Management of Severe and Refractory Ascites

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KEYWORDS

• Ascites • Portal hypertension • Cirrhosis • Albumin • TIPS • Liver transplantation
• Large-volume paracentesis

KEY POINTS

- As soon as refractory ascites is diagnosed, LT must be considered as it is the only curative treatment.
- Special care must be given to control the underlying liver disease and to sodium restriction.
- TIPS is then proposed, both as a final treatment or as a waiting therapeutic in bridge to LT.
- Careful selection to each treatment is essential to avoid further decompensation but also to limit therapeutic complications.

INTRODUCTION

Ascites is one of the most common complications of cirrhosis, as 50% to 60% of cirrhotic patients will develop ascites within 10 years after diagnosis.[1] After a first episode of ascites, refractory ascites will develop in 10% of the patients.[2] The occurrence of refractory ascites is a milestone in the history of the disease, as it is associated with a 2-year mortality of 65%,[3] poor quality of life, and an increased risk of spontaneous bacterial peritonitis (SBP) and hepatorenal syndrome (HRS). It is for these reasons that any patient with refractory ascites should be considered for (LT). However, a minority of them are candidates for LT, and the waiting time on list could be very long. Therefore, other options must be considered. Choosing between the different therapeutic options must be done regarding the improvement in the prognosis and focusing on quality of life and nutritional status improvement. Ascites is uncomplicated when it is not infected, refractory, or associated with HRS.

In this review, the authors focus on the management of refractory ascites.

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Box 1
Classification of ascites stage

Grade 1 (mild): Ascites is only detectable by ultrasound examination

Grade 2 (moderate): Clinically perceptible

Grade 3 (large): Marked abdominal distention

DEFINITIONS

First-line treatment of patients with cirrhosis and moderate or large ascites (**Box 1** provides a classification of grading) consists of sodium restriction (80–120 mmol per day with diet education) and single morning doses of oral spironolactone and furosemide, beginning with 100 mg of the former and 40 mg of the latter.

According to the International Club of Ascites, diagnostic criteria of refractory ascites rely on lack of response to diuretic treatment, early ascites recurrence, or diuretic induced complications. They are summarized in **Box 2**.

Ascites is defined as refractory when it cannot be mobilized or whenever its early recurrence cannot be prevented by medical therapy. The definition encompasses 2 different situations:

- Diuretic-resistant ascites: Patients do not respond to sodium restriction at the maximum doses of diuretics (400 mg of spironolactone and 160 mg of furosemide).
- Diuretic-intractable ascites: Patients cannot be treated by diuretics because of diuretics-induced complications that preclude the use of an effective dosage.

Box 2
Diagnostic criteria of refractory ascites

- Diuretic-resistant ascites: patients do not respond to sodium restriction at the maximum doses of diuretics (400 mg of spironolactone and 160 mg of furosemide).
- Diuretic-intractable ascites: patients cannot be treated by diuretics because of diuretics-induced complications that preclude the use of an effective dosage.
  - Diuretic treatment duration:
    Spironolactone 400 mg per day and Furosemide 160 mg per day for at least 1 week, together with a low-sodium diet (<5.2 g per day)
  - Lack of response to diuretic treatment:
    Mean weight loss of less than 800 g over 4 days and urinary sodium output less than oral intake
  - Early ascites recurrence:
    Reappearance of grade 2 or 3 ascites within 4 weeks of initial mobilization
  - Diuretic-induced complications:
    Hepatic encephalopathy without any other precipitating factor
    Renal impairment with an increase of serum creatinine by greater than 100% to a value greater than 2 mg/dL
    Hyponatremia with a decrease of serum sodium by greater than 10 mmol/L to less than 125 mmol/L
    Hypokalemia or hyperkalemia to less than 3 mmol/L or greater than 6 mmol/L

Adapted from: Moore KP, Wong F, Gines P, Bernardi M, Ochs A, Salerno F, Angeli P, Porayko M, Moreau R, Garcia-Tsao G, Jimenez W, Planas R, Arroyo V. The management of ascites in cirrhosis: report on the consensus conference of the International Ascites Club. Hepatology. 2003 Jul;38(1):258-66. https://doi.org/10.1053/jhep.2003.50315. PMID: 12830009; with permission.

