VRAAG 1: WELKE (NIET-)MEDICAMENTEUZE BEHANDELINGEN ZIJN EFFECTIEF BIJ PATIËNTEN IN DE PALLIATIEVE FASE MET ASCITES (DOOR KANKER OF LEVERAANDOENING)?

Systematische reviews

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Benmassaoud 2020	• Design: systematic review + meta-analysis • Funding: National Institute for Health Research (NIHR), UK; CoI: none • Search date: May 2019 • Databases: CENTRAL, MEDLINE, Embase, Science Citation Index Expanded, World Health Organization International Clinical Trials Registry Platform, and trials registers • Study designs: RCTs • N included studies: N=49 RCTs	• Eligibility criteria: adult trial participants (18 years old and above) undergoing treatment for ascites with decompensated liver cirrhosis • Exclusion: previously undergone liver transplantation	Relevant interventions: Diuretics Large volume paracentesis	CRITICAL OUTCOMES • Ascites-free period: not reported • Decrease of ascites: resolution of ascites (by ultrasound) at maximal follow-up ○ Aldosterone antagonists plus paracentesis plus fluid replacement versus paracentesis plus fluid replacement alone: HR 30.63 (95%CI 5.06 to 692.98; 1 trial; N=36; low-certainty evidence) ○ No active treatment versus aldosterone antagonists plus loop diuretics: HR 0.15 (95%CI 0.04 to 0.43; 1 trial; N=43; low-certainty evidence) ○ Loop diuretics versus aldosterone antagonists plus loop diuretics plus paracentesis plus fluid replacement: HR 1.90 (95%Ci 1.03 to 3.76; 1 trial; N=84; low-certainty evidence) ○ Aldosterone antagonists versus paracentesis plus reinfusion: HR 1.11 (95%CI 0.69 to 1.79; 1 trial; N=131; very low-certainty evidence) • Adverse events: ○ Loop diuretics plus aldosterone antagonists versus paracentesis plus fluid replacement: OR 3.54 (95%Ci 0.43 to 27.41; 2 trials; N=84; very low-certainty evidence) • Time to next intervention: not reported IMPORTANT OUTCOMES • Quality of life: EQ-5D ○ 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%CI 0.03 to 0.09; 1 trial; N=431; low-certainty evidence)	• Review process in duplicate • Relevant RCTs: Bari 2012, Caraceni 2018, Chesta 1990, Descos 1983, Fernandez-Esparrach 1997, Gentilini 1999, Gregory 1977, Hagege 1992, Licata 2009, Romanelli 2006, Salerno 1987, Singh 2006, Singh 2008, Strauss 1991

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Kietpeerakool 2019	• Design: systematic review • Funding: Long-term Institutional Development HUBs (LID-HUBs), the Human Reproduction Programme (HRP) Alliance for Research Capacity Strengthening, Department of Reproductive Health and Research, World Health Organization, Geneva, Switzerland; CoI: none • Search date: Nov 2019 • Databases: CENTRAL, MEDLINE, Embase; clinical trial registries, grey literature, reports of conferences, citation lists of included studies, and key textbooks • Study designs: RCTs • N included studies: N=1 RCT	• Eligibility criteria: women with malignant ascites who had a confirmed histological diagnosis of all types of gynaecological cancer	Drainage	• No relevant comparison	• Review process in duplicate • Included RCT evaluated comparison that was not relevant to the PICO question
Leache 2022	• Design: systematic review + meta-analysis • Funding: none; CoI: see article • Search date: May 2022 • Databases: Medline, Embase, CENTRAL; clinicaltrials.gov; reference lists • Study designs: RCTs • N included studies: N=53 RCTs	• Eligibility criteria: adults with liver cirrhosis	Albumin	CRITICAL OUTCOMES • Ascites-free period: ○ Recurrence of ascites: ▪ Albumin vs. other plasma expanders, after paracentesis: 3 studies (Hernandez-Perez 1995, Moreau 2006, Zhao 2000), RR 0.86 (95%CI 0.65-1.12; p=0.27) ▪ Albumin vs. no albumin, long-term: 2 studies (Gentilini 1999, Romanelli 2006), RR 0.40 (0.17-0.92; p=0.79) ○ Requirement of paracentesis: ▪ Albumin vs. other plasma expanders, after paracentesis: 5 studies (Altman 1998, Fassio 1992, Hernandez-Perez 1995, Planas 1990, Sola-Vera 2003), RR 1.19 (0.85-1.65; p=0.31) ▪ Albumin vs. vasoconstrictors, after paracentesis: 3 studies (Bari 2012, Singh 2006, Singh 2008), RR 1.04 (0.54-1.97; p=0.31) • Decrease of ascites: not reported	• Review process in duplicate • Relevant RCTs: Abdel-Khalek 2010, Altman 1998, Bari 2012, Caraceni 2018, Fassio 1992, Garcia-Compean 2002, Gentilini 1999, Hernandez-Perez 1995, Moreau 2006, Planas 1990, Romanelli 2006, Salerno 1991, Singh 2006, Singh 2008, Sola-Vera 2003, Zhao 2000

