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REVIEW ARTICLE

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Optimal management of ascites

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Abstract

Ascites is the most common complication of cirrhosis, which develops in 5%-10% of patients per year. Its management is based on symptomatic measures including restriction of sodium intake, diuretics and paracentesis. Underlying liver disease must always be treated and may improve ascites. In some patients, ascites is not controlled by medical therapies and has a major impact on quality of life and survival. TIPS placement and liver transplantation must therefore be discussed. More recently, repeated albumin infusions and Alfapump® have emerged as new therapies in ascites. In this review, the current data on these different options are analysed and an algorithm to help the physician make clinical decisions is suggested.

KEYWORDS

ascites, cirrhosis, portal hypertension

1 | INTRODUCTION

Ascites is the most common complication of cirrhosis, with 5%-10% of patients with cirrhosis developing this complication per year. Ascites has a major impact on quality of life and is associated with a poor outcome. Management involves two different approaches. The first approach is symptomatic, based on restriction of sodium intake, diuretics, albumin infusion and paracentesis. These symptomatic options should always be associated with treatment of the underlying cause of liver disease to improve liver function. Most patients recover with medical therapy.

When medical therapy fails, transjugular intrahepatic portosystemic shunts (TIPS) are the first-line treatment to be discussed in these patients as TIPS have been shown to improve ascites as well as survival compared to repeated paracentesis. TIPS are contraindicated in patients with the most severe presentation, with a high MELD or a high Child-Pugh score, or with hepatic encephalopathy (HE), and liver transplantation is the only curative option. An age of more than 65 or 70 years old is another important issue, as it may be a contra-indication for both TIPS placement and liver transplantation.

In this review, we will first focus on the pathophysiology of ascites in cirrhosis, and then discuss the different therapeutic options. Finally, we will suggest an algorithm to help the physician in different clinical situations. The management of hepatorenal syndrome, a severe complication that has the same pathophysiology than ascites, will not be discussed in this review.

2 | PATHOPHYSIOLOGY OF ASCITES IN CIRRHOSIS

Ascites is defined as an accumulation of fluid in the peritoneal cavity and is because of cirrhosis in about 80% of cases. It can be graded according to its severity: grade 1 (mild ascites) if only detectable by ultrasound, grade 2 (moderate ascites) with moderate symmetrical distension of abdomen and grade 3 (large ascites) with marked abdominal distension.[1] Ascites affects 5%-10% of patients with compensated cirrhosis per year and is considered to be the most common complication of cirrhosis. Moreover, its prognosis is poor (2-year mortality of 40%). It appears later than

Abbreviations: ACLF, acute-on-chronic liver failure; AP, Alphapump®; HE, hepatic encephalopathy; LT, liver transplantation; LVP, large volume paracentesis; MDRO, multidrug-resistant organisms; MELD, model for end-stage liver disease; PTFE-covered, polytetrafluoroethylene-covered; RA, recurrent ascites; RCT, randomized controlled trial; SBP, spontaneous bacterial peritonitis; SMT, standard medical treatment; TIPS, transjugular intrahepatic portosystemic shunt; XDRO, extended drug-resistant organisms.

variceal bleeding in the natural history of cirrhosis, with a more severe outcome.[2]

Ascites is known to be multifactorial and seems to result from the combination of portal hypertension and liver insufficiency. Several hypotheses have been suggested to explain its pathophysiology, in particular that ascites reflects a reorganization of haemodynamics in cirrhosis. Indeed, the reorganization of the hepatic structure in cirrhosis is responsible for an increase in hydrostatic pressure in the sinusoid capillaries, which leads to an increase in local synthesis of vasodilator substances, such as nitric oxide. Thus, there is a decrease in splanchnic arterial resistance.[3] Compensatory mechanisms then occur, especially an increase in cardiac output and activation of metabolic pathways to increase effective volaemia (sympathetic nervous system and renin-angiotensin-aldosterone pathway). Synthesis of anti-natriuretic substances is then increased and results in sodium and water retention in the proximal tubule, loop of Henle and distal tubule.[3] This can result in dilutional hyponatraemia, which may worsen the prognosis and makes treatment of ascites more difficult. In a final stage, the severe systemic vasodilation and subsequent renal vasoconstriction are responsible for acute kidney injury by decreasing renal blood flow, defining the hepatorenal syndrome. Moreover, hypoalbuminaemia owing to hepatic insufficiency is responsible for a decrease in oncotic pressure, which facilitates the fluid leakage from the intravascular sector to interstitial space.[3] Because of the reorganization of the hepatic structure in cirrhosis, the capillaries are no longer fenestrated and protein concentration is then poor in this fluid.