PATHOPHYSIOLOGY

Ascites results from both portal hypertension and liver insufficiency. Ascites generally develops when portal pressure gradient exceeds 10 mm Hg. In cirrhosis, portal pressure increases first because of an increased resistance to portal blood flow at the level of the liver vascular bed. Increased resistance is secondary to a mechanical component (modifications of the liver architecture) but also to a dynamic one (decrease of vasodilator agents and increase in vasoconstrictor agents) leading to an increased intrahepatic vascular tone.

Secondary portosystemic collateral develops, and splanchnic vasodilatation is responsible for an increase in blood flow. Vasodilatation results in a decrease of systemic vascular resistance and in an effective arterial hypovolemia. Increased cardiac output, activation of sympathetic, antidiuretic, and renin-angiotensin-aldosterone systems aim to counteract the effective hypovolemia but contribute to renal vasoconstriction and water and sodium retention.

Hypoalbuminemia owing to hepatic insufficiency is responsible for a decrease in oncotic pressure leading to a fluid leakage to interstitial sector.[4]

Moreover, advanced cirrhosis is an inflammatory state whereby there are higher levels of proinflammatory cytokines that increase arterial nitric oxide production and exacerbate splanchnic vasodilatation and subsequent effective arterial underfilling. Decreased effective volume predisposes to the development of refractory ascites. Bacterial translocation following intestinal dysbiosis and increased intestinal permeability is frequent and contributes to the release of proinflammatory cytokines.[5]

MANAGEMENT AND THERAPEUTIC OPTIONS

General Measures

One of the most important steps is to treat the underlying liver disease (abstinence of alcohol, antiviral therapy, and so forth). It can result in resolution of ascites, and it clearly demonstrates that refractory ascites can be transient. In randomized studies comparing transjugular intrahepatic portosystemic shunt (TIPS) to repeated paracenteses, up to 20% of the patients did not require further repeated large-volume paracenteses probably because of the control of the etiologic factor resulting in an improvement of portal hypertension and/or liver functions.

Diuretics have usually been discontinued in patients with refractory ascites. The European guideline recommends discontinuing diuretics if the urine sodium is less than 30 mmol per day during diuretic therapy.

A precipitating factor must be sought for hepatocellular carcinoma, portal vein thrombosis, acute alcoholic hepatitis, SBP, and similar.

The safety of nonselective beta-blockers in patients with refractory ascites has been recently questioned. A detrimentary effect could be due to their negative impact on arterial blood pressure, the increase rate of postparacentesis circulatory dysfunction (PPCD), and an impairment of renal function and of systolic function.[6] Blood pressure and renal function should be monitored closely, and consideration should be given to discontinuing or not initiating beta-blockers in patients or situations with decreased organ perfusion or hypotension (systolic blood pressure <90 mm Hg, mean arterial pressure <65 mm Hg, acute kidney injury, SBP). At Baveno VI, it was proposed that after discontinuation of beta-blockers, they should be carefully reinitiated after the resolution of the event. In those situations, doses greater than 80 mg should be avoided.

Other agents known to be deleterious for renal function in such patients should be avoided, such as nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and aminoglycosides.

Large-Volume Paracentesis with Albumin Infusion

Large-volume paracentesis with albumin infusion (LVP + A; 8 g/L of ascites removed is the dose commonly used) is the standard and the first-line treatment of tense ascites.[7] It rapidly relieves abdominal distension, diminishing pain and discomfort, and can be performed in an outpatient setting. However, recurrence of ascites is the rule because this is a local treatment with no beneficial impact on any mechanism involved in the ascites formation. Furthermore, LVP is associated with a risk of PPCD defined as an increase in plasma renin activity of greater than 50% to greater than 4 ng/mL/h on the sixth day after the procedure. PPCD is associated with a rapid recurrence of ascites and a high risk of HRS.[8] Albumin infusion in LVP of more than 5 L reduces the incidence of PPCD, and a meta-analysis of 17 trials showed a reduction in mortality with an odds ratio of death of 0.64 (95% confidence interval, 0.41–0.98) when albumin was used compared with other plasma expanders.[9]