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				• Adverse events: also less relevant RCTs included in meta-analysis • Time to next intervention: not reported IMPORTANT OUTCOMES • Quality of life: not reported	
Macken 2019	• Design: systematic review • Funding: funded by the by the National Institute for Health Research (NIHR) under its Research for Patient Benefit (RfPB) Programme (Grant Reference Number PB-PG-0214-33068) with additional support from Kent Surrey and Sussex (KSS) Deanery.; CoI: none • Search date: Mar 2018 • Databases: Medline, Embase, Cinahl, Google Scholar, Cochrane Database of Systematic Reviews; reference lists • Study designs: RCTs, cohort studies, case series • N included studies: N=1 RCT	• Eligibility criteria: adult patients with refractory ascites in the context of end-stage liver disease	Permanent indwelling peritoneal catheters	• No evidence from RCTs	• Selection process partly in duplicate • Quality assessment with Newcastle-Ottawa Scale • Independent data extraction • English articles only • The only RCT included 1 patient in each arm (Ahmed 2018)
Sandi 2021	• Design: systematic review + meta-analysis • Funding: none; CoI: none • Search date: May 2020 • Databases: Medline, Embase • Study designs: RCTs • N included studies: N=5 RCTs	• Eligibility criteria: RCTs evaluating long-term albumin administration for adult patients with cirrhosis and ascites • Exclusion: studies were excluded if albumin was planned to be administered for less than 3 months	Long-term albumin	CRITICAL OUTCOMES • Ascites-free period: ○ Recurrence of ascites / need for paracentesis: 3 studies, RR 0.56 (95%CI 0.48-0.67; p<0.00001) • Decrease of ascites: ○ Refractory ascites: 2 studies, RR 0.86 (0.29-2.52; p=0.78) • Adverse events: ○ Overall: 5 studies, RR 0.98 (0.91-1.06; p=0.61) ○ Bacterial peritonitis: 2 studies, RR 0.87 (0.25-2.96; p=0.82) ○ Hepatic encephalopathy: 2 studies, RR 1.03 (0.68-1.57; p=0.88)	• Review process in duplicate • Relevant included RCTs: Gentilini 1999, Romanelli 2006, Caraceni 2018

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				○ Gastrointestinal bleeding: 3 studies, RR 1.01 (0.37-2.76; p=0.98) • Time to next intervention: not reported IMPORTANT OUTCOMES • Quality of life: not reported	
Shrestha 2021	• Design: systematic review • Funding: not reported; CoI: none • Search date: May 2021 • Databases: PubMed, PMC, Scopus, and Embase • Study designs: RCTs • N included studies: N=21 RCTs	• Eligibility criteria: adult patients (≥ 18 years old) diagnosed with tense and/or refractory ascites due to cirrhosis	Human serum albumin following paracentesis	CRITICAL OUTCOMES • Ascites-free period: ○ Re-appearance of ascites: 5 studies, OR 0.82 (95%CI 0.51-1.32) • Decrease of ascites: not reported • Adverse events: also less relevant RCTs included in meta-analysis • Time to next intervention: not reported IMPORTANT OUTCOMES • Quality of life: not reported	• Unclear if review process in duplicate • Included relevant RCTs: Abdel-Khalek 2010, Altman 1998, Gines 1988, Fassio 1992, Garcia-Compean 2002, Moreau 2006, Planas 1990, Salerno 1987, Salerno 1991, Singh 2006, Singh 2008, Sola-Vera 2003
Stukan 2017	• Design: systematic review • Funding: not reported; CoI: none • Search date: July 2016 • Databases: Medline, Cochrane Library, Web of Science, Academic Search Complete, ScienceDirect, Scopus, Nature Publishing Group, Oxford Journals, Wiley Online Library, and Clinical Key • Study designs: any • N included studies: N=0 RCTs	• Eligibility criteria: adult patients suffering from malignant ascites and with any background cancer, who underwent drainage of ascites	Drainage	• No evidence from RCTs	• Only one reviewer • No RCTs included
Will 2022	• Design: systematic review • Funding: not reported; CoI: none • Search date: Nov 2019 • Databases: Medline, Embase • Study designs: RCTs, prospective clinical trials, observational	• Eligibility criteria: patients with refractory ascites caused by liver cirrhosis • Exclusion: liver transplantation	Large volume paracentesis with albumin substitution, permanent indwelling peritoneal catheter	• No evidence from RCTs	• Only one reviewer • English and German articles only • No RCTs for catheters • No comparisons reported for paracentesis