Finally, some studies suggest that bacterial translocation, which is frequent in cirrhosis and responsible for local and systemic inflammation, plays a role. This mechanism may increase permeability of capillaries and facilitate fluid leakage to the peritoneal cavity.[3]

3 | OPTIMAL MANAGEMENT OF ASCITES

We will focus on the treatment of ascites in patients: (a) without refractory ascites, (b) with refractory ascites and (c) with spontaneous bacterial peritonitis (SBP). In patients with complicated ascites, that is with either refractory ascites or SBP, liver transplantation (LT) must be discussed.

3.1 | Patients without refractory ascites

3.1.1 | Classical treatments

The treatment of ascites is based on symptomatic therapies, including sodium restriction and diuretics, as patients with ascites have a positive sodium balance. Dietary sodium should be moderately restricted (80-120 mmol/day) to prevent a reduced calorie intake, which could impair nutritional status. The aim of diuretic therapy is weight loss of <0.5 kg/day (or 1 kg/day in the presence of peripheral oedema). Patients should receive an anti-mineralocorticoid drug alone, starting at 100 mg/day, with a stepwise increase to a maximum of 400 mg/day. Furosemide should be added in non-responders or in patients who develop hyperkaliaemia, at a dose of 40 mg/day to a maximum dose of 160 mg/day. Other general measures and treatments have also been evaluated: (a) it has not been shown that prolonged maintenance of the supine position improves the resolution of ascites; (b) there is evidence that the treatment of underlying liver disease can improve ascites, such as abstinence from alcohol or viral suppression; (c) the use of several drugs is contraindicated to avoid renal impairment, such as non-steroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors or aminoglycosides (except in patients with severe bacterial infections); (d) other treatments such as midodrine, terlipressine or clonidine are not recommended.

3.1.2 | New therapeutics in patients without refractory ascites: albumin and TIPS

Hypoalbuminaemia and the synthesis of dysfunctional albumin are increasingly recognized as key factors in the pathophysiology of the complications of cirrhosis including ascites. Patients with moderate ascites were considered to be the most appropriate candidates to evaluate the efficacy of repeated albumin infusions to improve survival, prevent further complications of cirrhosis including encephalopathy, sepsis, as well as to reduce ascites. In the ANSWER study,[4] patient with ascites who were receiving diuretics and were not considered refractory received either albumin (40 g twice a week for 2 weeks and then 40 g weekly) or standard medical treatment (SMT). Patients in the albumin group showed a 38% decrease in the mortality hazard ratio, fewer episodes of HE and sepsis, and a later need for paracentesis. Finally, during the 18 months of follow-up, fewer patients developed refractory ascites. Interestingly, a post hoc analysis (ILC 2019 presented data) of the ANSWER study showed that the albumin level after 1 month of treatment was strongly predictive of survival. In particular, 18-month survival reached 90% when the albumin level was >40 g/L. This suggests that the amount of albumin infused is highly important and may need to be adapted on a case by case basis. In another RCT, patients awaiting liver transplantation received either midodrine 15-30 mg/day and albumin 40 g/day or placebo. There was no difference between the groups, for survival on the waiting list for the complications of cirrhosis or control of ascites.[5] However, rapid access to LT (median treatment 80 days in both groups) may have prevented this trial from more significant results.