Transjugular Intrahepatic Portosystemic Shunt

TIPS is a side-to-side portocaval shunt inside the liver connecting a main portal branch with a large hepatic vein. It reduces ascites formation by decreasing portal pressure, increasing at least transiently the effective arterial blood volume and decompressing both the portal venous system and the hepatic microcirculation, leading to a decreased formation of lymph. A decrease in plasma renin activity, plasma aldosterone, and noradrenalin concentrations is observed following TIPS implantation. This leads to an improvement in renal perfusion.[10] Six randomized studies aiming to compare TIPS and LVP in the treatment of patients with refractory ascites were performed (**Table 1**). All these studies clearly showed that TIPS is more effective than LVP in preventing recurrence of ascites. However, patients treated with TIPS were consistently found to have an increased risk of encephalopathy. The results regarding survival are discrepant according to the different reports. Many meta-analyses have also been published. The first one found TIPS was more effective in preventing recurrence of ascites, but the risk of encephalopathy was increased, and survival was unchanged compared with LVP. However, in the sole meta-analysis with individual data performed by Salerno and colleagues,[18] the actuarial probability of transplant-free survival was better in patients allocated to the TIPS arm than to the LVP group (63% and 52% at 1 year, respectively). It suggests that some patients would benefit

Table 1
Randomized controlled trials comparing transjugular intrahepatic portosystemic shunt versus large-volume paracenteses in patients with recurrent ascites

Study	Stent	Patients (TIPS vs LVP + A)	Survival Rate (TIPS vs LVP + A)
Lebrec et al.[11] J Hepatol 1996	Bare	13 vs 12	29% vs 56% at 2 y[a]
Rössle et al.[12] N Engl J Med 2000	Bare	29 vs 31	58% vs 32% at 2 y
Ginès et al.[13] Gastroenterology 2002	Bare	20 vs 18	26% vs 30% at 2 y
Sanyal et al.[14] Gastroenterology 2003	Bare	52 vs 57	35% vs 33% at 2 y
Salerno et al.[15] Hepatology 2004	Bare	33 vs 33	59% vs 29% at 2 y[a]
Narahara et al.[16] J gastroenterol 2011	Bare	30 vs 30	64% vs 35% at 2 y[a]
Bureau et al.[17] Gastroenterology 2017	Covered	29 vs 33	93% vs 52% at 1 y[a]

[a] Significant difference.

from the procedure. The parameters associated with mortality in multivariate analysis were an older age, a higher bilirubin level, and a lower plasma sodium level and treatment allocation. In another study, it has been shown that bilirubin level and platelets count could be useful to select good candidates for the TIPS procedure. Finally, bare metallic stents were used in all the six first randomized controlled trials (RCT). The use of covered stents improves the primary patency of the shunt. The most recent RCT comparing TIPS using polytetrafluoroethylene-covered stents with LVP + A showed a better transplantation-free survival at 1 year (93% in the TIPS group vs 52% in the LVP + A group).[17]

As mentioned above, a careful selection of patients is crucial. TIPS creation is contraindicated in patients with advanced liver failure (Child Pugh > C11 or model for end-stage liver disease [MELD] >18), heart failure, or recurrent/chronic hepatic encephalopathy. A preprocedural assessment is needed, including liver function tests, cardiac evaluation (nt-pro BNP, transthoracic echocardiography [TTE] with diastolic dysfunction screening), and encephalopathy screening. Contraindications are listed in **Box 3**.[19]

Three main complications may develop after TIPS creation: liver failure, hepatic encephalopathy, and cardiac failure. Liver failure is now a rare event after a planned procedure when the selection of candidates is accurate. Hepatic encephalopathy occurs in 25% to 50% of cases, irrespective of the type of stent used.[20] In the RCT comparing covered TIPS versus standard of care (LVP + A), the 1-year probability of remaining free of overt hepatic encephalopathy was 65% in both groups.[17] Recent data suggest that underdilatation of a covered stent could lower the risk of hepatic encephalopathy.[21] However, underdilated stents have been reported to passively autoexpand to their nominal diameter some weeks after the procedure.[22] New controlled expansion stents have been introduced in 2016, but few data about their efficacy are available.[23] Preliminary results of a recent RCT comparing Rifaximin to placebo after TIPS creation found the occurrence of hepatic encephalopathy was lowered to 39% in the Rifaximin group versus 66% in the placebo group within the 6 months after TIPS creation.[24]

