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[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% CrI 1.93 to 62.68) and adding aldosterone antagonists to paracentesis plus fluid replacement (HR 30.63; 95% CrI 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% CrI 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?

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

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

Outcomes	Aldosterone antagonists plus loop diuretics		Paracentesis plus systemic vasoconstrictors		Aldosterone antagonists plus loop diuretics plus paracentesis plus fluid replacement		Transjugular intrahepatic portosystemic shunt	
Mortality at maximal follow-up								
Paracentesis plus fluid replacement 368 per 1000 (36.8%)	**HR 1.05** (0.70 to 1.69) **Network estimate**	**18 more per 1000** (109 fewer to 253 more)	**HR 1.64** (0.46 to 6.32) **Network estimate**	**235 more per 1000** (200 fewer to 632 more)	**HR 1.24** (0.62 to 2.59) **Network estimate**	**88 more per 1000** (141 fewer to 587 more)	**HR 0.84** (0.60 to 1.18) **Network estimate**	**59 fewer per 1000** (148 fewer to 65 more)
	Very low[1,2,3]		**Very low**[1,2,3]		**Very low**[1,2,3]		**Very low**[1,2,3]	
	Based on 211 participants (4 RCTs)		Based on 165 participants (5 RCTs)		No direct RCT		Based on 452 participants (7 RCTs)	
Serious adverse events (number of events)								
Paracentesis plus fluid replacement 0 per 1000 (0 per 100 participants)	**Rate ratio 1.30** (0.27 to 6.99) **Direct estimate**	**Not estimable**	-		-		**Not estimable** (10 serious adverse events in 35 participants)	
	Very low[1,2,3]						**Very low**[1,2,3]	
	Based on 41 participants (1 RCT)						Based on 70 participants (1 RCT)	
Any adverse events (number of people)								

Paracentesis plus fluid replacement 100 per 1000 (10%)	**OR 3.54** (0.43 to 27.41) **Network estimate**	**182 more per 1000** (54 fewer to 653 more)	**OR 1.63** (0.30 to 11.66) **Network estimate**	**53 more per 1000** (68 fewer to 464 more)	-	-		
	Very low[1,2,3]		**Very low**[1,2,3]					
	Based on 84 participants (2 RCTs)		Based on 145 participants (4 RCTs)					
Any adverse events (number of events)								
Paracentesis plus fluid replacement 118 per 1000 (11.8 per 100 participants)	**Rate ratio 4.12** (0.87 to 34.02) **Network estimate**	**367 more per 1000** (15 fewer to 3885 more)	**Rate ratio 1.37** (0.36 to 5.82) **Network estimate**	**43 more per 1000** (76 fewer to 567 more)	-	-		
	Very low[1,2,3]		**Very low**[1,2,3]					
	Based on 31 participants (1 RCT)		Based on 25 participants (1 RCT)					
Liver transplantation at maximal follow-up								
Paracentesis plus fluid replacement 121 per 1000 (12.1%)	-		**HR 1.08** (0.11 to 10.35) **Network estimate**	**10 more per 1000** (108 fewer to 879 more)	-		**HR 0.87** (0.52 to 1.44) **Network estimate**	**15 fewer per 1000** (58 fewer to 54 more)
			Very low[1,2,3]				**Very low**[1,2,3]	
			Based on 145 participants (4 RCTs)				Based on 427 participants (6 RCT)	
Resolution of ascites at maximal follow-up (by ultrasound)								
Paracentesis plus fluid replacement 158 per 1000 (15.8%)	**HR 1.10** (0.12 to 10.74) **Network estimate**	**16 more per 1000** (140 fewer to 842 more)	-		**HR 1.17** (0.01 to 98.79) **Network estimate**	**27 more per 1000** (156 fewer to 842 more)	**HR 9.44** (1.93 to 62.68) **Network estimate**	**842 more per 1000** (147 more to 842 more)
	Very low[1,2,3,4]				**Very low**[1,2,3,4]		**Very low**[1,2,4]	
	Based on 125 participants (3 RCTs)				No direct RCT		Based on 392 participants (6 RCTs)	

Other features of decompensation at maximal follow-up								
Paracentesis plus fluid replacement 439 per 1000 (43.9 per 100 participants)	**Rate ratio 2.04** (1.37 to 3.10) **Network estimate**	**458 more per 1000** (164 more to 922 more)	**Rate ratio 0.76** (0.14 to 3.61) **Network estimate**	**107 fewer per 1000** (377 fewer to 1144 more)	**Rate ratio 1.04** (0.56 to 1.93) **Network estimate**	**16 more per 1000** (195 fewer to 409 more)	**Rate ratio 1.17** (0.92 to 1.49) **Network estimate**	**76 more per 1000** (33 fewer to 217 more)
	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.

[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

Vasodil = Systemic vasodilator
ThiazD = Thiazide diuretics

TIPS = Transjugular intrahepatic portosystemic shunt

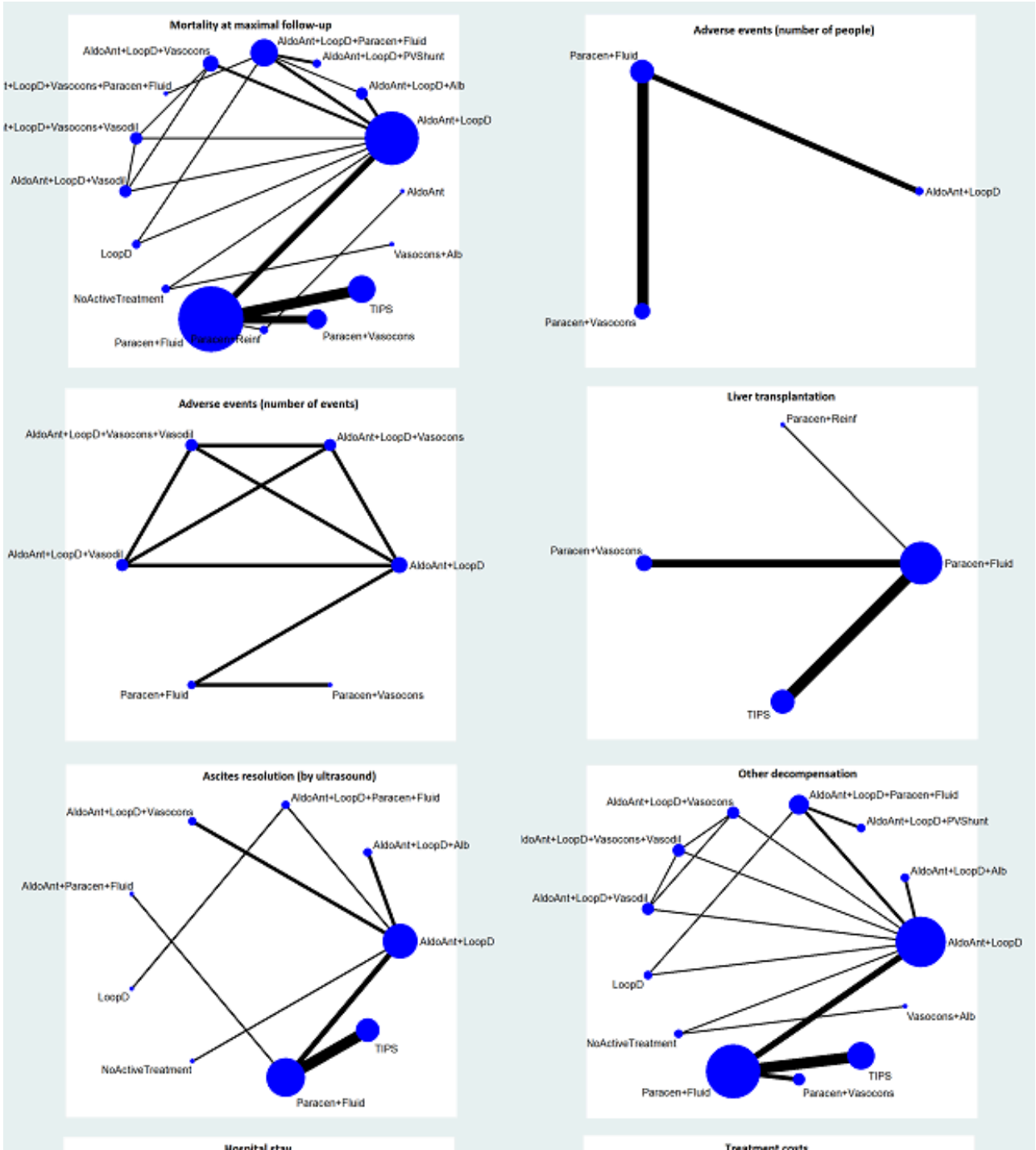


Figure 1. (Continued)

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					
Interventions	**Relative effect (95% CrI)**	**Anticipated absolute effect* (95% CrI)**			**Quality of evidence**
		Paracentesis plus fluid replacement	**Various interventions**	**Difference**	
Mortality at maximal follow-up **Total studies: 32** **Total participants: 2448**					
Paracentesis plus fluid replacement	**Reference**				
Aldosterone antagonists plus loop diuretics (4 RCTs; 211 participants)	**HR 1.05** (0.70 to 1.69) **Network estimate**	**368 per 1000**	**387 per 1000** (260 to 621)	**18 more per 1000** (109 fewer to 253 more)	**Very low**[1,2,3]
Paracentesis plus systemic vasoconstrictors (5 RCTs; 165 participants)	**HR 1.64** (0.46 to 6.32) **Network estimate**	**368 per 1000**	**604 per 1000** (168 to 1000)	**235 more per 1000** (200 fewer to 632 more)	**Very low**[1,2,3]

Aldosterone antagonists plus loop diuretics plus paracentesis plus fluid replacement (No direct RCT)	**HR 1.24** (0.62 to 2.59) **Network estimate**	**368 per 1000**	**457 per 1000** (227 to 955)	**88 more per 1000** (141 fewer to 587 more)	**Very low**[1,2,3]
Transjugular intrahepatic portosystemic shunt (7 RCTs; 452 participants)	**HR 0.84** (0.60 to 1.18) **Network estimate**	**368 per 1000**	**309 per 1000** (221 to 433)	**59 fewer per 1000** (148 fewer to 65 more)	**Very low**[1,2,3]
No active treatment (No direct RCT)	**HR 1.66** (0.46 to 6.99) **Network estimate**	**368 per 1000**	**611 per 1000** (170 to 1000)	**243 more per 1000** (199 fewer to 632 more)	**Very low**[1,2,3]
Loop diuretics (No direct RCT)	**HR 0.71** (0.23 to 2.16) **Network estimate**	**368 per 1000**	**263 per 1000** (84 to 797)	**105 fewer per 1000** (284 fewer to 429 more)	**Very low**[1,2,3]
Paracentesis plus reinfusion (1 RCT; 24 participants)	**HR 0.77** (0.23 to 2.68) **Network estimate**	**368 per 1000**	**284 per 1000** (84 to 987)	**84 fewer per 1000** (285 fewer to 619 more)	**Very low**[1,2,3]
Aldosterone antagonists plus loop diuretics plus albumin (No direct RCT)	**HR 1.06** (0.57 to 2.16) **Network estimate**	**368 per 1000**	**392 per 1000** (209 to 795)	**23 more per 1000** (159 fewer to 427 more)	**Very low**[1,2,3]
Aldosterone antagonists plus loop diuretics plus peritoneovenous shunt (No direct RCT)	**HR 0.97** (0.40 to 2.43) **Network estimate**	**368 per 1000**	**358 per 1000** (148 to 894)	**10 fewer per 1000** (221 fewer to 526 more)	**Very low**[1,2,3]
Aldosterone antagonists plus loop diuretics plus systemic vasoconstrictors (No direct RCT)	**HR 0.42** (0.15 to 1.22) **Network estimate**	**368 per 1000**	**153 per 1000** (55 to 450)	**215 fewer per 1000** (313 fewer to 82 more)	**Very low**[1,2,3]
Aldosterone antagonists (No direct RCT)	**HR 1.92** (0.24 to 20.64) **Network estimate**	**368 per 1000**	**708 per 1000** (90 to 1000)	**340 more per 1000** (278 fewer to 632 more)	**Very low**[1,2,3]
Aldosterone antagonists plus loop diuretics plus systemic vasoconstrictors plus paracentesis plus fluid replacement (No direct RCT)	**HR 1.11** (0.02 to 39.77) **Network estimate**	**368 per 1000**	**408 per 1000** (9 to 1000)	**40 more per 1000** (360 fewer to 632 more)	**Very low**[1,2,3]
Aldosterone antagonists plus loop diuretics plus systemic vasoconstrictors plus systemic vasodilator	**HR 0.61** (0.02 to 9.17) **Network estimate**	**368 per 1000**	**226 per 1000** (9 to 1000)	**142 fewer per 1000** (360 fewer to 632 more)	**Very low**[1,2,3]