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	cohorts and case-control studies • N included studies: N=77				

Primaire studies

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Abecasis 2001	• Design: RCT • Funding: not reported; CoI: not reported • Setting: single university centre, Argentina • Sample size: N=46 • Duration: recruitment Oct 1995 – June 1997	• Eligibility criteria: cirrhotic patients with uncomplicated ascites • Exclusion criteria: patients with albumin serum-ascitic gradient less than 1.1 g/dl, renal failure (serum urea >50 mg/dl and/or serum creatinine >1.5 mg/dl), recent gastrointestinal bleeding (in the previous 4 weeks), cardiovascular disease, encephalopathy, bacterial infections or hepatocellular carcinoma • *A priori* patient characteristics: ○ M/F: 12/10 vs. 15/9 ○ Mean age: 55 vs. 57y ○ Child-Pugh C: 10/22 vs. 7/24	Torsemide 20 mg/day, stepwise increased to 60 mg/day (N=22) vs. Furosemide 40 mg/day, stepwise increased to 120 mg/day (N=24) Spironolactone was administered in both groups	CRITICAL OUTCOMES • Ascites-free period: not reported • Decrease of ascites: ascites resolution 16/22 vs. 18/24 • Adverse events: 7/22 vs. 12/24 ○ Renal failure: 4/22 vs. 5/24 ○ Encephalopathy: 2/22 vs. 1/24 ○ Hyponatremia: 2/22 vs. 6/24 ○ Hyperkalemia: 1/22 vs. 1/24 ○ Bacterial peritonitis: 1/22 vs. 1/24 • Time to next intervention: not reported IMPORTANT OUTCOMES • Quality of life: not reported	Level of evidence: unclear risk of bias • Randomisation with random number table • Unclear allocation concealment • Unclear blinding
Angeli 2010	• Design: RCT • Funding: orted in part by a grant ‘‘ex 60%’’ from the Ministry of Scientific Research and of the University of Italy; CoI: none • Setting: 4 centres, Italy • Sample size: N=100 • Duration: recruitment April 2005 – Sep 2008	• Eligibility criteria: non-azotaemic patients with cirrhosis and ascites; (1) grade 2 ascites, (2) serum creatinine less than 1.2 mg/dl, (3) serum sodium >130 mEq/l, and (4) serum potassium within 3.5 and 4.5 mEq/l, at least 5 days after the withdrawal of diuretics and a 90 mmol/day Na diet • Exclusion criteria: (1) any therapeutic paracentesis for ascites before inclusion, (2) cardiac or respiratory disease, (3) gastrointestinal bleeding, hepatic encephalopathy, bacterial infections in the 4 weeks before inclusion, and (4) the use of non-steroidal anti-inflammatory drugs (NSAIDs) or nephrotoxic drugs in the 4 weeks before inclusion	Sequential diuretic treatment: (1) Potassium Canrenoate 200 to 400 mg/day, (2) Furosemide 50 to 100 mg/day (N=50) vs. Combined diuretic treatment: Potassium Canrenoate 200 mg/day + Furosemide 50 mg/day (with dose increase to 400 mg and 100 mg/day) (N=50)	CRITICAL OUTCOMES • Ascites-free period: not reported • Decrease of ascites: in patients who did not fail to respond to treatment (28 in Group A and 38 in Group B, p<0.05), the mean time for the resolution of ascites was shorter in Group B than in Group A (15.5 (SD 5.6) vs 20.7 (SD 6.4) days, p<0.001) • Adverse events: 19/50 vs. 10/50, p<0.05 ○ Renal failure: 8/50 vs. 6/50, NS ○ Hyponatremia: 4/50 vs. 4/50, NS ○ Hyperkalemia: 9/50 vs. 2/50, p<0.05 ○ Hypokalemia: 1/50 vs. 0/50, NS • Time to next intervention: not reported IMPORTANT OUTCOMES • Quality of life: not reported	Level of evidence: high risk of bias • Randomisation was performed using consecutively numbered, computer-generated envelopes • Unclear allocation concealment • Open trial