TIPS placement induces decompression of the portal circulation by shunting an intrahepatic portal branch into a hepatic vein. Its indications in the treatment of refractory ascites are better defined and will be discussed later in this manuscript. However, the benefit of TIPS insertion in less severe patients, such as in those with recurrent ascites (RA) remains uncertain. RA was first

defined in a 1996 consensus as ascites that recurs at least three times within 12 months despite sodium restriction and diuretic treatment.[6] Recently, EASL guidelines defined early RA as ascites that recurs earlier than 1 month after initial control.[1] None or very few of these patients were included in initial RCTs comparing TIPS with bare metal stents to standard medical treatment (SMT). Recently, a study by Bureau et al compared the prognosis of patients with RA receiving either TIPS with PTFE-covered stents or SMT.[7] However, these patients were more severe than the previous definition of RA. To be included, they had to have required at least two LVPs at least 3 weeks apart. It is important to note that 30% of patients had a history of variceal bleeding, and 20% had a history of renal failure, showing the severity of their circulatory dysfunction. There was a significant increase in 1-year survival without transplantation (93% vs 52% $P = .003$) in the TIPS group, which was the primary endpoint of the study. It is interesting to note that hepatic encephalopathy (HE) did not occur more frequently in the TIPS group. These results, obtained in patients with RA, moderate hepatic insufficiency and an absence of previous overt HE, illustrate the importance of defining which patients are the best candidates for TIPS and the more severely ill patients, who should be listed for transplantation.

3.2 | Patients with refractory ascites

3.2.1 | Definition of refractory ascites

According to the International Ascites Club, refractory ascites is defined as "ascites that cannot be mobilized or the early recurrence of which cannot be satisfactorily prevented by medical therapy."[6] This definition includes diuretic-resistant ascites, (ascites that cannot be mobilized or the early recurrence of which cannot be prevented because of a lack of response to sodium restriction and diuretic treatment), and diuretic-intractable ascites, (ascites that cannot be mobilized or the early recurrence of which cannot be prevented because of the development of diuretic-induced complications that preclude the use of an effective diuretic dosage). From a practical point of view, it is very difficult to reach the maximal doses of diuretics and 90% of patients have intractable ascites. HE, renal failure, hyponatraemia, hypo- or hyper-kaliaemia and muscle cramps are the main reasons for the withdrawal of diuretics.[1]

3.2.2 | Large volume paracentesis

Large volume paracentesis (LVP) is the first-line treatment of refractory ascites.[6] Plasma volume expansion is needed to prevent post-paracentesis dysfunction. In a meta-analysis of randomized controlled trials, albumin infusion has been shown to be more effective than other plasma expanders in the prevention of post-paracentesis dysfunction.[8] Albumin infusion should therefore be performed in patients undergoing LVP >5L (8 g/L of ascites removed).[1]

3.2.3 | Albumin

Long-term administration of albumin has also been shown to reduce mortality in patients with refractory ascites. The single center, non-randomized study by Di Pascoli et al, evaluated the prognosis of patients with refractory ascites treated with 40 g albumin twice a week vs SMT.[9] Two-year mortality, which was the primary endpoint, was significantly lower in the albumin group (41.6% vs 65.5%, $P = .032$). This study has many limitations including TIPS as an alternative therapy in these patients. However, long-term administration of albumin, which was shown to improve survival in more severe patients, such as those with refractory ascites, could be an interesting option in selected patients, especially liver transplantation candidates.

3.2.4 | Transjugular intrahepatic portosystemic shunt

Transjugular intrahepatic portosystemic shunt (TIPS) placement induces decompression of the portal circulation by shunting an intrahepatic portal branch into a hepatic vein. In an evaluation of refractory ascites, six prospective randomized controlled trials (RCT) compared non-covered TIPS and LVP for recurrence of ascites, hepatic encephalopathy and survival (Tables 1 and 2).[10-15] The results were analysed in several meta-analyses. In the meta-analysis of individual data by Salerno et al ascites recurrence and transplant-free survival were better in the TIPS group, compared to LVP.[16] However, the average number of HE episodes was higher in the TIPS group. It seems important to note that these studies were published before the use of PTFE-covered stents. More recent results obtained in recurrent ascites suggest that the earlier results would probably have been better using covered stents.[7] To date, no prospective controlled trial has been published using covered stents in refractory ascites. In the study published by Bureau et al, patients were included in case of recurrent ascites, defined by two LVPs at least 3 weeks apart, and excluding those who had undergone >6 LVP in the last 3 months. These criteria were quite different from both the historical definition of recurrent ascites and those of refractory ascites, as previously discussed.