(No direct RCT)					
Aldosterone antagonists plus loop diuretics plus systemic vasodilator (No direct RCT)	**HR 0.62** (0.03 to 9.10) **Network estimate**	**368 per 1000**	**228 per 1000** (12 to 1000)	**140 fewer per 1000** (357 fewer to 632 more)	**Very low**[1,2,3]
Systemic vasoconstrictors plus albumin (No direct RCT)	**HR 2.62** (0.41 to 19.28) **Network estimate**	**368 per 1000**	**965 per 1000** (151 to 1000)	**596 more per 1000** (218 fewer to 632 more)	**Very low**[1,2,3]
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)	**Rate ratio 1.30** (0.27 to 6.99) **Direct estimate**	**0 per 1000**	**Not estimable**		**Very low**[1,2,3]
Transjugular intrahepatic portosystemic shunt (1 RCT; 70 participants)	Not estimable (10 serious adverse events in 35 participants)	**0 per 1000**	**Not estimable**		**Very low**[1,2,3]
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: 6** **Total participants: 229**					
Paracentesis plus fluid replacement	**Reference**				
Paracentesis plus systemic vasoconstrictors (4 RCTs; 145 participants)	**OR 1.63** (0.30 to 11.66) **Network estimate**	**100 per 1000**	**153 per 1000** (32 to 564)	**53 more per 1000** (68 fewer to 464 more)	**Very low**[1,2,3]
Aldosterone antagonists plus loop diuretics (2 RCT; 84 participants)	**OR 3.54** (0.43 to 27.41) **Network estimate**	**100 per 1000**	**282 per 1000** (46 to 753)	**182 more per 1000** (54 fewer to 653 more)	**Very low**[1,2,3]
Any adverse events (number of events) **Total studies: 3**					

Total participants: 116					
Paracentesis plus fluid replacement	**Reference**				
Aldosterone antagonists plus loop diuretics (1 RCT; 31 participants)	**Rate ratio 4.12** (0.87 to 34.02) **Network estimate**	**118 per 1000**	**485 per 1000** (103 to 4003)	**367 more per 1000** (15 fewer to 3885 more)	**Very low**[1,2,3]
Paracentesis plus systemic vasoconstrictors (1 RCT; 25 participants)	**Rate ratio 1.37** (0.36 to 5.82) **Network estimate**	**118 per 1000**	**161 per 1000** (42 to 685)	**43 more per 1000** (76 fewer to 567 more)	**Very low**[1,2,3]
Aldosterone antagonists plus loop diuretics plus systemic vasoconstrictors (No direct RCT)	**Rate ratio 3.30** (0.38 to 38.51) **Network estimate**	**118 per 1000**	**388 per 1000** (45 to 4531)	**271 more per 1000** (73 fewer to 4413 more)	**Very low**[1,2,3]
Aldosterone antagonists plus loop diuretics plus systemic vasoconstrictors plus systemic vasodilator (No direct RCT)	**Rate ratio 4.25** (0.53 to 46.99) **Network estimate**	**118 per 1000**	**501 per 1000** (62 to 5529)	**383 more per 1000** (55 fewer to 5411 more)	**Very low**[1,2,3]
Aldosterone antagonists plus loop diuretics plus systemic vasodilator (No direct RCT)	**Rate ratio 2.41** (0.24 to 29.67) **Network estimate**	**118 per 1000**	**284 per 1000** (28 to 3490)	**166 more per 1000** (89 fewer to 3372 more)	**Very low**[1,2,3]
Liver transplantation at maximal follow-up **Total studies: 11** **Total participants: 596**					
Paracentesis plus fluid replacement	**Reference**				
Paracentesis plus systemic vasoconstrictors (4 RCTs; 145 participants)	**HR 1.08** (0.11 to 10.35) **Network estimate**	**121 per 1000**	**131 per 1000** (14 to 1000)	**10 more per 1000** (108 fewer to 879 more)	**Very low**[1,2,3]
Transjugular intrahepatic portosystemic shunt (6 RCTs; 427 participants)	**HR 0.87** (0.52 to 1.44) **Network estimate**	**121 per 1000**	**106 per 1000** (63 to 175)	**15 fewer per 1000** (58 fewer to 54 more)	**Very low**[1,2,3]
Paracentesis plus reinfusion (1 RCT; 24 participants)	**HR 2.56** (0.20 to 90.92) **Network estimate**	**121 per 1000**	**310 per 1000** (25 to 1000)	**189 more per 1000** (97 fewer to 879 more)	**Very low**[1,2,3]
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**					
Paracentesis plus fluid replacement	**Reference**				
Aldosterone antagonists plus loop diuretics (3 RCTs; 125 participants)	**HR 1.10** (0.12 to 10.74) **Network estimate**	**158 per 1000**	**174 per 1000** (18 to 1000)	**16 more per 1000** (140 fewer to 842 more)	**Very low**[1,2,3,4]
Aldosterone antagonists plus loop diuretics plus paracentesis plus fluid replacement (No direct RCT)	**HR 1.17** (0.01 to 98.79) **Network estimate**	**158 per 1000**	**185 per 1000** (2 to 1000)	**27 more per 1000** (156 fewer to 842 more)	**Very low**[1,2,3,4]
Transjugular intrahepatic portosystemic shunt (6 RCTs; 392 participants)	**HR 9.44** (1.93 to 62.68) **Network estimate**	**158 per 1000**	**1000 per 1000** (305 to 1000)	**842 more per 1000** (147 more to 842 more)	**Very low**[1,2,4]
No active treatment (No direct RCT)	**HR 0.16** (0.00 to 17.37) **Network estimate**	**158 per 1000**	**26 per 1000** (0 to 1000)	**132 fewer per 1000** (158 fewer to 842 more)	**Very low**[1,2,3,4]
Loop diuretics (No direct RCT)	**HR 2.26** (0.01 to 846.41) **Network estimate**	**158 per 1000**	**357 per 1000** (1 to 1000)	**199 more per 1000** (157 fewer to 842 more)	**Very low**[1,2,3,4]
Aldosterone antagonists plus loop diuretics plus albumin (No direct RCT)	**HR 3.28** (0.09 to 118.39) **Network estimate**	**158 per 1000**	**517 per 1000** (15 to 1000)	**360 more per 1000** (143 fewer to 842 more)	**Very low**[1,2,3,4]
Aldosterone antagonists plus loop diuretics plus systemic vasoconstrictors (No direct RCT)	**HR 8.81** (0.06 to 1908.36) **Network estimate**	**158 per 1000**	**1000 per 1000** (10 to 1000)	**842 more per 1000** (148 fewer to 842 more)	**Very low**[1,2,3,4]
Aldosterone antagonists plus paracentesis plus fluid replacement (1 RCT; 36 participants)	**HR 30.63** (5.06 to 692.98) **Direct estimate**	**158 per 1000**	**1000 per 1000** (799 to 1000)	**842 more per 1000** (641 more to 842 more)	**Low**[1,2]
Other features of decompensation at maximal follow-up **Total studies: 25** **Total participants: 1756**					
Paracentesis plus fluid replacement	**Reference**				
Aldosterone antagonists plus loop diuretics	**Rate ratio 2.04**	**439 per 1000**	**896 per 1000**	**458 more per 1000**	**Very low**[1,2,4]

(4 RCTs; 242 participants)	(1.37 to 3.10) **Network estimate**		(602 to 1360)	(164 more to 922 more)	
Paracentesis plus systemic vasoconstrictors (3 RCTs; 114 participants)	**Rate ratio 0.76** (0.14 to 3.61) **Network estimate**	**439 per 1000**	**332 per 1000** (62 to 1582)	**107 fewer per 1000** (377 fewer to 1144 more)	**Very low**[1,2,3,4]
Aldosterone antagonists plus loop diuretics plus paracentesis plus fluid replacement (No direct RCT)	**Rate ratio 1.04** (0.56 to 1.93) **Network estimate**	**439 per 1000**	**455 per 1000** (244 to 848)	**16 more per 1000** (195 fewer to 409 more)	**Very low**[1,2,3,4]
Transjugular intrahepatic portosystemic shunt (7 RCTs; 452 participants)	**Rate ratio 1.17** (0.92 to 1.49) **Network estimate**	**439 per 1000**	**515 per 1000** (405 to 655)	**76 more per 1000** (33 fewer to 217 more)	**Very low**[1,2,3,4]
No active treatment (No direct RCT)	**Rate ratio 3.34** (0.85 to 13.94) **Network estimate**	**439 per 1000**	**1466 per 1000** (374 to 6115)	**1028 more per 1000** (64 fewer to 5677 more)	**Very low**[1,2,3,4]
Loop diuretics (No direct RCT)	**Rate ratio 0.95** (0.40 to 2.23) **Network estimate**	**439 per 1000**	**418 per 1000** (176 to 977)	**21 fewer per 1000** (262 fewer to 538 more)	**Very low**[1,2,3,4]
Aldosterone antagonists plus loop diuretics plus albumin (No direct RCT)	**Rate ratio 1.56** (0.84 to 2.87) **Network estimate**	**439 per 1000**	**682 per 1000** (369 to 1260)	**244 more per 1000** (69 fewer to 821 more)	**Very low**[1,2,3,4]
Aldosterone antagonists plus loop diuretics plus peritoneovenous shunt (No direct RCT)	**Rate ratio 0.84** (0.41 to 1.70) **Network estimate**	**439 per 1000**	**369 per 1000** (180 to 747)	**70 fewer per 1000** (258 fewer to 308 more)	**Very low**[1,2,3,4]
Aldosterone antagonists plus loop diuretics plus systemic vasoconstrictors (No direct RCT)	**Rate ratio 0.53** (0.02 to 4.98) **Network estimate**	**439 per 1000**	**233 per 1000** (7 to 2185)	**205 fewer per 1000** (431 fewer to 1747 more)	**Very low**[1,2,3,4]
Aldosterone antagonists plus loop diuretics plus systemic vasoconstrictors plus systemic vasodilator (No direct RCT)	**Rate ratio 0.53** (0.02 to 4.99) **Network estimate**	**439 per 1000**	**233 per 1000** (8 to 2190)	**206 fewer per 1000** (431 fewer to 1751 more)	**Very low**[1,2,3,4]
Aldosterone antagonists plus loop diuretics plus systemic vasodilator (No direct RCT)	**Rate ratio 0.53** (0.02 to 5.11) **Network estimate**	**439 per 1000**	**231 per 1000** (7 to 2241)	**208 fewer per 1000** (431 fewer to 1802 more)	**Very low**[1,2,3,4]

Systemic vasoconstrictors plus albumin (No direct RCT)	**Rate ratio 3.90** (0.96 to 16.98) **Network estimate**	**439 per 1000**	**1712 per 1000** (422 to 7447)	**1274 more per 1000** (16 fewer to 7009 more)	**Very low**[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.
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.

[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 (Tsochatzis 2014; NCBI 2018a). The major causes of liver cirrhosis include excessive alcohol consumption, viral hepatitis, non-alcohol-related fatty liver disease, autoimmune liver disease, and metabolic liver disease (Williams 2014; Ratib 2015; Setiawan 2016). The global prevalence of liver cirrhosis is difficult to estimate as most estimates correspond to chronic liver disease (which includes liver fibrosis and liver cirrhosis). In studies from the USA, the prevalence of chronic liver disease varies between 0.3% to 2.1% (Scaglione 2015; Setiawan 2016); in the UK, the prevalence was 0.1% in one study (Fleming 2008). In 2010, liver cirrhosis was responsible for an estimated 2% of all global deaths, equivalent to one million deaths (Mokdad 2014). There is an increasing trend of cirrhosis-related deaths in some countries, such as the UK, while there is a decreasing trend in other countries, such as France (Mokdad 2014; Williams 2014). The major cause of complications and deaths in people with liver cirrhosis is due to the development of clinically significant portal hypertension (hepatic venous pressure gradient at least 10 mmHg) (De Franchis 2015). Some of the clinical features of decompensation include jaundice, coagulopathy, ascites, variceal bleeding, hepatic encephalopathy, and renal failure (De Franchis 2015; McPherson 2016; EASL 2018). Decompensated cirrhosis is the most common indication for liver transplantation (Merion 2010; Adam 2012).

Ascites

Ascites is accumulation of free fluid in the abdomen (peritoneal cavity) (NCBI 2018b), and is a feature of liver decompensation (Tsochatzis 2017). Approximately 20% of people with cirrhosis have ascites (D'Amico 2014). Approximately 1% to 4% of people with cirrhosis develop ascites each year (D'Amico 2006; D'Amico 2014). Ascites is the first sign of liver decompensation in about a third of people with compensated liver cirrhosis (D'Amico 2014). Ascites can be graded as grade 1 ascites, which is mild ascites only detectable by ultrasound examination; grade 2 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 splanchnic circulation (dilation of the blood vessels supplying the digestive organs in the abdomen such as liver, pancreas, and intestines) (Ginès 2009; Moore 2013). This activates the renin–angiotensin system (Ginès 2009; Moore 2013), leading to fluid retention (Moore 2013). In addition, the vessel wall permeability is increased due to the pathological increase in vascular endothelial growth factor (VEGF) (Colle 2008), and the oncotic pressure is decreased due to decreased albumin synthesis by the diseased liver leading to leaky splanchnic blood vessels in people with portal hypertension (Moore 2013). This results in fluid accumulation in the peritoneal cavity, that is, ascites (Moore 2013).

Description of the intervention

Although people with cirrhosis and grade 2 ascites, grade 3 ascites, and refractory ascites should be considered for liver transplantation (EASL 2010; Runyon 2013; EASL 2016; EASL 2018), cirrhotic ascites alone without other features of end-stage liver disease, such as 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 suggests that midodrine (a vasoconstrictor) should be considered in people with refractory ascites (Runyon 2013), while midodrine is not recommended by EASL guidelines (EASL 2018).