TIPS creation causes an increased cardiac preload, leading to an increased ventricular filling pressure, and can reveal an underlying cirrhotic cardiomyopathy. Cardiac failure occurs in up to 20% within the first year after TIPS, in a median of 30 days (2–210 days).[25] Pre-TIPS cardiac evaluation is therefore mandatory. Pulmonary

Box 3
Usual contraindications to transjugular intrahepatic portosystemic shunt placement in patients with refractory ascites

Advanced liver failure defined as:
- Child-Pugh greater than C11
- MELD greater than 18,
- Bilirubin greater than 50 μmol/L,
- INR greater than 2,
- Platelets less than 75 G/L

Recurrent overt hepatic encephalopathy

Cardiac dysfunction: Pulmonary hypertension (PAPm $\geq$ 45 mm Hg)
- Aortic stenosis
- Diastolic dysfunction (E/A > 1.5, E/E' > 10, LAVI > 34 mL/m^2)
- Systolic dysfunction (LVEF < 50%)

Abbreviations: LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; INR, international normalized ratio; PAPM, mean pulmonary arterial pressure; RA, refractory ascites.

hypertension and aortic stenosis are contraindications for shunt creation. When the nt-pro BNP value is greater than 125 pg/mL, a complete TTE is needed. TTE parameters identified signs of diastolic dysfunction to predict cardiac failure after shunt creation: an E/A ratio greater than 1.5 or an E/e′ ratio greater than 10 or a left atrial volume index greater than 34 mL/m^2.

Automated Low-Flow Ascites Pump

The automated low-flow ascites pump (alfapump system) consists of a subcutaneous implantable and rechargeable device, which diverts ascitic fluid from the peritoneal cavity to the urinary bladder, allowing a daily slow and continuous evacuation. The daily amount of ascitic fluid to be removed can be adjusted. An RCT showed that alfapump reduces the need for LVP, and this procedure was associated with an improvement of nutritional status and quality of life.[26] However, survival was similar in the group of patients treated by alfapump compared with those treated by LVP. That is the reason it should be indicated in patients who are ineligible for TIPS and LT, with an expected survival of greater than 3 months. Contraindications are renal failure with creatinine greater than 132 μmol/L or estimated glomerular filtration rate less than 30 mL/min/1.32 m^2, at least 2 or more systemic or local abdominal infections in the previous 6 months, recent intra-abdominal surgery, history of bladder cancer, previous solid organ transplantation, and bilirubin level greater than 85 μmol/L.[27]

Routine prophylactic antibiotic use (norfloxacin 400 mg/d or ciprofloxacin 750 mg/d) has reduced the incidence of bacterial infections.[28]

Even if the pump performs a continuous small paracentesis, it has been shown that the dispositive was associated with impairment of renal function by activating vasoconstrictors systems. Acute kidney injury was reported in 30% of patients, and creatinine levels increased by a mean of 23 μmol/L after pump insertion.[29] Whether albumin infusion should be systematic in all or in patients at high risk of renal failure requires further investigations.[30]

Liver Transplantation

It is worth noting that patients with refractory ascites should be evaluated for a LT as soon as the diagnosis is completed, as it is the only way to treat the underlying liver disease and to improve long-term prognosis. LT is the only curative option in patients with a high MELD score or a high Child-Pugh score and in patients with prior recurrent or chronic hepatic encephalopathy. Either TIPS or the alfapump system should be used while awaiting treatments.

Other Therapeutic Options

Albumin infusions

Albumin infusions could have several beneficial effects: they work as a plasma expander but also have homeostatic properties as a potent scavenger, anti-inflammatory, and antioxidant molecule. Recently, 2 randomized studies investigated the long-term use of albumin administration in patients with ascites. The ANSWER study enrolled 431 patients with persisting ascites, either in the standard of care group or in the albumin group (40 g twice a week for 2 weeks and then 40 g weekly) for 18 months.[31] The investigators observed a better control of ascites, a decreased rate of other cirrhosis-related complications, and a better overall survival in patients treated in the albumin group (survival 77% vs 66%). A prospective nonrandomized study including 70 patients with cirrhosis and refractory ascites (albumin 20 g twice a week) showed similar results.[32] However, a placebo-controlled trial in patients on the waiting list for LT failed to show any difference