TIPS insertion is contraindicated in patients with heart failure, advanced liver failure, defined by a Child-Pugh score >13 or a MELD score >19, and significant HE. Thus, patients must be carefully selected for TIPS placement. Although exclusion criteria in RCT were heterogeneous, there were certain similarities, such as >70 or 75 years old, HE on the day of TIPS placement, Child-Pugh >11, HCC outside of the Milan criteria and heart failure.

Three main complications negatively influence prognosis after TIPS placement: (a) liver failure and death; (b) refractory HE and (c) heart failure. One study presented a simple predictive model of survival combining platelet count and total bilirubin level[17] and showed that the actuarial 1-year survival rate in patients with both a platelet count >75 × 10^9/L and a total bilirubin level <50 μmol/L

TABLE 1 Main studies comparing LVP and other therapeutics in patients with refractory or recurrent ascites

			Enrolled patients (n)		Improvement of ascites (%)		Development of hepatic encephalopathy (%)		Survival (%)	
			TIPS	LVP	TIPS	LVP	TIPS	LVP	TIPS	LVP
Bare TIPS	Refractory ascites	Randomized controlled studies								
		Lebrec et al[10] 1996	13	12	38	0	15	6	29	60
		Gines et al[11] 2002	35	35	51	17	60	34	26	30
		Sanyal et al[12] 2003	52	57	58	16	38	21	35	33
		Narahara et al[13] 2011	30	30	87	30	20	5	20	5
	Refractory + recurrent ascites	Rössle et al[14] 2000	29	31	84	43	23	13	58	32
		Salerno et al[15] 2004	33	33	79	42	61	39	59	29
		Meta-analysis for refractory ascites								
		Salerno et al[16] 2007	149	156	58	11	58	38	56	50
Covered TIPS	Recurrent ascites	Randomized controlled study								
		Bureau et al[7] 2017	29	33	89	29	34	33	93	52

Abbreviations: LVP, large volume paracentesis; TIPS, tranjugular intrahepatic portosystemic shunt.

TABLE 2 Outcome of Alfapump® for patients with cirrhosis and refractory ascites

			Number of LVP per patient per month (median)		Development of adverse effects (n)				Child-Pugh score (mean)			MELD score (mean)				Improvement of Quality of life (HRQoL score)	
	Enrolled patients (n)	Length of follow-up (months)	At baseline	At the end of follow-up	Infections	Catheter issues	Pump malfunction	Alfapump® explant	At baseline	At 6 mo	At the end of follow-up	At baseline	At 6 mo	At the end of follow-up	Death, n (%)	Abdominal symptoms	Activity scores
Observational studies																	
Bellot et al[20] 2013	40	6	3.4	0.2	24 (60%)	10 (25%)	2 (5%)	3 (7.5%)	8.5	8.6	8.6	12.6	11.7	11.7	9 (22%)		
Stirnimann et al[21] 2017	56	24	2.2	0.2		28 (50%)	11 (20%)	27 (48%)	8.8	9.8	7.5	13.42	17.04	9.11	23 (41%)		
Randomized controlled study																	
Bureau et al[22] 2017	27	6	1.6	0.3	25 (93%)	5 (9%)	4 (7%)	3 (5.4%)	8.2			12.2			15 (56%)	+1.25	+0.80

Abbreviation: LVP, large volume paracentesis.

[3 mg/dL] was 73.1% compared to 31.2%, in patients with a platelets count <75 × 10^9/L or a total bilirubin level >50 μmol/L. In another study several risk factors for the worsening of HE were described: older age, poor liver function, a previous episode of HE, sarcopenia and minimal hepatic encephalopathy. Nevertheless, there is no predictive model for the selection of patients according to their risk of developing HE. We recently recommended excluding TIPS as a non-urgent option in patients with a history of at least two episodes of HE, or with HE on the day of TIPS placement.[18] Moreover, our group suggested that TIPS placement be discussed on a case-by-case basis in patients older than 70. Finally a very recent prospective study has shown that cardiac decompensation occurs in about 20% of patients following TIPS placement.[19] The authors reported that a combination of a BNP <40 pg/mL and a NT-proBNP <125 pg/mL before TIPS and the exclusion of diastolic dysfunction on echocardiography excluded the risk of cardiac decompensation.