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

How the intervention might work

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

splanchnic vasodilation which is another mechanism of developing ascites.

Paracentesis involves removing the ascitic fluid. Removal of up to 5 litres of fluid in one session of paracentesis is unlikely to cause circulatory shock (EASL 2010; Runyon 2013), but removal of more than this volume can lead to circulatory shock. Various methods to 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 canrenoate);
- 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. We

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.
- Unclear risk of bias: the method of sequence generation was not specified.
- High risk of bias: the sequence generation method was not random or only quasi-randomised. We 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 (RaR) 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 (tau^2 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 I^2 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 2012). 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% CrI 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) in graphs (SUCRA) (Salanti 2011). We plotted the probability that each intervention was best, second best, third best, etc. for each of the different outcomes (rankograms), which are generally considered more informative (Salanti 2011; Dias 2012b), 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 vasoconstrictors, 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.

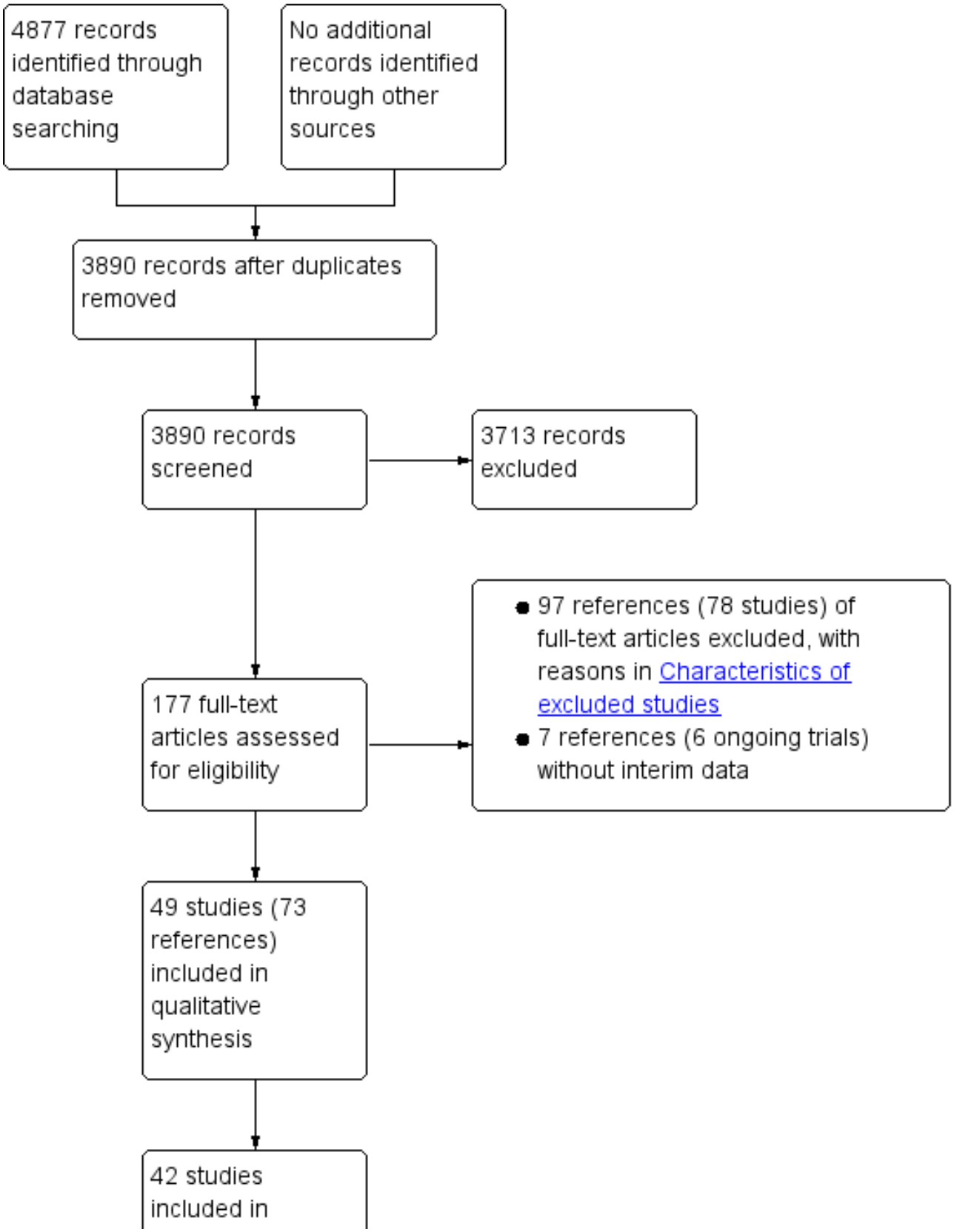
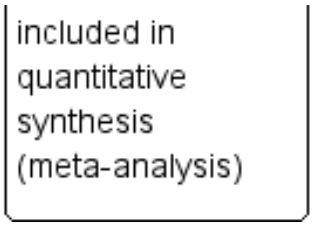


Figure 2. (Continued)



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; Hagege 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; Moreau 2002; Sanyal 2003; Salerno 2004; Romanelli 2006; Singh 2006a; Singh 2006b; Lata 2007; Appenrodt 2008; Singh 2008; Licata 2009; Narahara 2011; Raza 2011; Al Sebaey 2012; Amin 2012; Bari 2012; Singh 2012a; Singh 2013; Ali 2014; Hamdy 2014; Tuttolomondo 2016; Bureau 2017c; Rai 2017; Caraceni 2018; Sola 2018). A total of 3521 participants were randomised to different interventions. The number of participants within each trial ranged from 20 to 440. A total of 2870 participants from 42 trials were included in one or more outcomes (Gregory 1977; Fogel 1981; Descos 1983; Gines 1987; Salerno 1987; Chesta 1990; Ginès 1991; Strauss 1991; Acharya 1992; Hagege 1992; Ljubici 1994; Sola 1994; Ginès 1995; Schaub 1995; Lebrec 1996; Fernandez-Esparrach 1997; Graziotto 1997; Mehta 1998; Gentilini 1999a; Rossle 2000; Ginès 2002; Moreau 2002; Sanyal 2003; Salerno 2004; Romanelli 2006; Singh 2006a; Singh 2006b; Lata 2007; Singh 2008; 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; Hagege 1992; Ljubici 1994; Sola 1994; Ginès 1995; Lebrec 1996; Chang 1997; Fernandez-Esparrach 1997; Graziotto 1997; Mehta 1998; Gentilini 1999a; Rossle 2000; Ginès 2002; Moreau 2002; Sanyal 2003; Salerno 2004; Romanelli 2006; Singh 2006a; Singh 2006b; Lata 2007; Appenrodt 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; Ginès 1991; Strauss 1991; Acharya 1992; Bruno 1992; Hagege 1992; Ljubici 1994; Sola 1994; Ginès 1995; Lebrec 1996; Chang 1997; Fernandez-Esparrach 1997; Graziotto 1997; Mehta 1998; Gentilini 1999a; Rossle 2000; Ginès 2002; Moreau 2002; Sanyal 2003; Salerno 2004; Romanelli 2006; Singh 2006a; Singh 2006b; Lata 2007; Appenrodt 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; Hagege 1992; Ljubici 1994; Schaub 1995; Chang 1997; Fernandez-Esparrach 1997; Mehta 1998; Moreau 2002; Singh 2006a; Singh 2006b; Lata 2007; Appenrodt 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).

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; Moreau 2002; Singh 2006a; Singh 2006b; Lata 2007; Appenrodt 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; Hamdy 2014; Tuttolomondo 2016; Bureau 2017c; Rai 2017); in the remaining trial, the proportion of participants who had refractory or recurrent ascites was 85.0% (Acharya 1992). Forty-one trials reported the proportion of participants who had alcohol-related cirrhosis: in two trials, none of the participants had alcohol-related cirrhosis (Chang 1997; Raza 2011); in four trials, all the participants had alcohol-related cirrhosis (Gregory 1977; Stanley 1989b; Ljubici 1994; Schaub 1995); in the remaining 35 trials, the proportion of participants who had alcohol-related cirrhosis ranged from 2.0% to 90.6% (Gines 1987; Salerno 1987; Chesta 1990; Ginès 1991; Strauss 1991; Acharya 1992; Bruno 1992; Hagege 1992; Sola 1994; Ginès 1995; Lebrec 1996; Fernandez-Esparrach 1997; Mehta 1998; Gentilini 1999a; Rossle 2000; Ginès 2002; Moreau 2002; Sanyal 2003; Salerno 2004; Romanelli 2006; Singh 2006a; Singh 2006b; Lata 2007; Appenrodt 2008; Singh 2008; Licata 2009; Narahara 2011; Bari 2012; Singh 2012a; Singh 2013; Tuttolomondo 2016; Bureau 2017c; Rai 2017; Caraceni 2018; Sola 2018). Thirty-three trials reported the proportion of participants who had viral-related cirrhosis: in four trials, none of the participants had viral-related cirrhosis (Gregory 1977; Stanley 1989b; Chesta 1990; Ljubici 1994); in one trial, all the participants had viral-related cirrhosis (Chang 1997); in the remaining 28 trials, the proportion of participants who had viral-related cirrhosis ranged from 5.6% to 95.0% (Gines 1987; Salerno 1987; Ginès 1991; Strauss 1991; Acharya 1992; Bruno 1992; Ginès 1995; Schaub 1995; Lebrec 1996;

Gentilini 1999a; Moreau 2002; Sanyal 2003; Salerno 2004; Romanelli 2006; Singh 2006a; Singh 2006b; Appenrodt 2008; Singh 2008; Licata 2009; Narahara 2011; Raza 2011; Bari 2012; Singh 2012a; Singh 2013; Tuttolomondo 2016; Bureau 2017c; Rai 2017; Caraceni 2018; Sola 2018). Twenty-two trials reported the proportion of participants who had autoimmune disease-related cirrhosis: in 17 trials, none of the participants had autoimmune disease-related cirrhosis (Gregory 1977; Salerno 1987; Ginès 1991; Ljubici 1994; Ginès 1995; Lebrec 1996; Chang 1997; Gentilini 1999a; Moreau 2002; Romanelli 2006; Singh 2006b; Appenrodt 2008; Licata 2009; Raza 2011; Singh 2013; Tuttolomondo 2016; Rai 2017); in the remaining five trials, the proportion of participants who had autoimmune disease-related cirrhosis ranged from 2.5% to 12.0% (Chesta 1990; Singh 2006a; Singh 2008; Bari 2012; Singh 2012a). Only two trials reported whether the participants received antibiotic prophylaxis for spontaneous bacterial peritonitis (Ginès 2002; Caraceni 2018). In one trial, all participants received antibiotic prophylaxis (Ginès 2002); in the other trial, 19.3% of participants received antibiotic prophylaxis, but the reason for only a proportion of participants receiving antibiotic prophylaxis was not stated (Caraceni 2018). In 38 trials, patients with active other decompensation events such as active gastrointestinal bleeding, hepatorenal syndrome, or grade III or grade IV hepatic encephalopathy were excluded (Descos 1983; Gines 1987; Salerno 1987; Chesta 1990; Ginès 1991; Strauss 1991; Acharya 1992; Bruno 1992; Hagege 1992; Ljubici 1994; Sola 1994; Ginès 1995; Lebrec 1996; Chang 1997; Fernandez-Esparrach 1997; Graziotto 1997; Mehta 1998; Gentilini 1999a; Ginès 2002; Moreau 2002; Sanyal 2003; Salerno 2004; Romanelli 2006; Singh 2006a; Singh 2006b; Singh 2008; Narahara 2011; Raza 2011; Al Sebaey 2012; Bari 2012; Singh 2012a; Singh 2013; Ali 2014; Hamdy 2014; Bureau 2017c; Rai 2017; Caraceni 2018; Sola 2018). In the remaining 11 trials, it was not clear whether patients with active other decompensation events were included (Gregory 1977; Fogel 1981; Mchutchison 1989; Stanley 1989b; Schaub 1995; Rossle 2000; Lata 2007; Appenrodt 2008; Licata 2009; Amin 2012; Tuttolomondo 2016). The interval between diagnosis and treatment was not reported in any of the trials.

A total of 21 interventions were compared in these trials. Forty-two trials (2870 participants) reported one or more outcomes for this review (Gregory 1977; Fogel 1981; Descos 1983; Gines 1987; Salerno 1987; Chesta 1990; Ginès 1991; Strauss 1991; Acharya 1992; Hagege 1992; Ljubici 1994; Sola 1994; Ginès 1995; Schaub 1995; Lebrec 1996; Fernandez-Esparrach 1997; Graziotto 1997; Mehta 1998; Gentilini 1999a; Rossle 2000; Ginès 2002; Moreau 2002; Sanyal 2003; Salerno 2004; Romanelli 2006; Singh 2006a; Singh 2006b; Lata 2007; Singh 2008; 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 important characteristics, potential effect modifiers, and follow-up in each trial is reported in Table 2. Overall, there does not seem to be any systematic differences between the comparisons.