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		• *A priori* patient characteristics: ○ M/F: 13/37 vs. 20/30 ○ Mean age: 54 vs. 57y ○ Child-Pugh C: 23/50 vs. 24/50			
Gu 2012	• Design: RCT • Funding: not reported; CoI: none • Setting: single university centre, China • Sample size: N=200 • Duration: recruitment Jan 2007 – May 2000	• Eligibility criteria: cirrhotic patients with ascites diagnosed based on clinical manifestation, laboratory examination and B-type ultrasound; increased or normal alanine transaminase and total bilirubin • Exclusion criteria: hepatic failure, combination with hepatic encephalopathy, upper digestive tract bleeding, spontaneous bacterial peritonitis, hepatorenal syndrome, renal disease, hepatic cancer, shock, and heart and lung insufficiency • *A priori* patient characteristics: ○ M/F: 61/37 vs. 65/37 ○ Mean age: 52.4 vs. 52.7y ○ Child-Pugh C: 73.5% vs. 72.6%	Sodium-unrestricted diet (N=98) vs. Sodium-restricted diet (N=102)	CRITICAL OUTCOMES • Ascites-free period: not reported • Decrease of ascites: ascites disappeared in higher proportion of patients in sodium-unrestricted group (44 cases, 45.36%) than in sodium-restricted group (16 cases, 15.84%) (p<0.001) • Adverse events: adverse events such as hypertension, heart failure and cerebral edema did not occur in any group • Time to next intervention: not reported IMPORTANT OUTCOMES • Quality of life: not reported	Level of evidence: high risk of bias • Random numeral table was used to assign patients randomly by statistician • No blinding because of the nature of the intervention • 1 patient lost to follow-up in both groups
Jatoi 2012	• Design: RCT • Funding: funded by National Cancer Institute, K24CA131099; CoI: not reported • Setting: multicentre trial, US • Sample size: N=33 • Duration: unclear	• Eligibility criteria: (1) patient age of 6 18 years at the time of enrollment; (2) histologic or cytologic proof of malignancy other than lymphoma; (3) the treating oncologist believed current ascites was malignant; (4) therapeutic paracentesis was planned in max 3 days after randomization or was completed in the 2 days prior to therapy; (5) the patient viewed ascites as problematic, and (6) the patient was willing to provide an ascites sample for research purposes, and, if it was a Mayo Clinic patient, was willing to provide a blood sample for research • Exclusion criteria: (1) history of cholecystitis with no prior cholecystectomy; (2) allergic reaction to octreotide and/or	Long-acting octreotide depot 30 mg IM every month (N=16) vs. Placebo (N=17)	CRITICAL OUTCOMES • Ascites-free period: not reported • Decrease of ascites: median number of paracenteses over duration of study 1 vs. 1, p=0.68 • Adverse events: ○ Among octreotide-treated patients, 10 grade 4 events occurred among 6 patients; these events include abdominal pain, hyperkalemia, cognitive dysfunction, dehydration, neutropenia, fatigue, hypoxia, and anemia ○ Among placebo-exposed patients, 4 grade 4 events occurred among 3 patients; these included abdominal pain, fatigue, and hepatic failure and again are presented regardless of attribution ○ No patient stopped the study intervention because of drug-related adverse events • Time to next intervention: median time to next paracentesis 28 vs. 14 days, p=0.17; adjusted HR 0.52, 95%CI 0.21-1.28, p=0.15	Level of evidence: unclear risk of bias • Unclear randomisation method and allocation concealment • Unclear blinding • ITT analysis • Slow accrual prompted early study closure that led to enrollment of slightly under half of the intended cohort of 68 patients