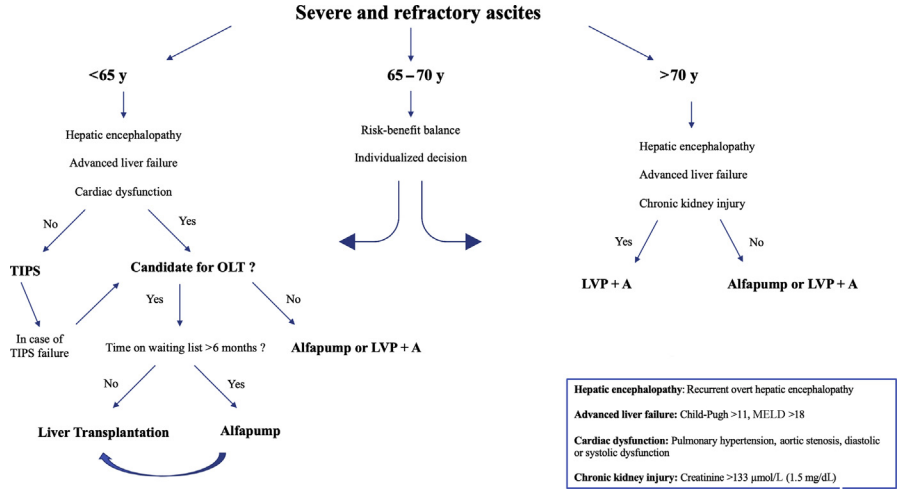

Fig. 1. Proposed algorithm for the treatment of severe and refractory ascites.

in clinical outcomes in patients treated by albumin infusion (40 g of albumin every 2 weeks + midodrine 15–30 mg/d) compared with placebo.[33] Many differences between the 2 studies can explain the different results observed (characteristics of patients, doses used, short follow-up in the latter), but perspectives could be to tailor the administration of albumin-to-serum albumin concentration.[34]

Vasopressors

Vasoconstrictors have been investigated in reducing the incidence of PPCD, but the data are controversial.

Oral midodrine (alpha-1-adrenergic agonist) 7.5 mg 3 times daily has been shown in a randomized trial to increase urine volume, urinary sodium, mean arterial pressure, and survival.

A randomized study found no significant difference between albumin infusions group and midodrine (for 2 days after LVP or for 30 days after LVP) in developing renal impairment, hyponatremia, or mortality at 1 month.[35]

Vasoconstrictors, mainly terlipressin, are used in variceal bleeding and HRS. Terlipressin could have a beneficial effect in patients with ascites by reducing splanchnic vasodilatation and by improving hyperdynamic state.[36] However, although some reports suggest that terlipressin reduces the need for paracenteses, the results of a double-blind randomized study failed to show any difference between patients treated by placebo or terlipressin.[37]

Vasopressin receptors antagonists

Vaptans are a selective oral vasopressin v2-receptor antagonist used in euvolemic or hypovolemic hyponatremia. In a large dedicated RCT in patients with cirrhosis and ascites, no benefit of satavaptan alone or in combination with diuretics was demonstrated. Moreover, the mortality was higher in the group treated by satavaptan.[38]

An RCT evaluating the effect of midodrine alone, tolvaptan alone, or midodrine + tolvaptan versus standard medical therapy (sodium restriction, diuretics, and LVP) showed midodrine alone and combination of midodrine and tolvaptan but not tolvaptan alone were better to control refractory ascites than standard medical therapy at 3 months ($P<.5$). The morbidity and mortality were the same in all groups.[39]

SUMMARY

Considering the poor prognosis, severe and refractory ascites is a milestone in cirrhotic patients. LT must be considered first. In the case of contraindication to LT or when the waiting period is estimated to be more than 6 months, TIPS should be discussed in eligible patients. When TIPS is contraindicated, either alfapump or LVP + A may be discussed regarding the risk-benefit balance and the quality of life. The place of albumin infusion must be specified. Regardless of the type of treatment, a careful selection of patients is crucial to avoid further decompensation and specific complications of each treatment (**Fig. 1**).

CONFLICT OF INTEREST

H. Larrue: none. J.P. Vinel: none. C. Bureau: Gore (speaker fees), Sequana Medical (participation to the European trial sponsored by Sequana Medical).