Funding: the source of funding for four trials was industries who would benefit from the results of the study (Stanley 1989b; Fernandez-Esparrach 1997; Caraceni 2018; Sola 2018); 24 trials received no additional funding or were funded by neutral organisations with no vested interests in the results of the study (Descos 1983; Gines 1987; Ginès 1991; Sola 1994; Ginès 1995; Chang 1997; Gentilini 1999a; Ginès 2002; Sanyal 2003; Salerno 2004; Romanelli 2006; Singh 2006a; Singh 2006b; Appenrodt 2008; Singh 2008; Licata 2009; Bari 2012; Singh 2012a; Singh 2013; Ali 2014; Hamdy 2014; Tuttolomondo 2016; Bureau 2017c; Rai 2017); the source of funding for the remaining 21 trials was unclear (Gregory 1977; Fogel 1981; Salerno 1987; Mchutchison 1989; Chesta 1990; Strauss 1991; Acharya 1992; Bruno 1992; Hagege 1992; Ljubici 1994; Schaub 1995; Lebrec 1996; Graziotto 1997; Mehta 1998; Rossle 2000; Moreau 2002; Lata 2007; Narahara 2011; Raza 2011; Al Sebaey 2012; Amin 2012).

Excluded studies

The reasons for exclusion is provided in the Characteristics of excluded studies table.

Risk of bias in included studies

The risk of bias is summarised in Figure 3, Figure 4, and in Table 3. All the trials were at unclear or high risk of bias in at least one of the domains and were considered to be at high risk of bias overall.

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

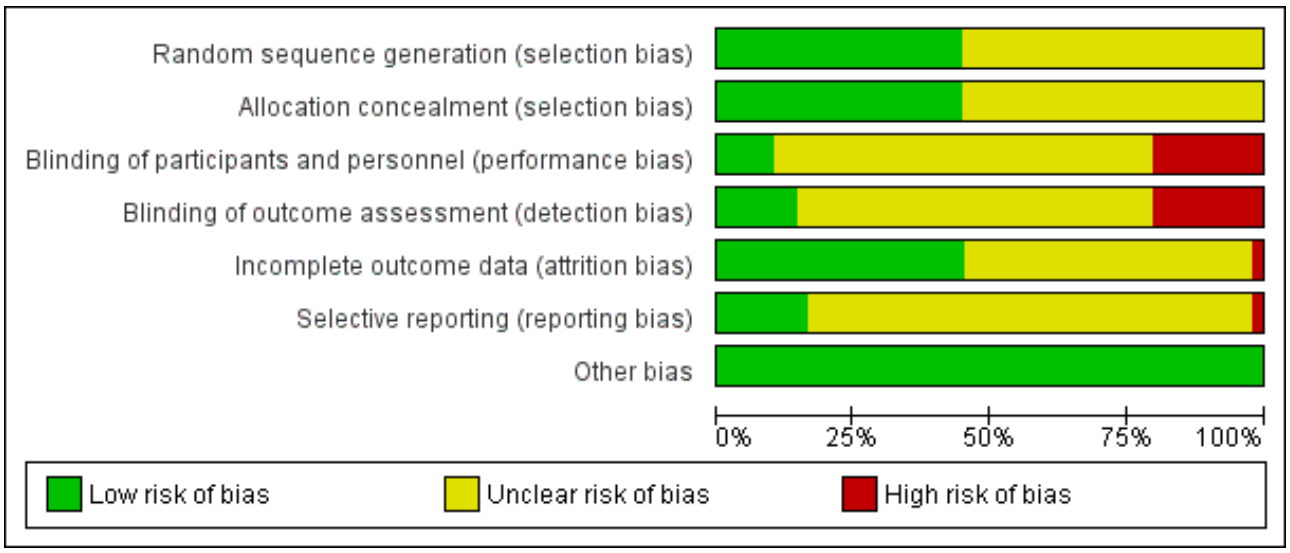


Figure 4. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

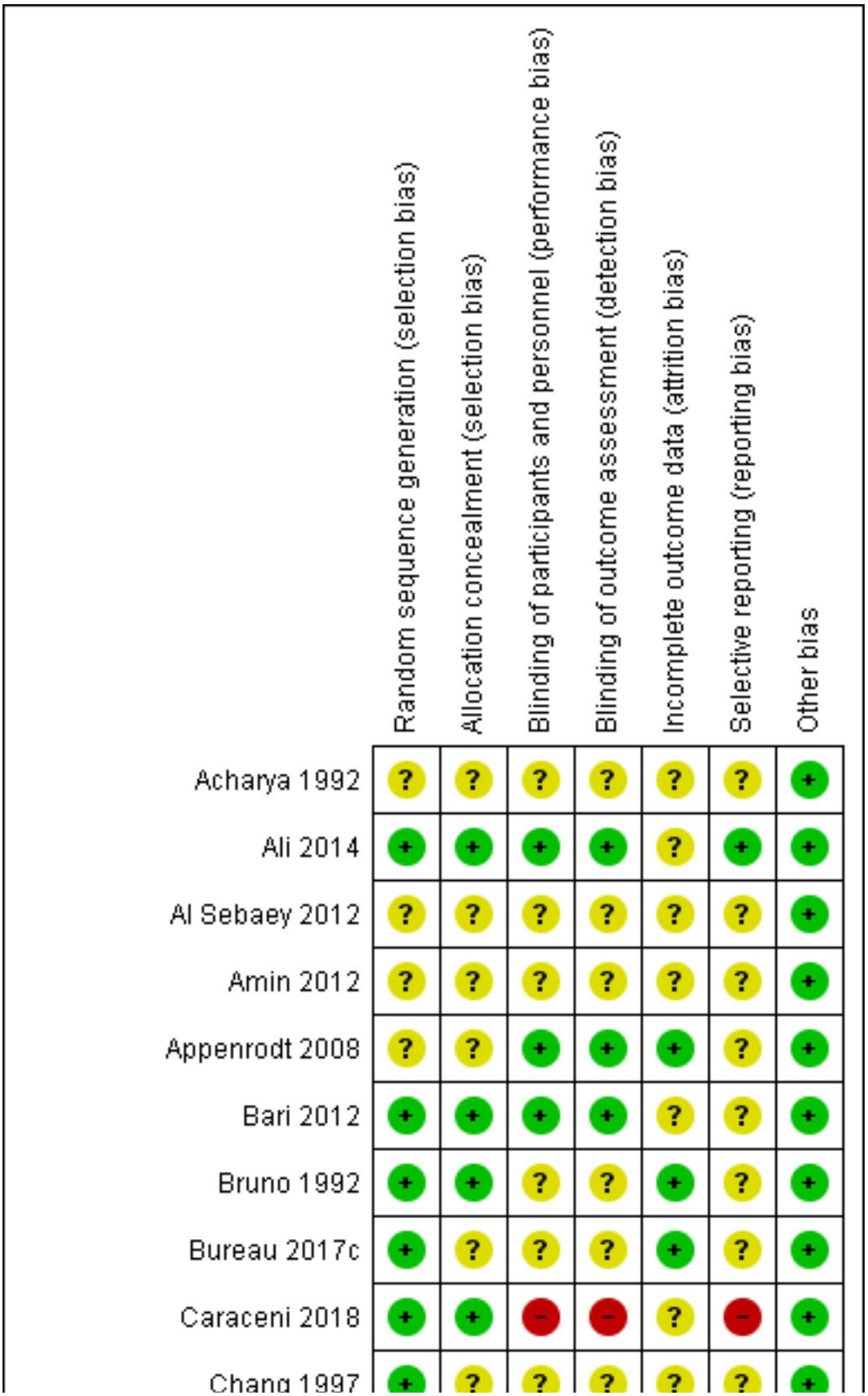
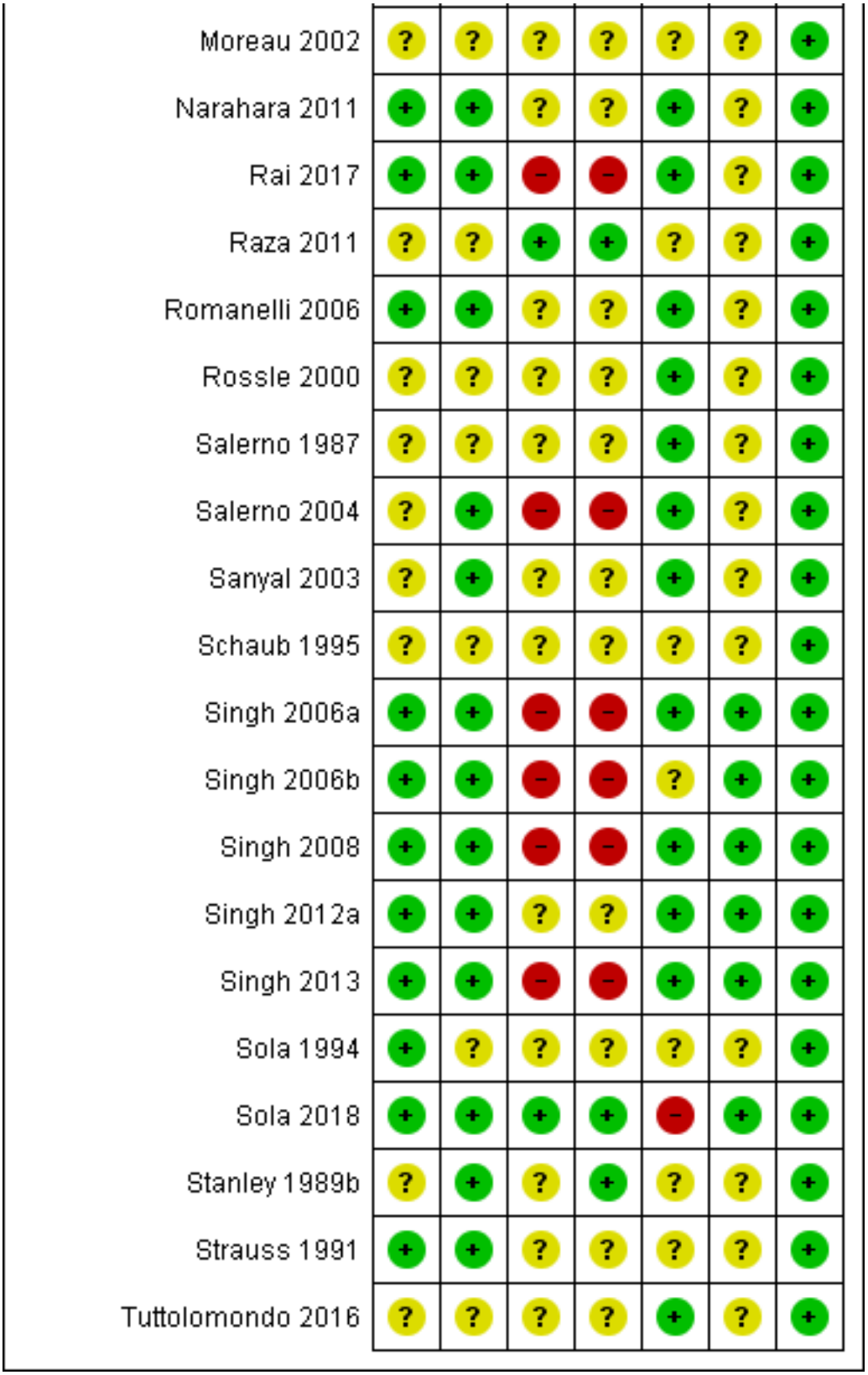


Figure 4. (Continued)

Figure 4. (Continued)



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; Romanelli 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 1989; Stanley 1989b; Chesta 1990; Acharya 1992; Ginès 1995; Schaub 1995; Lebrec 1996; Fernandez-Esparrach 1997; Graziotto 1997; Mehta 1998; Gentilini 1999a; Rossle 2000; Ginès 2002; Moreau 2002; Sanyal 2003; Salerno 2004; Lata 2007; Appenrodt 2008; Raza 2011; Al Sebaey 2012; Amin 2012; Hamdy 2014; Tuttolomondo 2016).

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; Romanelli 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; Gines 1987; Salerno 1987; Mchutchison 1989; 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; Gines 1987; Salerno 1987; Mchutchison 1989; Stanley 1989b; 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; Romanelli 2006; Lata 2007; Licata 2009; Narahara 2011; Al Sebaey 2012; Amin 2012; Singh 2012a; Hamdy 2014; Tuttolomondo 2016; Bureau 2017c); 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).