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		latex; (3) history of chronic renal failure with a creatinine twice the institution's upper limit of normal; (4) life expectancy of <4 weeks; (5) pregnant or nursing or, if of childbearing potential, unwilling to employ contraception; (6) concurrently receiving octreotide or intraperitoneal chemotherapy; (7) uncontrolled diabetes; (8) receiving warfarin or at high risk for bleeding from a procedure; (9) concurrently or about to receive first-line chemotherapy for any malignancy other than exocrine pancreas cancer; (10) concurrently receiving bevacizumab, and (11) cirrhosis or portal hypertension • *A priori* patient characteristics: ○ M/F: 6/10 vs. 5/12 ○ Median age: 62 vs. 69y ○ Cancer type: ovarian/peritoneal N=9, gastrointestinal N=6		IMPORTANT OUTCOMES • Quality of life: ○ Placebo-exposed patients described worse abdominal bloating (p=0.01), abdominal discomfort (p=0.02), and shortness of breath (p=0.007) ○ Questionnaire items for fatigue, pain, sleepiness, desire to eat, strength, trouble lifting, anxiety, energy, happiness, drowsiness, irritability, difficulty sleeping, impact of the disease on family members, mood swings, inability to fall asleep, muscle cramps, dry mouth, trouble concentrating, itching, and other factors were not statistically different between study arms	
Lenaerts 2005	• Design: RCT • Funding: not reported; CoI: not reported • Setting: single university centre, Belgium • Sample size: N=24 • Duration: recruitment Oct 2001 – Oct 2003	• Eligibility criteria: alcoholic cirrhotic patients with refractory ascites and increased sympathetic nervous system activity (plasma norepinephrine > 300 pg/mL) • Exclusion criteria: patients with serum bilirubin concentration > 45 mg/dl, prothrombin time < 40%, platelet count < $40x10^9$/l, serum creatinine concentration > 2 mg/dl, with gastro-intestinal haemorrhage due to variceal rupture within the previous two months unless sclerotherapy was performed, with diabetes, hepatocellular carcinoma, respiratory or cardiac failure • *A priori* patient characteristics: ○ M/F: 5/5 vs. 5/5 ○ Mean age: 60.7 vs. 60.5y ○ Child-Pugh C: unclear	Repeated large volume paracentesis (4 to 5 liters per paracentesis every 48 hours) plus intravenous albumin (7 gr per liter of ascites) (N=12) vs. Clonidine (0.075 mg twice daily) and spironolactone (200 to 400 mg daily) (N=12)	CRITICAL OUTCOMES • Ascites-free period: not reported • Decrease of ascites: ○ Disappearance: +/- 10/12 vs. 0/10 • Adverse events: ○ No local complications related to paracentesis occurred ○ Total: 6/10 vs. 2/10, NS ○ Encephalopathy: 2/10 vs. 0/10 ○ Gastrointestinal bleeding: 2/10 vs. 0/10 ○ Bacterial infection: 2/10 vs. 1/10 ○ Hypotension: 0/10 vs. 1/10 • Time to next intervention: readmissions because of ascites 37 vs. 3 IMPORTANT OUTCOMES • Quality of life: not reported	Level of evidence: unclear risk of bias • Patients were randomized using a closed list in 4 blocks of 6 units • Unclear allocation concealment • Unclear blinding but probably not • Two patients in each group were excluded just after the start of the study because of poor compliance

