appendix 1. Search strategies

<table>
<thead>
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<th>Database</th>
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<th>Search strategy</th>
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| Central Register of Controlled Trials (CENTRAL) in the Cochrane Library | Issue 5, 2019 | #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 May 2019 | 1. 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. |
(Continued)

<table>
<thead>
<tr>
<th>Database</th>
<th>Start Date to End Date</th>
<th>Query</th>
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</table>
| Embase Ovid               | January 1974 to May 2019                      | 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 May 2019                  | #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-analy*  
#4 #1 AND #2 AND #3 |
| ClinicalTrials.gov        | May 2019                                      | cirrhosis | Interventional Studies | Ascites | Phase 2, 3, 4 |
| World Health Organization International Clinical Trials Registry Platform | May 2019                                      | ascites |
(Continued)
form (apps.who.int/trialsearch/Default.aspx)

European Medical Agency (www.ema.europa.eu/ema/) and USA
Food and Drug Administration (www.fda.gov) May 2019 ascites; cirrhosis; random

Appendix 2. Data
This table is too wide to be displayed in RevMan. This table can be found at: https://doi.org/10.5281/zenodo.3604801.

CONTRIBUTIONS OF AUTHORS

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

Review
Co-ordinating the review: KG
Study selection: KG, AB, LP, MP, DR
Data extraction: KG, AB, LP, MP, DR
Writing the review: KG and AB
Providing advice on the review: SF, AJS, NH, EJM, MC, DT, CSP, BRD, ET
Securing funding for the review: KG

DECLARATIONS OF INTEREST
None known for any of the authors

SOURCES OF SUPPORT

Internal sources
• University College London, UK.
  Writing equipment, software, etc

External sources
• National Institute for Health Research (NIHR), UK.
  Payment for writing reviews, writing equipment, software

DIFFERENCES BETWEEN PROTOCOL AND REVIEW
1. We used the 'paracentesis plus fluid replacement' as the reference group (from 'no active intervention'), as 'paracentesis plus fluid replacement' was the commonest intervention compared in the trials.
2. We did not perform Trial Sequential Analysis (TSA) because the risk of false positive results with Bayesian meta-analysis is probably less or at least equivalent to TSA.
3. We used the latest guidance from the GRADE Working group (Yepes-Nunez 2019) rather than the previous guidance (Puhan 2014) for presenting the 'Summary of Findings' table.

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4. The trials did not report the proportion of people with other episodes of decompensation but reported the number of episodes of decompensation. Therefore, we treated this as a count outcome and used the Poisson likelihood to calculate the rate ratio.

5. In the absence of a protocol published prior to the start of the study, we classified the risk of bias as low for selective reporting bias only when mortality, adverse events, and resolution from ascites were reported, as we anticipated these outcomes to be routinely measured in clinical trials of this nature.

6. We used 30,000 iterations (instead of 10,000 iterations) as a minimum for burn-in of the simulation sampler used to estimate quantities in the statistical models to ensure convergence of the simulation sampler.

7. We did not present some information such as ranking probability tables, rankograms, and surface area under the curve (SUCRA plots) because of the concern about the misinterpretation of the results. We have highlighted this clearly within the text of the review along with the reasons for not presenting them.

**NOTES**

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).