With regards to blinding of outcome assessors, six trials were at low risk of bias (Fernandez-Esparrach 1997; Appenrodt 2008; Raza 2011; Bari 2012; Ali 2014; Sola 2018); 33 trials, which did not provide sufficient information, were at unclear risk of bias (Gregory 1977; Descos 1983; Gines 1987; Salerno 1987; Mchutchison 1989; Stanley 1989b; Chesta 1990; Ginès 1991; Strauss 1991; Acharya 1992; Bruno 1992; Ljubici 1994; Sola 1994; Ginès 1995; Schaub 1995; Lebrec 1996; Chang 1997; Graziotto 1997; Gentilini 1999a; Rossle 2000; Ginès 2002; Moreau 2002; Sanyal 2003; Romanelli 2006; Lata 2007; Licata 2009; Narahara 2011; Al Sebaey 2012; Amin 2012; Singh 2012a; Hamdy 2014; Tuttolomondo 2016; Bureau 2017c); 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; Romanelli 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; Gines 1987; Mchutchison 1989; 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; Caraceni 2018), 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; Gines 1987; Salerno 1987; Mchutchison 1989; Stanley 1989b; 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; Mehta 1998; Gentilini 1999a; Rossle 2000; Ginès 2002; Moreau 2002; Sanyal 2003; Salerno 2004; Romanelli 2006; Lata 2007; Appenrodt 2008; Licata 2009; Narahara 2011; Raza 2011; Al Sebaey 2012; Amin 2012; Bari 2012; Hamdy 2014; Tuttolomondo 2016; Bureau 2017c; Rai 2017), 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)

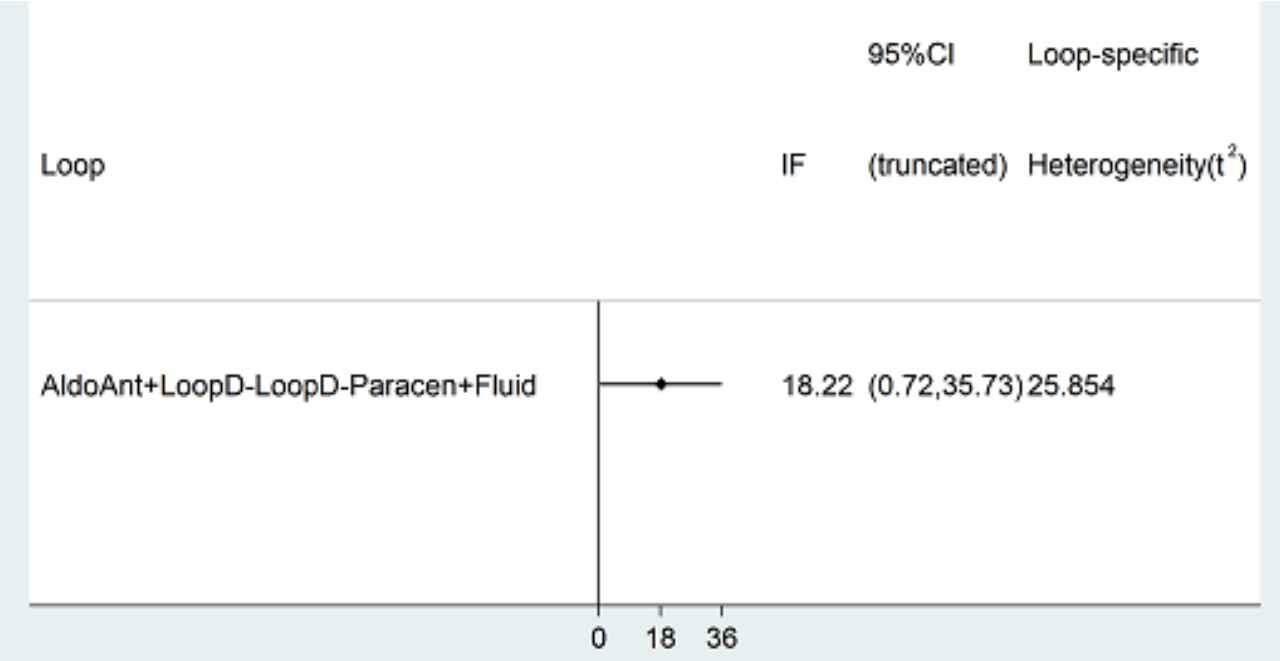


Figure 6. Forest plots showing the outcomes for which the random-effects model were different from the fixed-effect model. The more conservative random-effects model was used. In this figure, mortality at maximal follow-up, any adverse events (number of people), and resolution of ascites are shown. Figure 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
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Reinf = Reinfusion
Vasocons = Systemic vasoconstrictors
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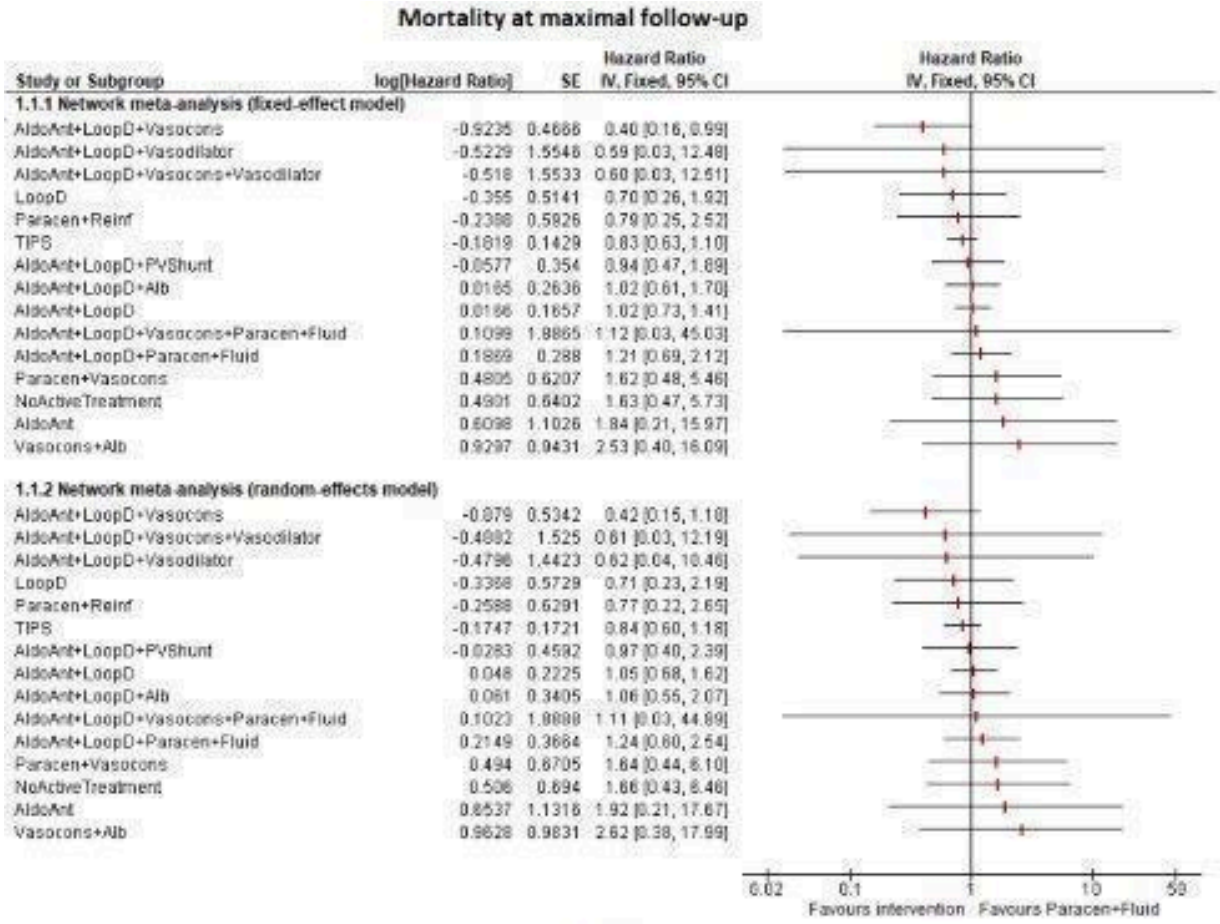
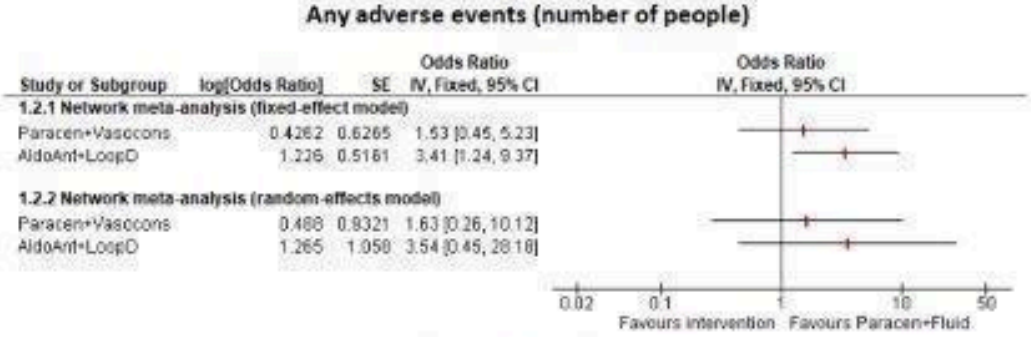
TIPS = Transjugular intrahepatic portosystemic shunt





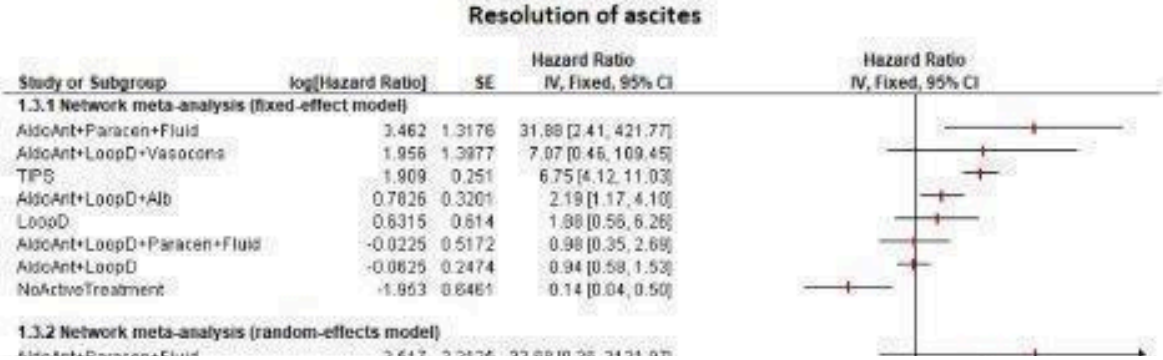


Figure 6. (Continued)