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Macken 2020 Cooper 2021	• Design: RCT • Funding: funded by the • National Institute for Health Research; CoI: see article • Setting: 5 centres, UK • Sample size: N=36 • Duration: recruitment Nov 2015 – June 2018; follow-up 12 weeks	• Eligibility criteria: ascites that recurred rapidly after LVP, requiring one or more LVPs/month (participants undergoing a minimum of two LVPs prior to recruitment), age ≥18 years, Child Pugh Score ≥ 9 (unless felt to be palliative despite lower CPS) and capacity to give informed consent • Exclusion criteria: loculated or chylous ascites, the presence of >grade 1 hepatic encephalopathy, evidence of active infection including spontaneous bacterial peritonitis during screening and eligibility for liver transplantation • *A priori* patient characteristics: ○ M/F: 13/4 vs. 14/5 ○ Mean age: 66.3 vs. 67.9y ○ Child-Pugh C: 3/17 vs. 4/18	Long-term abdominal drains (N=17) vs. Large-volume paracentesis (N=19)	CRITICAL OUTCOMES • Ascites-free period: not reported • Decrease of ascites: ○ Median amount of ascitic fluid (L) drained/week: 3.85 (IQR 2.85-4.51) vs. 4.42 L (3.00-6.09) ○ Median number of visits per week for drainage: 1.9 (0.6-2.5) vs. 0.33 (0.17-0.5) • Adverse events: ○ Worsening renal function: 6/17 vs. 7/19 ○ Peritonitis: 1/17 vs. 2/19 • Time to next intervention: not reported IMPORTANT OUTCOMES • Quality of life: ○ SFLDQOL: at 12 weeks ▪ Symptoms: MD 1.3 (95%CI -19.7 to 22.2) ▪ Effect: MD 1.0 (-26.3 to 28.4) ▪ Memory: MD -9.5 (-33.8 to 14.7) ▪ Distress: MD -22.8 (-59.0 to 13.4) ▪ Sleep: MD 3.5 (-11.3 to 18.3) ▪ Loneliness: MD -37.1 (-60.4 to -13.9) ▪ Hopelessness: MD -19.2 (-41.7 to 3.4) ▪ Stigma: MD -3.4 (-29.6 to 22.7) ▪ Sex: - ○ EQ-5D-5L: at 12 weeks ▪ Index: MD 0.02 (95%CI -0.18 to 0.22) ▪ VAS: MD 10.6 (-9.2 to 30.4)	Level of evidence: high risk of bias • Randomisation using web-based system hosted by King's Clinical Trials Unit, central allocation • No blinding • No ITT analysis for QOL
Santos 2003	• Design: RCT • Funding: supported in part by a grant from the Instituto Carlos III (C03/02); CoI: none • Setting: multicentre trial, Spain • Sample size: N=100 • Duration: unclear	• Eligibility criteria: nonazotemic cirrhotic patients with grade 2 ascites, serum creatinine ≤1.5 mg/dl, urinary sodium excretion <50 mmol/day, serum sodium ≥ 125 mmol/l, and serum potassium <5.5 mmol/l, after 5 days on a 50 mmol/day sodium diet and without diuretics, as well as absence of gastrointestinal bleeding, hepatic encephalopathy, infection, advanced hepatocellular carcinoma, and severe liver disease (serum bilirubin >10 mg/dl and prothrombin rate <40%). • Exclusion criteria: patients with respiratory, cardiac or renal	Increasing doses of spironolactone (from 100-200 mg/day to 400 mg/day) in combination with furosemide (from 40-80 mg/day to 160 mg/day) (N=50) vs. Spironolactone alone (from 100-200 mg/day to 400 mg/day; if no response: also furosemide) (N=50)	CRITICAL OUTCOMES • Ascites-free period: ○ Median response time: 9.8 vs. 10.3 days, NS • Decrease of ascites: 46/47 vs. 44/47, NS • Adverse events: N patients 3/47 vs. 6/47, NS ○ Muscle cramps: 1/47 vs. 0/47 ○ Hypokalemia: 1/47 vs. 0/47 ○ Renal failure: 1/47 vs. 0/47 ○ Hyperkalemia: 0/47 vs. 3/47 ○ Hyponatremia: 0/47 vs. 2/47 ○ Hepatic encephalopathy: 0/47 vs. 1/47 • Time to next intervention: not reported IMPORTANT OUTCOMES • Quality of life: not reported	Level of evidence: unclear risk of bias • Unclear randomisation method and allocation concealment • Unclear blinding • Six of 100 patients were not evaluable because of the early development of a severe complication of cirrhosis: three patients from Group 1 (variceal bleeding in two and spontaneous bacterial peritonitis in one) and three from Group 2 (variceal bleeding, sepsis and spontaneous bacterial peritonitis)