REFERENCES

1. Ginés P, Quintero E, Arroyo V, et al. Compensated cirrhosis: natural history and prognostic factors. Hepatology 1987;7(1):122–8.
2. Planas R, Montoliu S, Ballesté B, et al. Natural history of patients hospitalized for management of cirrhotic ascites. Clin Gastroenterol Hepatol 2006;4(11):1385–94.
3. D'Amico G, Morabito A, D'Amico M, et al. Clinical states of cirrhosis and competing risks. J Hepatol 2018;68(3):563–76.
4. Fortune B, Cardenas A. Ascites, refractory ascites and hyponatremia in cirrhosis. Gastroenterol Rep (Oxf) 2017;5(2):104–12.
5. Clària J, Stauber RE, Coenraad MJ, et al. Systemic inflammation in decompensated cirrhosis: characterization and role in acute-on-chronic liver failure. Hepatology 2016;64(4):1249–64.
6. Téllez L, Ibáñez-Samaniego L, Pérez Del Villar C, et al. Non-selective beta-blockers impair global circulatory homeostasis and renal function in cirrhotic patients with refractory ascites. J Hepatol 2020. https://doi.org/10.1016/j.jhep.2020.05.011.
7. European Association for the Study of the Liver, Electronic address: easloffice@easloffice.eu, European Association for the Study of the Liver. EASL clinical practice guidelines for the management of patients with decompensated cirrhosis. J Hepatol 2018;69(2):406–60.
8. Ginès P, Tító L, Arroyo V, et al. Randomized comparative study of therapeutic paracentesis with and without intravenous albumin in cirrhosis. Gastroenterology 1988;94(6):1493–502.
9. Bernardi M, Caraceni P, Navickis RJ, et al. Albumin infusion in patients undergoing large-volume paracentesis: a meta-analysis of randomized trials. Hepatology 2012;55(4):1172–81.
10. Rössle M, Gerbes AL. TIPS for the treatment of refractory ascites, hepatorenal syndrome and hepatic hydrothorax: a critical update. Gut 2010;59(7):988–1000.
11. Lebrec D, Giuily N, Hadengue A, et al. Transjugular intrahepatic portosystemic shunts: comparison with paracentesis in patients with cirrhosis and refractory ascites: a randomized trial. French Group of Clinicians and a Group of Biologists. J Hepatol 1996;25(2):135–44.
12. Rössle M, Ochs A, Gülberg V, et al. A comparison of paracentesis and transjugular intrahepatic portosystemic shunting in patients with ascites. N Engl J Med 2000;342(23):1701–7.

13. Ginès P, Uriz J, Calahorra B, et al. Transjugular intrahepatic portosystemic shunting versus paracentesis plus albumin for refractory ascites in cirrhosis. Gastroenterology 2002;123(6):1839–47.
14. Sanyal AJ, Genning C, Reddy KR, et al. The North American Study for the treatment of refractory ascites. Gastroenterology 2003;124(3):634–41.
15. Salerno F, Merli M, Riggio O, et al. Randomized controlled study of TIPS versus paracentesis plus albumin in cirrhosis with severe ascites. Hepatology 2004; 40(3):629–35.
16. Narahara Y, Kanazawa H, Fukuda T, et al. Transjugular intrahepatic portosystemic shunt versus paracentesis plus albumin in patients with refractory ascites who have good hepatic and renal function: a prospective randomized trial. J Gastroenterol 2011;46(1):78–85.
17. Bureau C, Thabut D, Oberti F, et al. Transjugular intrahepatic portosystemic shunts with covered stents increase transplant-free survival of patients with cirrhosis and recurrent ascites. Gastroenterology 2017;152(1):157–63.
18. Salerno F, Cammà C, Enea M, et al. Transjugular intrahepatic portosystemic shunt for refractory ascites: a meta-analysis of individual patient data. Gastroenterology 2007;133(3):825–34.
19. Fagiuoli S, Bruno R, Debernardi Venon W, et al. Consensus conference on TIPS management: techniques, indications, contraindications. Dig Liver Dis 2017; 49(2):121–37.
20. Riggio O, Nardelli S, Moscucci F, et al. Hepatic encephalopathy after transjugular intrahepatic portosystemic shunt. Clin Liver Dis 2012;16(1):133–46.
21. Schepis F, Vizzutti F, Garcia-Tsao G, et al. Under-dilated TIPS associate with efficacy and reduced encephalopathy in a prospective, non-randomized study of patients with cirrhosis. Clin Gastroenterol Hepatol 2018;16(7):1153–62.e7.
22. Pieper CC, Jansen C, Meyer C, et al. Prospective evaluation of passive expansion of partially dilated transjugular intrahepatic portosystemic shunt stent grafts-a three-dimensional sonography study. J Vasc Interv Radiol 2017;28(1): 117–25.
23. Miraglia R, Maruzzelli L, Di Piazza A, et al. Transjugular intrahepatic portosystemic shunt using the new Gore Viatorr controlled expansion endoprosthesis: prospective, single-center, preliminary experience. Cardiovasc Intervent Radiol 2019;42(1):78–86.
24. Bureau C, Thabut D, Jezequel C, et al. The use of rifaximin in the prevention of overt hepatic encephalopathy after transjugular intrahepatic portosystemic shunt: a randomized controlled trial. Ann Intern Med 2021. [Epub ahead of print].
25. Billey C, Billet S, Robic MA, et al. A prospective study identifying predictive factors of cardiac decompensation after transjugular intrahepatic portosystemic shunt: the Toulouse algorithm. Hepatology 2019;70(6):1928–41.
26. Bureau C, Adebayo D, Chalret de Rieu M, et al. Alfapump® system vs. large volume paracentesis for refractory ascites: a multicenter randomized controlled study. J Hepatol 2017;67(5):940–9.
27. Wong F, Bendel E, Sniderman K, et al. Improvement in quality of life and decrease in large-volume paracentesis requirements with the automated low-flow ascites pump. Liver Transpl 2020;26(5):651–61.
28. Bellot P, Welker M-W, Soriano G, et al. Automated low flow pump system for the treatment of refractory ascites: a multi-center safety and efficacy study. J Hepatol 2013;58(5):922–7.