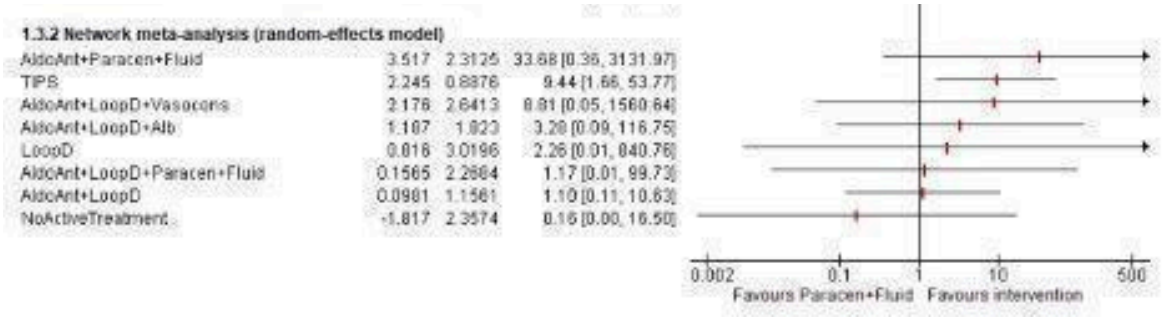


Figure 7. Forest plots showing the outcomes for which the random-effects model were different from the fixed-effect model. The more conservative random-effects model was used. In this figure, other decompensation events and length of hospital stay are shown. Figure 6 shows the remaining outcomes (mortality 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
AldoAnt = Aldosterone antagonists
Fluid = Fluid replacement
LoopD = Loop diuretics
No active treatment = No active treatment
OsmoD = Osmotic diuretics
Paracen = Paracentesis
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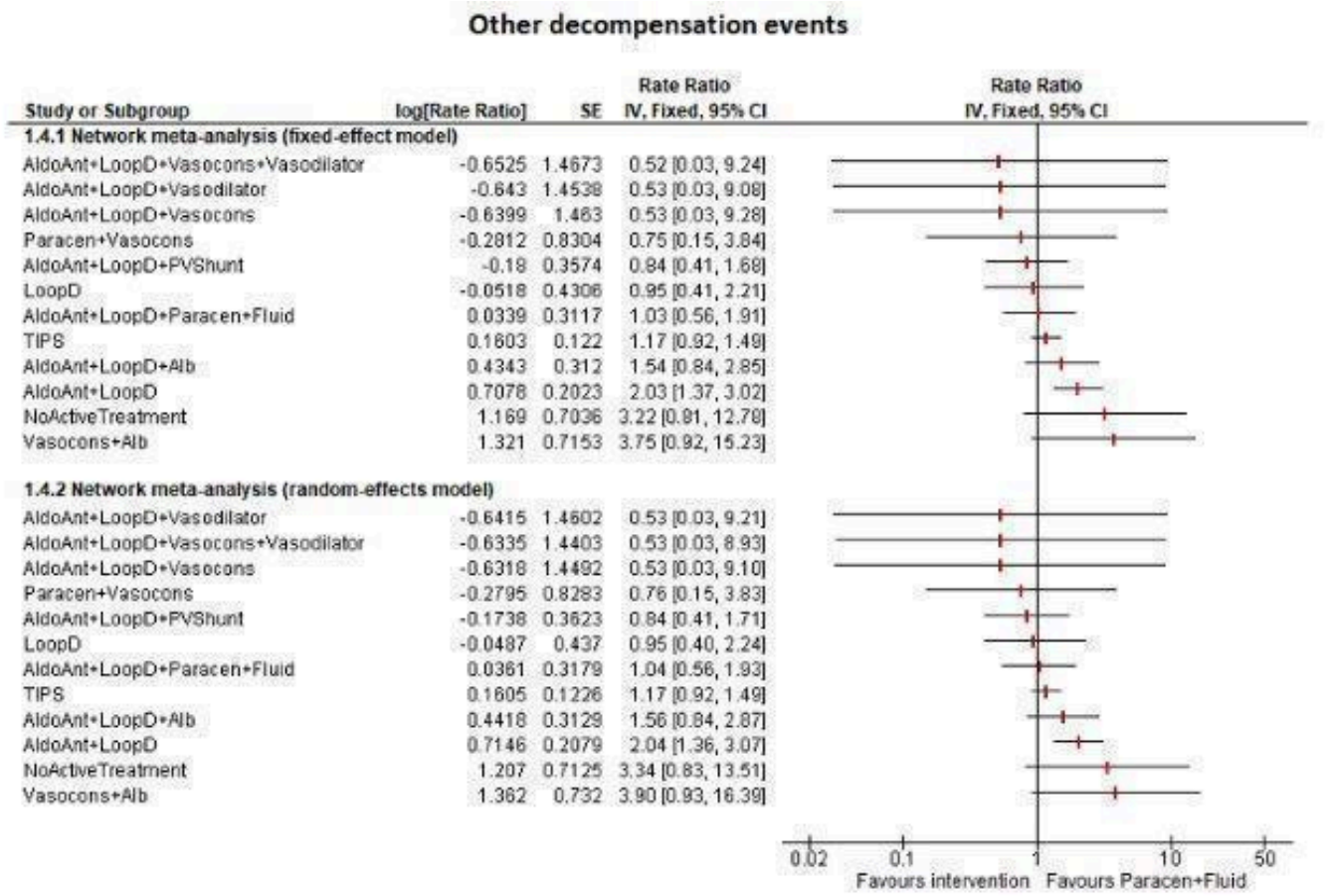
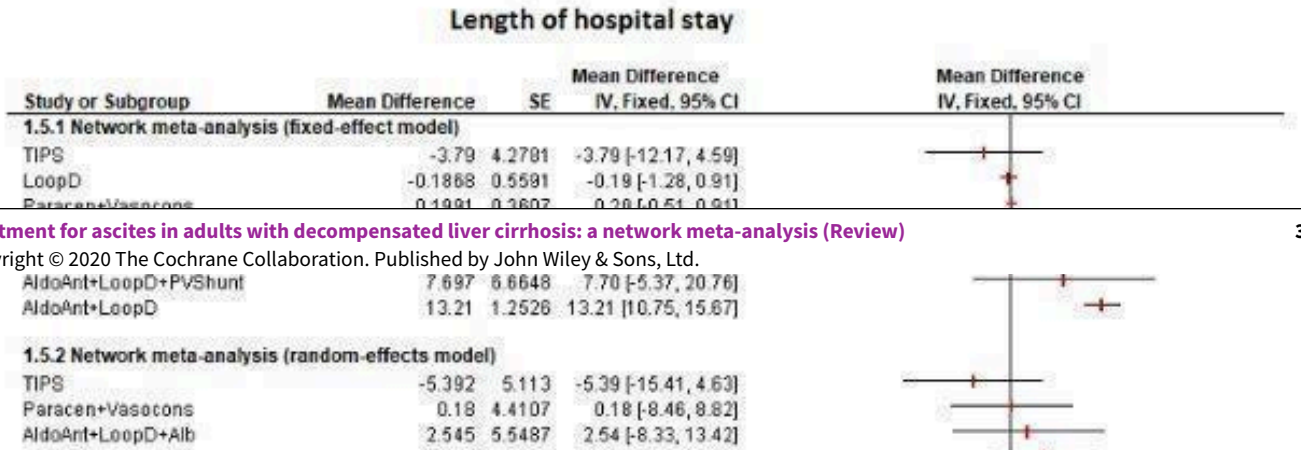
Vasocons = Systemic vasoconstrictors
Vasodil = Systemic vasodilator
ThiazD = Thiazide diuretics
TIPS = Transjugular intrahepatic portosystemic shunt





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 decompensation 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; Ginès 1991; Acharya 1992; Hagege 1992; Ljubici 1994; Sola 1994; Ginès 1995; Lebrec 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; Narahara 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 comparisons and had zero events in one of the intervention groups (Acharya 1992; Ali 2014), and thus were excluded from the analysis. The network had 16 connected treatments (32 trials; 2448 participants). There was no evidence of inconsistency according to model fit, inconsistency factor, and the 'between-design' variance 0.16 (95% CrI 0.00 to 10.02). 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 0.02 (95% CrI 0.00 to 0.27).

There was no evidence of differences between interventions in any of the direct comparisons or in the comparisons included in the 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). The sensitivity analysis indicated that the different scenarios (best-best and worst-worst scenarios) for imputing missing data showed different interpretation of results; therefore, the results have to be interpreted with caution.

There was also no evidence of differences between the comparisons not included in the network meta-analysis.

- Aldosterone antagonists plus paracentesis plus fluid replacement (0/20; 0%) versus aldosterone antagonists plus loop diuretics (1/20; 5%) (1 trial; 40 participants; very low-certainty evidence);
- Systemic vasoconstrictors (1/30; 3.3%) versus no active intervention (0/30; 0%) (1 trial; 60 participants; very low-certainty evidence).

Serious adverse events

Fourteen trials (761 participants) reported serious adverse events (with respect to number of people) (Acharya 1992; Hagege 1992; Ljubici 1994; Singh 2006a; Singh 2006b; Lata 2007; Singh 2008; Narahara 2011; Raza 2011; Singh 2012a; Singh 2013; Ali 2014; Rai 2017; Sola 2018). A total of 14 treatments were compared in these trials. Ten trials were not connected to the network because they had zero events in both intervention groups (Hagege 1992; Singh 2006a; Singh 2006b; Singh 2008; Narahara 2011; Raza 2011; Singh 2012a; Singh 2013; Ali 2014; Rai 2017); 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 (Ljubici 1994; Lata 2007); the remaining trials had no common treatments, and therefore were not connected (Acharya 1992; Sola 2018). Only two treatments were compared in each of the remaining trials (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% CrI 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 vasoconstrictors plus systemic vasodilator: OR 0.84 (95% CrI 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 vasoconstrictors (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; Ginès 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 (Ginès 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 advents 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; Salerno 2004; Romanelli 2006; Singh 2006a; Singh 2006b; Singh 2008; Narahara 2011; Bari 2012; Singh 2012a; Singh 2013; Bureau 2017c; 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 plus systemic vasoconstrictors (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 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 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 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 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 vasodilator (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; Gentilini 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 reinfusion (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 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 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 paracentesis plus fluid replacement (5/13; 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 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 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 vasodilator (0/15; 0%) (1 trial; 30 participants; very low-certainty evidence)

Other features of decompensation at maximal follow-up

Twenty-seven trials (1821 participants) reported other features of decompensation at maximal follow-up (Gregory 1977; Fogel 1981; Gines 1987; Salerno 1987; Chesta 1990; Ginès 1991; Strauss 1991; Acharya 1992; Hagege 1992; Sola 1994; Ginès 1995; Lebrec 1996; Gentilini 1999a; Rossle 2000; Ginès 2002; Sanyal 2003; Salerno 2004; Romanelli 2006; Lata 2007; Singh 2008; Licata 2009; Narahara 2011; Bari 2012; Singh 2013; Bureau 2017c; Rai 2017; Sola 2018). A total of 15 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 (Acharya 1992; Rai 2017). The network had 13 connected treatments (25 trials; 1756 participants). There was no evidence of inconsistency according to the inconsistency factor plot or model fit. We could not obtain convergence for the design-by-treatment analysis. The random-effects model was used because it was more conservative and had a large between-study variance of 6.25 (95% CrI 0.02 to 23.78), even though the model fit was similar to the fixed-effect model.

The following direct comparisons were in favour of:

- 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 vasoconstrictors: 7/12 (0.6 other decompensation events per participant) versus 0/13 (no decompensation 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 plus paracentesis plus fluid replacement versus aldosterone antagonists plus loop diuretics: 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 vasoconstrictors 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 vasoconstrictors 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).

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

- Aldosterone antagonists plus paracentesis plus fluid replacement (0/20; 0 events) versus aldosterone antagonists plus loop diuretics (3/20; 15 events per 100 participants) (1 trial; 40 participants; very low-certainty evidence)
- Aldosterone antagonists plus loop diuretics plus systemic vasoconstrictors plus paracentesis plus fluid replacement (0/13; 0 events) versus aldosterone antagonists plus loop diuretics plus paracentesis plus fluid replacement (7/12; 58.3 events per 100 participants) (1 trial; 25 participants; very low-certainty evidence).

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.

DISCUSSION

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;

Chesta 1990; Ginès 1991; Strauss 1991; Acharya 1992; Hagege 1992; Ljubici 1994; Sola 1994; Ginès 1995; Schaub 1995; Lebrec 1996; Fernandez-Esparrach 1997; Graziotto 1997; Mehta 1998; Gentilini 1999a; Rossle 2000; Ginès 2002; Moreau 2002; Sanyal 2003; Salerno 2004; Romanelli 2006; Singh 2006a; Singh 2006b; Lata 2007; Singh 2008; 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).

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 decompensation 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 decompensation 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 decompensation events per 100 participants in the paracentesis plus fluid replacement group. In addition to causing death, decompensation usually results in hospital admissions and significant costs to the health service. Therefore, 'any decompensation 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 decompensation 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 decompensation 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 decompensation 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 decompensation 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 decompensation 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 decompensation features. Therefore, the results of the review are only applicable to people without active other decompensation events. Accordingly, more evidence on ascites treatment seems to be needed in populations with ascites and other signs of decompensation.

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, blinding 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 decompensation 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 decompensation 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 decompensation 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 decompensation events separately. Therefore, we are unable to comment on whether hepatic encephalopathy was increased with TIPS compared to paracentesis plus fluid replacement.

AUTHORS' CONCLUSIONS

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).

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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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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Acharya 1992

Methods	Randomised clinical trial
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%)

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	Group 1: Aldosterone antagonists plus paracentesis plus fluid replacement (n = 20) 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) Group 2: Aldosterone antagonists plus loop diuretics (n = 20) Further details: Spironolactone 200 mg/day + furosemide 40 mg/day doubled after third day for 15 days (route not stated)
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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
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

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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available.

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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation procedures were automated, using centrally-allocated computer-generated random numbers".
Allocation concealment (selection bias)	Low risk	Quote: "Randomisation procedures were automated, using centrally-allocated computer-generated random numbers".

Ali 2014 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "a double-blind, placebo-controlled, randomized trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "a double-blind, placebo-controlled, randomized trial"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	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.
Selective reporting (reporting bias)	Low risk	Comment: a pre-published protocol was not available, but the important outcomes were reported or obtained by email.
Other bias	Low risk	Comment: no other bias noted

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

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.

Amin 2012 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: a placebo was used, but the groups blinded were not reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: a placebo was used, but the groups blinded were not reported.
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

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. Thrombocytopaenia
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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Neither the patient nor the physician was aware of the treatment arm". Comment: placebo was used to achieve this.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Neither the patient nor the physician was aware of the treatment arm". Comment: placebo was used to achieve this.
Incomplete outcome data (attrition bias) All outcomes	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

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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "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)".
Allocation concealment (selection bias)	Low risk	Quote: "A list with allocation codes was sent to the pharmacy that assigned the participants to interventions based on allocation codes".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind, placebo-controlled trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind, placebo-controlled trial"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	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.
Selective reporting (reporting bias)	Unclear risk	Comment: pre-published protocol was not available.
Other bias	Low risk	Comment: no other bias noted

Bruno 1992

Methods	Randomised clinical trial
Participants	Country: Italy Period of recruitment: not stated Number randomised: 35 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 35 Average age (years): 54

Bruno 1992 *(Continued)*

	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 + polyamide 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.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomly assigned by the sealed envelope method on the basis of a computer generated list".
Allocation concealment (selection bias)	Low risk	Quote: "patients were randomly assigned by the sealed envelope method on the basis of a computer generated list".
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	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

Bureau 2017c

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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomization was generated online by computer".
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias)	Unclear risk	Comment: this information was not available.

Bureau 2017c *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	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

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: antialdosteronic 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: antialdosteronic 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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer-generated"
Allocation concealment (selection bias)	Low risk	Quote: "At the statistical data centre….blinded assignment sequence"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Neither patients, nor investigators, nor statisticians were masked to treatment assignment".
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Neither patients, nor investigators, nor statisticians were masked to treatment assignment".
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there were post-randomisation dropouts, but it was not clear whether they were related to the intervention or the outcome.
Selective reporting (reporting bias)	High risk	Comment: outcomes such as adverse events were collected but not reported adequately.
Other bias	Low risk	Comment: no other bias noted

Chang 1997

Methods	Randomised clinical trial
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)

Chang 1997 *(Continued)*

	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.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were then randomly allocated to two groups (random number table)".
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: two patients were excluded from the analysis it was not clear whether this was pre-randomisation or post-randomisation.
Selective reporting (reporting bias)	Unclear risk	Comment: pre-published protocol was not available.
Other bias	Low risk	Comment: no other bias noted

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.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
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

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

Descos 1983 *(Continued)*

	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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
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

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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Physicians participating in the study did not know the treatment assigned to each patient". Comment: a placebo was used, but it was not clear whether the participants were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Physicians participating in the study did not know the treatment assigned to each patient".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts.