3.2.5 | Alfapump®

Alfapump® (AP) is a fully implantable, programmable and rechargeable pump system that automatically diverts ascitic fluid from the peritoneal cavity to the urinary bladder, allowing fluid removal by micturition (Tables 1 and 2).[20,21] In a recent multicenter RCT in patients with refractory ascites, AP significantly reduced the number of LVP and improved the quality of life as well as nutritional parameters.[22] Quality of life was also shown to improve by AP in another study.[23] AP is contraindicated in patients with chronic renal failure, because it can cause acute, but reversible, renal failure. Moreover, some patients, especially with HE, may experience technical difficulties. Thus, it seems reasonable not to recommend AP as an alternative therapy in patients with HE unless there is a relative to take care of the device.

3.2.6 | Liver transplantation

LT should be discussed in all patients with refractory ascites because of the poor survival in this group. Nevertheless, despite the poor prognosis of this complication, some patients will present with a low MELD score that can delay LT. Liver transplantation could be prioritized based on a MELD score exception in these patients. However, prioritization can only be considered in patients with a strict contraindication to TIPS placement.[24] Thus, TIPS should be the first option in these patients.

3.2.7 | Summary of available therapeutics, indications

As previously mentioned, LVP should be performed in patients with refractory ascites (Figure 1). If LVP is the first-line treatment, a second line therapy has to been considered as soon as the diagnosis is made to improve the prognosis. A careful clinical, biological and morphological examination must be performed. This includes obtaining a clinical history, including age, and a systematic search for a previous episode of HE or heart decompensation. The physical examination should screen for confusion, flapping, sarcopenia and left or right signs of heart failure. The biological evaluation should include routine blood exams, hepatic function, renal and cardiac function with BNP and NT-proBNP. Finally, the morphological evaluation should include an abdominal ultrasound exam, CT scan and echocardiography. TIPS seems to be the best therapeutic option in patients under the age of 65, with no previous episodes of HE, a Child-Pugh score <13, a MELD score <19, total bilirubin levels <50 μmol/L, a platelet count >75 × 10^9/L, normal BNP/NT-proBNP values and normal echocardiography. TIPS should be contraindicated in patients over 70 years old, with history of more than two episodes of HE. AP can be considered in the latter unless they present with normal renal function (Cl Creat ≥50 mL/min). A case-by-case discussion is needed in patients considered to be at high risk, according to liver function, cardiac function, and the risk of HE after TIPS. As there is a theoretical risk of developing either liver failure or refractory HE after TIPS, we believe that liver transplantation should be discussed in all patients.

3.3 | Patients with spontaneous bacterial peritonitis

SBP is the most frequent site of bacterial infection in patients with cirrhosis. SBP is still associated with high mortality and may trigger worsening of liver function and other complications of cirrhosis such as HE, renal failure and bleeding. The increasing prevalence of multidrug-resistant organisms (MDRO) is a concern in the treatment of SBP. This mainly includes extended spectrum beta lactamases producing Enterobacteriaceae and beta lactams-resistant Gram-positive bacteria. The emergence of extended drug-resistant organisms (XDRO), in hospitalized patients but also in the community in some parts of the world, emphasizes the need for data on the use of new antibiotics in patients with cirrhosis. European data support a high prevalence of MDRO infections in decompensated or acute on chronic liver failure (ACLF) patients. About 29% of the strains isolated in the 264 culture-positive infections among the 1146 patients with decompensated cirrhosis or ACLF followed in the CANONIC cohort (2011) were MDRO.[25] There are large discrepancies among centres and countries, with a higher prevalence in Western European countries in these almost 10-year-old data. The only factors significantly associated with the occurrence of MDRO were nosocomial infections, hospitalization within the previous 3 months and intensive care unit admission. It is important to note that long-term exposure to norfloxacin was not identified as a risk factor. More recent data (2017-2018) in 883 European patients with decompensated cirrhosis showed that 39.7% of culture-positive infections among the 284 patients who developed infection were MDRO, which is a nearly 10% increase compared to 2011 data. It is interesting to note that there was a shift towards a higher prevalence in Eastern and Southern European countries. Worldwide, the study by Piano et al reported 1302 infections in hospitalized patients with cirrhosis.[26] MDRO were isolated in 34% of cases. Risk factors were nosocomial or healthcare-associated infections, antibiotic exposure within