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		disease and those treated with nonsteroidal anti-inflammatory drugs • *A priori* patient characteristics: ○ M/F: 12/38 vs. 13/37 ○ Mean age: 58.5 vs. 60.1y ○ Child-Pugh C: not reported			
Tapper 2020	• Design: RCT • Funding: National Institutes of Health through the Michigan Institute for Clinical and Health Research [KL2TR002241] and NIDDK [1K23DK117055-01A1].; CoI: one author with conflicts • Setting: single university centre, US • Sample size: N=40 • Duration: 12 weeks; recruitment June 2018 – June 2019	• Eligibility criteria: patients cirrhosis and severe/ symptomatic ascites; history of multiple paracenteses including at least one within the prior 30 days • Exclusion criteria: patients with creatinine >1.5 mg/dL, planned liver transplantation, or portosystemic-shunt procedure • *A priori* patient characteristics: ○ M/F: 22/18 ○ Median age: 54y ○ Child-Pugh C: not reported	Medically tailored meal with <2g sodium, >2100 kcal and >80g protein (N=20) vs. Standard of care with educational handout on low-sodium diets (N=20)	CRITICAL OUTCOMES • Ascites-free period: not reported • Decrease of ascites: N paracenteses per week: median 0.34 (IQR 0.14-0.54) vs. 0.46 (0.25-0.64) • Adverse events: not reported • Time to next intervention: not reported IMPORTANT OUTCOMES • Quality of life: ascites symptom inventory-7 ○ Improved to a greater degree in medically tailored meal group: +25% (IQR -11% to 61%) vs. +13% (-28% to 54%)	Level of evidence: unclear risk of bias • Unclear randomisation method and allocation concealment • Unclear blinding • ITT analysis
Uojima 2017	• Design: RCT • Funding: not reported; CoI: none • Setting: 2 centres, Japan • Sample size: N=60 • Duration: 5 weeks	• Eligibility criteria: age > 20 years, liver cirrhosis with ascites even after undergoing a natriuretic with a loop diuretic and an anti-aldosterone agent for at least 7 d, and a daily dose of ≥ 20 mg furosemide and ≥ 25 mg spironolactone • Exclusion criteria: patients with hepatic encephalopathy (coma scale ≥ Ⅱ), poorly controlled hepatocellular carcinoma, and patients receiving blood products including albumin for 7 d or less before initiating the trial drug treatment • *A priori* patient characteristics: ○ M/F: 17/11 vs. 15/13 ○ Mean age: 69.3 vs. 69.4y ○ Child-Pugh C: 12/28 vs. 13/28	Tolvaptan 7.5 mg/day for 1 week (N=30) vs. Furosemide 40 mg/day for 1 week (N=30) In addition to the standard therapy identical to that administered prior to enrolment in this study, which included sodium intake restrictions (< 6 g/d), ad libitum fluid intake, and natriuretic therapy	CRITICAL OUTCOMES • Ascites-free period: not reported • Decrease of ascites: ○ Ascites volume: significantly higher decrease in combination group (only reported in figure; p=0.0207) • Adverse events: ○ N patients: 13/30 vs. 16/30 ○ Encephalopathy: 1/30 vs. 4/30 ○ Abdominal infection: 0/30 vs. 1/30 ○ Dry mouth: 6/30 vs. 2/30 ○ Urinary frequency: 4/30 vs. 2/30 ○ Hypokalemia: 0/30 vs. 3/30 ○ Acute kidney injury: 2/30 vs. 4/30 • Time to next intervention: not reported IMPORTANT OUTCOMES • Quality of life: not reported	Level of evidence: high risk of bias • Permuted block randomization was used for the creation of the randomization list prepared by an investigator with no clinical involvement in the trial, and a randomization code was pre-assigned to each trial drug and used during drug administration • Open-label • Four patients with unstable vital signs or acute renal failure were withdrawn from the study by their physicians before the drugs were administered (2 patients in each group) • Three patients discontinued treatment (in furosemide group), two owing to adverse events (hepatic

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					encephalopathy and renal dysfunction, respectively), whereas the third required intervention following administration of standard diuretics therapy in the form of therapeutic abdominal paracentesis for uncontrollable ascites due to a bacterial infection

Abbreviations: 95%CI: 95% confidence interval; CoI: conflict of interest; HR: hazard ratio; IM: intramuscular ITT: intention-to-treat; IV: intravenous; IQR: interquartile range; M/F: male/female; MD: mean difference; NS: not significant; OR: odds ratio; po: per os; RCT: randomised controlled trial; RR: relative risk; SC: subcutaneously; SD: standard deviation; US: United States.

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