Fernandez-Esparrach 1997 *(Continued)*

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

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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "No blinding (author replies)"

Fogel 1981 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "No blinding (author replies)"
Incomplete outcome data (attrition bias) All outcomes	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

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 canreonate 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 canreonate 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 Scientilica e Tecnologica (Progetto Nazionale Epatiti Virali e Cirrosi Epatica), Rome, and the Italian Liver Foundation, Florence, Italy" Trial name/trial registry number: not stated Attempts were made to contact the authors in November 2018.

Gentilini 1999a *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	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

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 Cientffico 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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were then randomly allocated (random number table)".
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
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

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.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The patients from each hospital were then randomly assigned to two groups with use of a random-number table". Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
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

Ginès 1995

Methods	Randomised clinical trial
Participants	Country: Multiple

Ginès 1995 *(Continued)*

	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%) Prophylactic 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.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
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.

Ginès 1995 *(Continued)*

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 Investigacio´n Sanitaria (Spain) (FIS 97/2073 and 00/0616) and the Veterans Administration Merit Review and NIH-1K24-DK 02727 (USA)" Trial name/trial registry number: not stated Attempts were made to contact the authors in November 2018.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Low risk	Quote: "Randomization (sealed opaque envelopes) was centralized".
Blinding of participants and personnel (performance bias)	Unclear risk	Comment: this information was not available.

Ginès 2002 *(Continued)*

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

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 Dideco 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.

Risk of bias

Bias	Authors' judgement	Support for judgement

Graziotto 1997 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Low risk	Quote: "using a closed envelope system"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	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

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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: placebo was used but no information on blinding was provided.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: placebo was used but no information on blinding was provided.
Incomplete outcome data (attrition bias) All outcomes	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

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. Heptocellular carcinoma
Interventions	Group 1: Aldosterone antagonists plus loop diuretics (n = 27)

Hagege 1992 *(Continued)*

	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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The treatment was designated by random draw".
Allocation concealment (selection bias)	Low risk	Quote: "The treatment was designated by random draw".
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "No blinding (author replies)"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "No blinding (author replies)"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "there were patients excluded after randomization (author replies)". Comment: there were post-randomisation dropouts; it was not clear whether they were related to intervention or outcomes.
Selective reporting (reporting bias)	Low risk	Comment: a pre-published protocol was not available, but the important outcomes were reported or obtained by email.
Other bias	Low risk	Comment: no other bias noted

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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
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

Lata 2007

Methods	Randomised clinical trial
Participants	Country: Czech Republic Period of recruitment: 2002-2004

Lata 2007 *(Continued)*

	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.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
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

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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Low risk	Quote: "opaque envelope method"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.

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 + paracentesis 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.

Risk of bias

Bias	Authors' judgement	Support for judgement

Licata 2009 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned by the use of sequentially numbered boxes (prepared before starting the study by a computerized, non-alternating sequence)".
Allocation concealment (selection bias)	Low risk	Quote: "Patients were randomly assigned by the use of sequentially numbered boxes (prepared before starting the study by a computerized, non-alternating sequence)".
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	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

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)

Ljubici 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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "On the third day of admission, patients were randomly allocated to two groups (random number table)".
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: some patients were excluded, but it was not clear whether they were excluded pre-randomisation or post-randomisation.
Selective reporting (reporting bias)	Unclear risk	Comment: pre-published protocol was not available.
Other bias	Low risk	Comment: no other bias noted

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 *(Continued)*

	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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
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

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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "open"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "open"
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

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

Moreau 2002 *(Continued)*

	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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there were post-randomisation dropouts. at least one of them could be related to the treatment, but it was not clear whether this would have affected the treatment effect.
Selective reporting (reporting bias)	Unclear risk	Comment: pre-published protocol was not available.

Moreau 2002 *(Continued)*

Other bias	Low risk	Comment: no other bias noted

Narahara 2011

Methods	Randomised clinical trial
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 Exclusion criteria 1. Other features of decompensation 2. Cardiac or respiratory disease 3. Malignancy
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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed by selecting an opaque sealed envelope that was numbered according to a random number table".
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was performed by selecting an opaque sealed envelope that was numbered according to a random number table".
Blinding of participants and personnel (performance bias)	Unclear risk	Comment: this information was not available.

Narahara 2011 *(Continued)*

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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomization sequence was computer-generated and the allocation was concealed in opaque sealed envelopes".
Allocation concealment (selection bias)	Low risk	Quote: "The randomization sequence was computer-generated and the allocation was concealed in opaque sealed envelopes".
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Patients and investigators were not blinded to the treatment assignments".
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Patients and investigators were not blinded to the treatment assignments".
Incomplete outcome data (attrition bias) All outcomes	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

Raza 2011

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)*

	Further details: placebo
Outcomes	Outcomes reported: serious adverse events (number of people) Follow-up (months): 0.2
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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "It was a double-blind trial, so that neither the patient nor the observer knew whether drug or placebo was given".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "It was a double-blind trial, so that neither the patient nor the observer knew whether drug or placebo was given".
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

Romanelli 2006

Methods	Randomised clinical trial
Participants	Country: Italy Period of recruitment: 1993-2003 Number randomised: 100 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 100 Average age (years): 63 Females: 38 (38.0%) Ascites grade 2: 65 (65.0%) Ascites grade 3: 35 (35.0%) Refractory or recurrent ascites: not stated Alcohol-related cirrhosis: 2 (2.0%) Viral-related cirrhosis: 79 (79.0%) Autoimmune disease-related cirrhosis: 0 (0.0%) Other causes for cirrhosis: 19 (19.0%)

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 weekly 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.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Allocation schedule was generated using a computed random number generation system".
Allocation concealment (selection bias)	Low risk	Quote: "using sealed envelopes containing the treatment assignments"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	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

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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	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

Salerno 1987

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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.

Salerno 1987 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	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

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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.

Salerno 2004 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: "Randomization (sealed opaque envelopes)"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Unblinded"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Unblinded"
Incomplete outcome data (attrition bias) All outcomes	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

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 expectance 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

Sanyal 2003 *(Continued)*

	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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Low risk	Quote: "Subjects were then randomized centrally to either the medical therapy arm (defined by restriction of sodium, treatment with diuretics, and repeated TP as needed) or the transjugular intrahepatic portosystemic shunt arm".
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	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

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
Outcomes	Outcomes reported: length of hospital stay (days) (all admissions until maximal follow-up) Follow-up (months): 0.75
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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there were post-randomisation dropouts but the reasons were not reported; therefore, it was difficult to judge whether this would have led to biased treatment effect.
Selective reporting (reporting bias)	Unclear risk	Comment: pre-published protocol was not available.
Other bias	Low risk	Comment: no other bias noted

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
Interventions	Group 1: Paracentesis plus systemic vasoconstrictors (n = 20) Further details: Total paracentesis + noradrenaline 0.5 mg/hr titrated to maintain mean arterial pressure about 10 mmHg above baseline 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, treatment costs 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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer-generated (author replies)"
Allocation concealment (selection bias)	Low risk	Quote: "opaque sealed envelopes (author replies)"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "No blinding (author replies)"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "No blinding (author replies)"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: a pre-published protocol was not available, but the important outcomes were reported or obtained by email.
Other bias	Low risk	Comment: no other bias noted

Singh 2006b

Methods	Randomised clinical trial

Singh 2006b *(Continued)*

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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer-generated (author replies)"
Allocation concealment (selection bias)	Low risk	Quote: "opaque sealed envelopes (author replies)"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "No blinding (author replies)"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "No blinding (author replies)"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there were post-randomisation dropouts, but it was not clear whether these could be related to the intervention or outcomes.

Singh 2006b *(Continued)*

Selective reporting (reporting bias)	Low risk	Comment: a pre-published protocol was not available, but the important outcomes were reported or obtained by email.
Other bias	Low risk	Comment: no other bias noted

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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer-generated (author replies)"
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

Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "No blinding (author replies)"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: a pre-published protocol was not available, but the important outcomes were reported or obtained by email.
Other bias	Low risk	Comment: no other bias noted

Singh 2012a

Methods	Randomised clinical trial
Participants	Country: India Period of recruitment: 2007-2009 Number randomised: 40 Post-randomisation dropouts: 0 (0.0%) Revised sample size: 40 Average age (years): 47 Females: 3 (7.5%) Ascites grade 2: not stated Ascites grade 3: not stated Refractory or recurrent ascites: 40 (100.0%) Alcohol-related cirrhosis: 29 (72.5%) Viral-related cirrhosis: 10 (25.0%) Autoimmune disease-related cirrhosis: 1 (2.5%) Other causes for cirrhosis: 0 (0.0%) Prophylactic antibiotics for subacute bacterial peritonitis: not stated Exclusion criteria 1. Other features of decompensation Years of recruitment: 2007-2009
Interventions	Group 1: Aldosterone antagonists plus loop diuretics + systemic vasoconstrictors (n = 20) 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 Group 2: Aldosterone antagonists plus loop diuretics (n = 20) Further details: Spironolactone 100 to 400 mg/day + furosemide 40 to 160 mg/day, duration not stated
Outcomes	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) Follow-up (months): 6
Notes	Source of funding (quote): "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". Trial name/trial registry number: not stated Attempts were made to contact the authors in November 2018.

Risk of bias

Singh 2012a *(Continued)*

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

Singh 2013

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

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 endpoints 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

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

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)*

	Ascites grade 3: 71 (100.0%) Refractory or recurrent ascites: not stated Alcohol-related cirrhosis: 63 (88.7%) 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
Interventions	Group 1: Aldosterone antagonists plus loop diuretics + paracentesis plus fluid replacement (n = 38) 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 Group 2: Aldosterone antagonists plus loop diuretics (n = 33) Further details: Spironolactone 100 to 400 mg/day + furosemide 40 to 240 mg/day; duration not reported, probably end of follow-up
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'Investigaci6 Medica (IMIM) IM 876413601." Trial name/trial registry number: not stated Attempts were made to contact the authors in November 2018.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "random number table"
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there were post-randomisation dropouts, but it is not clear whether this could have led to biased treatment effects.
Selective reporting (reporting bias)	Unclear risk	Comment: pre-published protocol was not available.
Other bias	Low risk	Comment: no other bias noted

Sola 2018

Methods	Randomised clinical trial

Sola 2018 *(Continued)*

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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A computer-generated…"
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was performed at the CTU of the Hospital Clínic of Barcelona".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "All investigators and patients were blinded to treatment assignment..placebo".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All investigators and patients were blinded to treatment assignment..placebo".

Sola 2018 *(Continued)*

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

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, NJ.) 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

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Low risk	Quote: "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".
Blinding of participants and personnel (performance bias)	Unclear risk	Comment: this information was not available.

Stanley 1989b *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	Unclear 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

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 plus fluid replacement (n = 16) Further details: Repeated 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.
Risk of bias	

Strauss 1991 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "statistical table of random numbers"
Allocation concealment (selection bias)	Low risk	Quote: "system of sealed envelopes, numbered successively, after the selection of each patient for the study, the doctor made the opening of the next envelope"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	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.
Selective reporting (reporting bias)	Unclear risk	Comment: pre-published protocol was not available.
Other bias	Low risk	Comment: no other bias noted

Tuttolomondo 2016

Methods	Randomised clinical trial
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)

Tuttolomondo 2016 *(Continued)*

	Further details: Repeated paracentesis removing 4 to 6 litres per day + albumin 5 to 8 g/litre removed
Outcomes	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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	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

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]*

Study	Reason for exclusion
Abdel-Khalek 2010b	Comparison of variations in treatment
Altman 1998	Comparison of variations in treatment
Angeli 1994	Comparison of variations in treatment

Study	Reason for exclusion
Antillon 1993	Not a randomised clinical trial
Applefeld 1994	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.
Arrigoni 1988	Comparison of variations in treatment
Bories 1986	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.
Bostan 2019	Not a randomised clinical trial
Boyer 1983	Not a randomised clinical trial
Brater 2001	Not a randomised clinical trial
Bureau 2017a	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.
Cadranel 1992a	The unit of randomisation was the procedure (i.e. each patient underwent both procedures).
Cadranel 1992b	Not a randomised clinical trial
Castagnolo 1977	Not a randomised clinical trial
Chang 1998	Comparison of variations in treatment
Eknoyan 1970	Not a randomised clinical trial
Fassio 1992	Comparison of variations in treatment
Fuller 1977	In this cross-over randomised clinical trial, the cross-over took place after 6 days of treatment with just 6 days between the cross-over; this short duration of treatment and cross-over period was insufficient time to determine the objectives of this review.
Gadano 1997	Atrial natriuretic peptide was given for sodium retention and not for treatment of ascites.
Garcia-Compean 1993	Large volume paracentesis without fluid replacement or systemic vasoconstrictors was not one of the treatments included in this review.
Garcia-Compean 2002	Comparison of variations in treatment
Gentilini 1989b	Comparison of variations in treatment
Gerbes 1990a	Comparison of variations in treatment
Gines 1996	Large volume paracentesis without fluid replacement or systemic vasoconstrictors was not one of the treatments included in this review.
Ginès 1988	Comparison of variations in treatment
Giostra 2000	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.