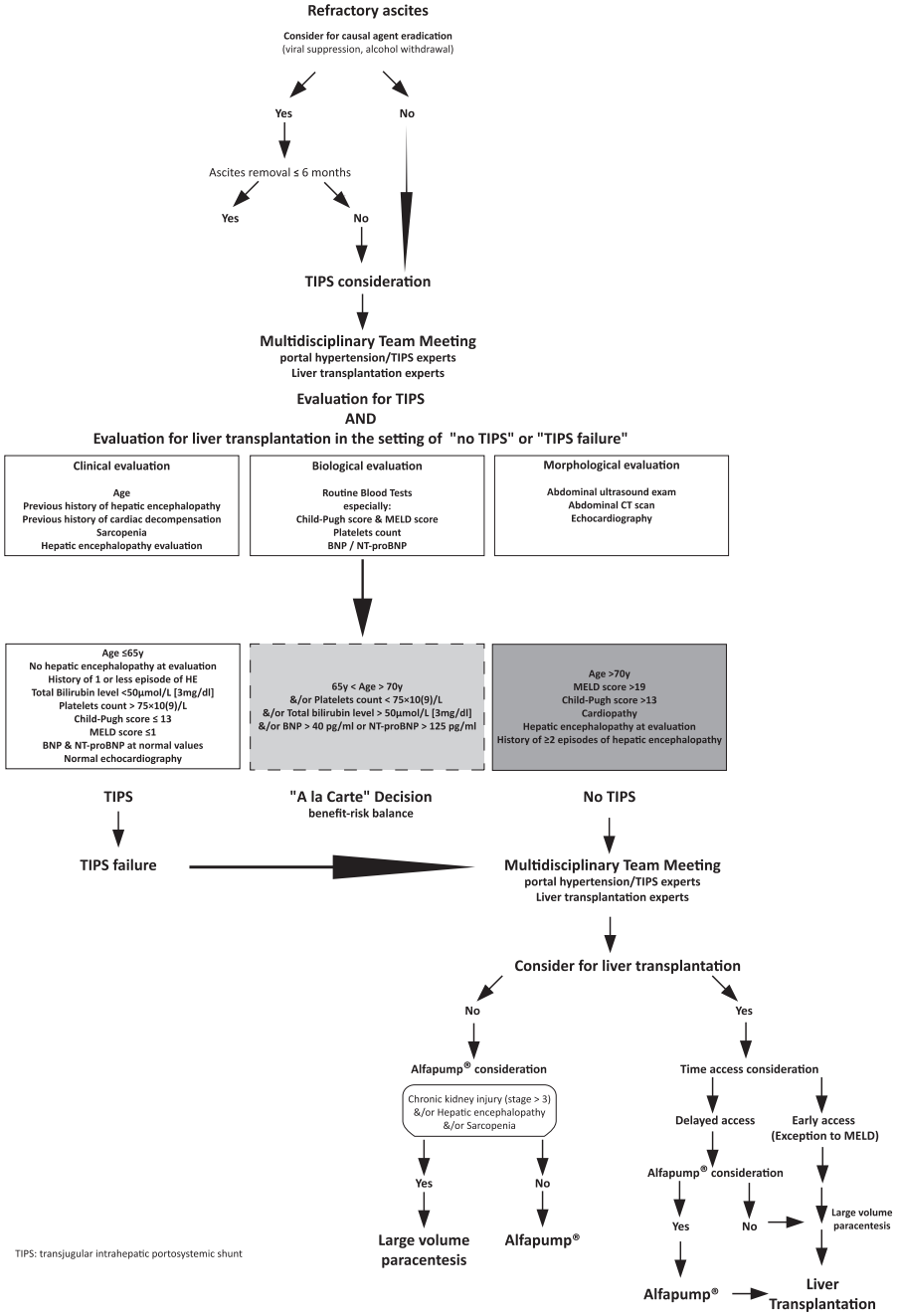

FIGURE 1 Algorithm for the management of refractory ascites in patients with cirrhosis