29. Lepida A, Marot A, Trépo E, et al. Systematic review with meta-analysis: automated low-flow ascites pump therapy for refractory ascites. Aliment Pharmacol Ther 2019;50(9):978–87.
30. Solà E, Sanchez-Cabús S, Rodriguez E, et al. Effects of alfapump™ system on kidney and circulatory function in patients with cirrhosis and refractory ascites. Liver Transpl 2017;23(5):583–93.
31. Caraceni P, Riggio O, Angeli P, et al. Long-term albumin administration in decompensated cirrhosis (ANSWER): an open-label randomised trial. Lancet 2018; 391(10138):2417–29.
32. Di Pascoli M, Fasolato S, Piano S, et al. Long-term administration of human albumin improves survival in patients with cirrhosis and refractory ascites. Liver Int 2019;39(1):98–105.
33. Solà E, Solé C, Simón-Talero M, et al. Midodrine and albumin for prevention of complications in patients with cirrhosis awaiting LT. A randomized placebo-controlled trial. J Hepatol 2018;69(6):1250–9.
34. Caraceni P, Tufoni M, Zaccherini G, et al. On-treatment serum albumin level can guide long-term treatment in patients with cirrhosis and uncomplicated ascites. J Hepatol 2020. https://doi.org/10.1016/j.jhep.2020.08.021.
35. Yosry A, Soliman ZA, Eletreby R, et al. Oral midodrine is comparable to albumin infusion in cirrhotic patients with refractory ascites undergoing large-volume paracentesis: results of a pilot study. Eur J Gastroenterol Hepatol 2019;31(3):345–51.
36. Bai Z, An Y, Guo X, et al. Role of terlipressin in cirrhotic patients with ascites and without hepatorenal syndrome: a systematic review of current evidence. Can J Gastroenterol Hepatol 2020;2020:5106958.
37. Carbonell N, Louvet A, Rousseau A, et al. Terlipressine plus albumine versus albumine seule chez des patients atteints de cirrhose avec ascite réfractaire traités par paracentèse: essai prospectif multicentrique français randomisé contre placebo (essai TERAS). Résumé n°CO-034 AFEF 2017 Nice.
38. Wong F, Watson H, Gerbes A, et al. Satavaptan for the management of ascites in cirrhosis: efficacy and safety across the spectrum of ascites severity. Gut 2012; 61(1):108–16.
39. Rai N, Singh B, Singh A, et al. Midodrine and tolvaptan in patients with cirrhosis and refractory or recurrent ascites: a randomised pilot study. Liver Int 2017;37(3): 406–14.