Study	Reason for exclusion
He 2012	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.
Heinrich 1983	Not clear whether this was a randomised clinical trial.
Hernandez 1995	Comparison of variations in treatment
Inoue 1969	Not a randomised clinical trial
Kalambokis 2007	This trial included non-ascites people and the randomisation was not stratified by presence of ascites or separate data was not available in those with ascites.
Kalambokis 2008	Not a randomised clinical trial
Knauf 1994	In this short-term study, the patients who did not respond to one treatment crossed over to the other treatment. Therefore, this design will not answer our objectives.
Krag 2007b	The diuretics used in the intervention and control group was variable - these may or may not have been used; therefore it was not possible to define the intervention or control group.
Krag 2008	The diuretics used in the intervention and control group was variable - these may or may not have been used; therefore it was not possible to define the intervention or control group.
Kurt 2011	Not a randomised clinical trial
Laffi 1992	Not an intervention included in the systematic review
Laffi 2003	Not a randomised clinical trial
Lai 1991	In this short-term study, the patients who did not respond to one treatment crossed over to the other treatment. Therefore, this design will not answer our objectives.
Leodolter 1972	Not a randomised clinical trial
Lieberman 1965	Not a randomised clinical trial
Lowenthal 1973	Not a randomised clinical trial
Luca 1995	Not an intervention included in the systematic review
Marra 1979	Quasi-randomised study (allocation by order of entry to ward)
Merino 1967	Not a randomised clinical trial
Misra 2010	In this cross-over RCT, the cross-over took place after 8 hours of treatment with just 24 hours between the cross-over.
Moreau 2006	Comparison of variations in treatment
Nakamura 2014	Not an intervention included in the systematic review
Narahara 2009	The diuretic regimen was different in the two groups.
Perez 1983	After 5 days, if there was no response, patients crossed-over; this short duration of treatment and cross-over period was insufficient time to determine the objectives of this review.

Study	Reason for exclusion
Perkins 2006	Not a randomised clinical trial
Planas 1990	Comparison of variations in treatment
Ring-Larsen 1988	The control group of diuretics was not defined; therefore it was not possible to assess whether the control group was defined.
Roseau 2000	Not a randomised clinical trial
Runyon 1989	The unit of randomisation was the procedures (i.e. some patients underwent both treatments).
Sadikali 1973	Not a randomised clinical trial
Salerno 1991	Comparison of variations in treatment
Salerno 1997	Comparison of variations in treatment
Santos 2003	After about 2 weeks, if there was no response, patients crossed over.
Sarin 1988	Included patients without cirrhosis
Sarti 1984	Not a randomised clinical trial
Schmukler 1968	Not a randomised clinical trial
Shafei 1967	Not a randomised clinical trial
Sohn 2017	Included only patients who developed acute kidney failure following treatment
Sola-Vera 2003	Comparison of variations in treatment
Stanley 1989a	Not a randomised clinical trial
Steigmann 1966	Not a randomised clinical trial
Tempini 1984	Comparison of variations in treatment
Thompson 1977	In this cross-over trial, the wash-out period was only 3 days; this will not answer the objectives of this systematic review.
Tsai 1996	Not a comparison of interest
Vizzutti 2001	In the control group, the diuretic regimen was variable.
Wapnick 1979	Appeared to be a quasi-randomised study or a nonrandomised study: authors stated "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".
Yakar 2016	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.
Yamada 1970	Not a randomised clinical trial
Yosry 2019	Quasi-randomised study (allocation by alternate assignment)

Study	Reason for exclusion
Zaak 2001	Not a randomised clinical trial
Zhang 2013	Not clear if all participants had cirrhosis
Zhao 2000	Comparison of variations in treatment

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

EUCTR 2018

Trial name or title	None
Methods	Randomised clinical trial
Participants	Ascites and cirrhosis
Interventions	Albumin versus placebo
Outcomes	1. Transplant-free survival 2. Overall survival 3. Non-resolution of ascites
Starting date	25 April 2018
Contact information	Instituto Grifols S.A. (IGregulatory.affairs@grifols.com)
Notes	EudraCT Number: 2016-001789-28

Macken 2018

Trial name or title	None
Methods	Randomised clinical trial
Participants	Refractory ascites and cirrhosis
Interventions	Tunnelled peritoneal catheter versus paracentesis plus fluid replacement
Outcomes	1. Overall survival 2. Adverse events 3. Health resource utilisation and quality of life
Starting date	1 October 2015
Contact information	Lucia Macken (lucia.macken@bsuh.nhs.uk)
Notes	ISRCTN30697116

NCT 03172273

Trial name or title	PETRA
Methods	Randomised clinical trial
Participants	Diuretic resistant ascites and cirrhosis
Interventions	Tunnelled peritoneal catheter versus paracentesis plus fluid replacement
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

NCT03027635

Trial name or title	None
Methods	Randomised clinical trial
Participants	Recurrant and refractory ascites and cirrhosis
Interventions	Transjugular intrahepatic portosystemic shunt versus paracentesis plus albumin
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

NCT03202524

Trial name or title	None
Methods	Randomised clinical trial
Participants	Grade 3 or refractory ascites and cirrhosis
Interventions	Paracentesis plus fresh frozen plasma plus albumin versus paracentesis plus albumin

NCT03202524 *(Continued)*

Outcomes	1. Incidence of post-paracentesis circulatory dysfunction
Starting date	December 2017
Contact information	Montefiore Medical Center
Notes	NCT03202524; Study withdrawn

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.

From: Moore 2003.

Table 2. Characteristics of included studies and potential effect modifiers

This table is too wide to be displayed in RevMan. This table can be found at: https://doi.org/10.5281/zenodo.3604600.

Table 3. Risk of bias

Study name	Sequence generation	Allocation concealment	Blinding of patients and healthcare providers	Blinding of outcome assessors	Missing outcome bias	Selective outcome reporting	Overall risk of bias
Chang 1997	Low	Unclear	Unclear	Unclear	Unclear	Unclear	High
Chesta 1990	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	High
Gines 1987	Low	Unclear	Unclear	Unclear	Unclear	Unclear	High
Hagege 1992	Low	Low	High	High	Unclear	Low	High
Salerno 1987	Unclear	Unclear	Unclear	Unclear	Low	Unclear	High
Schaub 1995	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	High
Al Sebaey 2012	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	High
Appenrodt 2008	Unclear	Unclear	Low	Low	Low	Unclear	High
Bari 2012	Low	Low	Low	Low	Unclear	Unclear	High
Hamdy 2014	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	High
Lata 2007	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	High
Moreau 2002	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	High
Singh 2006a	Low	Low	High	High	Low	Low	High
Singh 2006b	Low	Low	High	High	Unclear	Low	High
Singh 2008	Low	Low	High	High	Low	Low	High
Ljubici 1994	Low	Unclear	Unclear	Unclear	Unclear	Unclear	High
Sola 1994	Low	Unclear	Unclear	Unclear	Unclear	Unclear	High
Strauss 1991	Low	Low	Unclear	Unclear	Unclear	Unclear	High
Bureau 2017c	Low	Unclear	Unclear	Unclear	Low	Unclear	High

Table 3. Risk of bias *(Continued)*

Ginès 2002	Unclear	Low	Unclear	Unclear	Low	Unclear	High
Lebrec 1996	Unclear	Low	Unclear	Unclear	Unclear	Unclear	High
Narahara 2011	Low	Low	Unclear	Unclear	Low	Unclear	High
Rossle 2000	Unclear	Unclear	Unclear	Unclear	Low	Unclear	High
Salerno 2004	Unclear	Low	High	High	Low	Unclear	High
Sanyal 2003	Unclear	Low	Unclear	Unclear	Low	Unclear	High
Gregory 1977	Unclear	Unclear	Unclear	Unclear	Low	Unclear	High
Tuttolomondo 2016	Unclear	Unclear	Unclear	Unclear	Low	Unclear	High
Fogel 1981	Unclear	Unclear	High	High	Low	Unclear	High
Licata 2009	Low	Low	Unclear	Unclear	Low	Unclear	High
Bruno 1992	Low	Low	Unclear	Unclear	Low	Unclear	High
Graziotto 1997	Unclear	Low	Unclear	Unclear	Low	Unclear	High
Mehta 1998	Unclear	Unclear	High	High	Unclear	Unclear	High
Gentilini 1999a	Unclear	Unclear	Unclear	Unclear	Low	Unclear	High
Romanelli 2006	Low	Low	Unclear	Unclear	Low	Unclear	High
Caraceni 2018	Low	Low	High	High	Unclear	High	High
Ginès 1991	Low	Unclear	Unclear	Unclear	Unclear	Unclear	High
Ginès 1995	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	High
Singh 2012a	Low	Low	Unclear	Unclear	Low	Low	High
Singh 2013	Low	Low	High	High	Low	Low	High
Fernandez-Esparrach 1997	Unclear	Unclear	Unclear	Low	Low	Unclear	High

Table 3. Risk of bias *(Continued)*

Acharya 1992	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	High
Ali 2014	Low	Low	Low	Low	Unclear	Low	High
Amin 2012	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	High
Descos 1983	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	High
Rai 2017	Low	Low	High	High	Low	Unclear	High
Singh 2013	Low	Low	High	High	Low	Low	High
Singh 2013	Low	Low	High	High	Low	Low	High
Singh 2013	Low	Low	High	High	Low	Low	High
Singh 2013	Low	Low	High	High	Low	Low	High
Singh 2013	Low	Low	High	High	Low	Low	High
Raza 2011	Unclear	Unclear	Low	Low	Unclear	Unclear	High
Stanley 1989b	Unclear	Low	Unclear	Unclear	Low	Unclear	High
Sola 2018	Low	Low	Low	Low	High	Low	High
Mchutchison 1989	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	High

Table 4. Model fit

Mortality at maximal follow-up	**Fixed-effect model**	**Random-effects model**	**Inconsistency model**
Dbar	255.1	253.7	255.3
DIC	297.9	299.2	303.1
pD	42.8	45.5	47.75
Any adverse events (number of people)	**Fixed-effect model**	**Random-effects model**	**Inconsistency model**
Dbar	38.89	39.75	-
DIC	46.75	48.72	-
pD	7.862	8.96	-
Liver transplantation at maximal follow-up	**Fixed-effect model**	**Random-effects model**	**Inconsistency model**
Dbar	54.83	54.1	-
DIC	64.51	65.98	-
pD	9.684	11.88	-
Resolution of ascites at maximal follow-up (by ultrasound)	**Fixed-effect model**	**Random-effects model**	**Inconsistency model**
Dbar	182.7	135	-
DIC	206.4	165.3	-
pD	23.73	30.24	-
Other features of decompensation at maximal follow-up	**Fixed-effect model**	**Random-effects model**	**Inconsistency model**
Dbar	258	258.1	253
DIC	293.9	294	294.7
pD	35.89	35.92	41.71
Length of hospital stay (days) (all admissions until maximal follow-up)	**Fixed-effect model**	**Random-effects model**	**Inconsistency model**
Dbar	152.7	122.8	122.7
DIC	173.7	147.2	147.3
pD	20.95	24.39	24.56

Table 4. Model fit *(Continued)*

Treatment costs	Fixed-effect model	Random-effects model	Inconsistency model
Dbar	4961	34.09	-
DIC	4963	38.08	-
pD	2.023	3.998	-

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 6. Treatment costs (tabular results without meta-analysis)

Study name	Comparison	Mean in intervention group	Standard deviation in intervention group	Number of participants in intervention group	Mean in control group	Standard deviation in control group	Number of participants in control group	Mean difference and 95% confidence intervals (according to Review Manager formula)
Hamdy 2014	Paracentesis plus systemic vasoconstrictors versus paracentesis plus fluid replacement	10.5 USD	0.1 USD	25	856.1 USD	119.6 USD	25	-845.60 (95% CI -892.48 to -798.72)
Singh 2006a	Paracentesis plus systemic vasoconstrictors versus paracentesis plus fluid replacement	1629.0 USD	76.7 USD	20	3368.0 USD	82.5 USD	20	-1739.00 (95% CI -1788.37 to -1689.63)
Singh 2008	Paracentesis plus systemic vasoconstrictors versus paracentesis plus fluid replacement	29.4 USD	2.7 USD	20	105.7 USD	25.4 USD	20	-76.30 (95% CI -87.49 to -65.11)
Mehta 1998	Paracentesis plus reinfusion versus paracentesis plus fluid replacement	295 USD	not reported	10	440 USD	Not reported	10	- 105; no information to calculate the 95% confidence intervals

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

Database	Time span	Search strategy
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)

		6. 4 or 5 7. 3 and 6 8. randomized controlled trial.pt. 9. controlled clinical trial.pt. 10. randomized.ab. 11. placebo.ab. 12. drug therapy.fs. 13. randomly.ab. 14. trial.ab. 15. groups.ab. 16. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 17. exp animals/ not humans.sh. 18. 16 not 17 19. 7 and 18
Embase Ovid	January 1974 to 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-analys*) #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 Plat-	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.

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).