the previous 3 months but also geographical origin, in particular India where the rate of MDRO and XDRO was the highest. The sites most concerned by MDR infections were pneumonias and urinary tract infections. Prevalence was lower in SBP (27%), like in the CANONIC cohort (13.9% for SBP vs 29.3% all sites included). An Italian RCT has compared initial antibiotic therapy with meropenem plus daptomycin vs ceftazidim to treat nosocomial SBP. There was a significantly higher response to treatment for the decrease in neutrophils count in ascites in the meropenem plus daptomycin group, but 90-day transplant-free survival was similar in both groups. On multivariate analysis, ineffective first-line treatment was a significant predictor of mortality, as described in previous studies. Thus, recommendations about antibiotic therapy for SBP are very difficult and highly important for clinical outcome. They must depend on the local bacterial ecology and individual risk factors such as previous antibiotic therapy, healthcare associated, or nosocomial infections. The EASL guidelines for community acquired SBP recommend third generation cephalosporins or piperacillin plus tazobactam.[1] Meropenem is recommended for nosocomial SBP, in association with linezolid or daptomycin when the prevalence of drug-resistant Gram-positive bacteria is high. Administration of 20% albumin is also recommended during SBP at the dose of 1.5 g/kg at day 1 and 1 g/kg at day 3. Indeed, in the study by Sort et al, this treatment resulted in a significant decrease in hospital mortality and occurrence of renal failure compared to antibiotic therapy with cefotaxime

alone (10% vs 29%, respectively, P = .01) and (10% vs 33%, respectively, P = .02).[27] Severe patients (serum creatinine ≥88 μM or total bilirubin ≥68 μM) seemed to benefit most from treatment. Whether it should be administrated to all patients with cirrhosis is therefore a subject of debate.

Prophylaxis of SBP is another clinically important issue. Norfloxacin is the only drug recommended and concern is growing about its safety and efficacy because of the increasing prevalence of MDRO. Frequent neurological and osteo-articular side effects have led drug regulation agencies to issue warnings about this drug and advise limiting its use to when no alternative is available. In primary prophylaxis, norfloxacin is recommended when ascites fluid protein level is below 15 g/L in association with severe cirrhosis (Child-Pugh score ≥9 and total bilirubin level ≥3 mg/dL (51 μmol/L), with either impaired renal function or hyponatraemia).[1] A French RCT compared norfloxacin to placebo in Child Pugh C patients without previous SBP.[28] Six-month mortality was only significantly lower in patients with low ascitic fluid protein levels (<15 g/L), confirming that primary prophylaxis should be restricted to the most severe patients. However, these are not recent data (2010-2014) and cannot take into account the change in susceptibility of Gram-negative bacteria to fluoroquinolones, which may affect the effectiveness of prophylaxis. Norfloxacin use in secondary prophylaxis is an even greater issue because of the high prevalence of recurrent SBP after a first episode. It was shown to be effective in a single RCT published in 1990, significantly decreasing the rate of recurrent SBP from 68% in the placebo group to 20% in the norfloxacin group. There are no similar more recent results. However, a recent German observational study in patients receiving primary or secondary prophylaxis with norfloxacin suggests a significantly greater risk of SBP in patients with quinolone-resistant Gram-negative bacteria. These results in a population with a 50% rate of baseline MDRO highlight the importance of resistance to fluoroquinolones and suggest that routine screening patients for MDRO could be advisable. Finding an alternative to oral fluoroquinolones is also important. Preliminary results and a recent meta-analysis support the effectiveness of rifaximin in primary or secondary prophylaxis of SBP.[29] However, the results of a RCT including a larger number of patients, comparing rifaximin to oral fluoroquinolones are still awaited.

4 | CONCLUSION

Prognosis is poor in patients with complicated ascites, including refractory ascites or SBP. In these situations, TIPS placement and liver transplantation must both be discussed, because TIPS may be either contraindicated or with an uncertain outcome in patients at high risk of developing further liver failure, HE or cardiac decompensation. The recent study by Bureau et al conducted patients with recurrent ascites suggests that TIPS placement could be indicated at an earlier stage, before the development of refractory ascites. We believe that there should be a multidisciplinary discussion to improve selection of patients for the best therapeutic option.

CONFLICT OF INTEREST

MR: speaker for Gore, Gilead, Abbvie; MM: none; PS: none; CB: speaker for Gilead, Abbvie; DT: consultancy for Gore, Alfasigma, Gilead, MSD, AbbVie, Medday.

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