Review

JHEP|Reports

Innovative approaches to the management of ascites in cirrhosis

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Summary

Standard of care for the treatment of ascites in cirrhosis is to administer a sodium-restricted diet and diuretic therapy. The progression of cirrhosis will eventually lead to the development of refractory ascites, at which point diuretics will no longer be able to control the ascites. Second-line therapies such as a transjugular intrahepatic portosystemic shunt (TIPS) placement or repeat large volume paracentesis are then required. There is some evidence that regular infusions of albumin may delay the onset of refractoriness and improve survival, especially if given at an early stage in the natural history of ascites and for a long enough duration. The use of TIPS can eliminate ascites, but its insertion is associated with complications, especially cardiac decompensation and worsening of hepatic encephalopathy. New information is now available regarding how to best select patients for TIPS, what type of cardiac investigations are needed and how under-dilating the TIPS at the time of insertion may help. The use of a non-absorbable antibiotics, such as rifaximin, starting in the pre-TIPS period may also reduce the likelihood of post-TIPS hepatic encephalopathy. In patients who are not suitable for TIPS, the use of an alfapump to remove the ascites via the bladder can improve quality of life without significantly altering survival. In the future it may be possible to use metabolomics to help refine the management of patients with ascites, *e.g.* to assess their response to non-selective beta-blockers or to predict the development of other complications such as acute kidney injury.

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Introduction

Ascites is the most common first decompensating event in cirrhosis. Even the presence of ascites that is only detectable on ultrasound has been associated with 1-year mortality or need for liver transplant in 10% of patients.[1] Progression to refractory ascites, especially in patients who had grade 3 ascites at index presentation, was associated with a 1-year mortality of 17%, irrespective of model of end-stage liver disease (MELD) score.[2] Therefore, there has been a recent shift in philosophy in the management of patients with cirrhosis, with prevention of ascites gaining more prominence. As ascites progresses through its natural history, treatment changes from judicious dietary sodium restriction (without calorie restriction) and diuretic therapy to second-line therapies, such as large volume paracentesis (LVP) or transjugular intrahepatic portosystemic shunt (TIPS) placement.[3] However, these second-line therapies are associated with unique complications. Liver transplantation is the definitive treatment for patients who have ascites and significant liver dysfunction, but the lack of resources means that many eligible patients die while waiting for a graft. Therefore, this review will focus on innovative approaches to delay the onset of ascites in cirrhosis and improve its management once it has developed.

Treatments to delay the onset of ascites

Delaying the onset of ascites in the natural history of cirrhosis can be achieved through manipulations of the various pathogenetic mechanisms involved in the formation of ascites. The presence of portal hypertension, which is the pivotal pathogenetic factor, can lead to splanchnic vasodilatation and increased bacterial translocation (Fig. 1). Within the intrahepatic circulation, however, the balance of vasoactive substances favours vasoconstriction. This maintains the obstruction to portal flow and hence portal hypertension. Bacterial products have vasodilatory and pro-inflammatory properties, contributing to splanchnic vasodilatation and the inflammatory milieu of cirrhosis. Within the liver, the pro-inflammatory environment promotes further fibrosis; within the splanchnic circulation, inflammation promotes splanchnic thrombosis.[4,5] These processes significantly worsen portal hypertension, which in turn will encourage the transfer of vasodilators from the splanchnic to the systemic circulation, leading to systemic vasodilatation, which is then compensated by activation of various vasoconstrictor systems and renal sodium retention (Fig. 1) – this is sustained by a degree of cardiac incompetence that is possibly related to the presence of cirrhotic cardiomyopathy. Overall intravascular volume expands, which spills into the

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peritoneal cavity as ascites.[6] Therefore, measures to reduce portal pressure have been the main strategy to delay the onset of or treat ascites, especially in patients with clinically significant portal hypertension (CSPH), defined as a hepatic venous pressure gradient (HVPG) of ≥10 mmHg.[7] Other pathophysiological processes that could be manipulated include bacterial translocation.

Key points

- The use of non-selective beta-blockers could potentially delay the onset of ascites in compensated cirrhosis.
- Long-term albumin infusions in patients with uncomplicated ascites could improve survival.
- Careful cardiac investigations, and pre-TIPS prophylactic treatment of encephalopathy can reduce post-TIPS complications.
- Under-dilation of controlled expansion TIPS can significantly reduce the incidence of post-TIPS encephalopathy.
- Alfapump can be used to manage ascites in patients who are unsuitable for TIPS, with improved ascites control.

The use of beta-blockers

Classical non-selective beta-blockers (NSBBs) such as propranolol and nadolol reduce cardiac output (β1 action) and allow for the unopposed action of the α-adrenergic tone on the splanchnic vessels (β2 action); both these actions reduce portal inflow. Carvedilol is a more recent NSBB that also has intrinsic anti-α1-adrenergic effects and hence a more potent portal pressure-lowering effect than propranolol or nadolol because of its ability to induce intrahepatic vasodilatation.

The PREDESCI trial enrolled 201 patients with CSPH to assess whether a NSBB (propranolol 40-160 mg twice daily or carvedilol 6.25-25 mg daily) was effective in delaying the onset of ascites *vs.* placebo in patients with compensated cirrhosis.[8] During a median follow-up of 37 months, the incidence of ascites was significantly decreased in patients who received an NSBB, 9% *vs.* 20% in the placebo group (p = 0.03), observed mostly in those patients whose HVPG was decreased to <10 mmHg or by 10% and evident only after a follow-up of 2 years. Therefore, early treatment with a NSBB could alter the natural history of cirrhosis.

However, the PREDESCI trial was criticised for its invasive trial design (*i.e.* requiring measurement of HVPG).[9] Furthermore, other studies have not shown the benefits of early NSBB treatment.[10,11] However, an individual patient data meta-analysis consisting of four randomised-controlled trials (RCTs), using a time-to-event and competing-risk approach,[12] was able to show that carvedilol reduced the likelihood of decompensation compared to placebo (p = 0.017), with death and liver transplant as competing events; this was mainly the result of a reduced

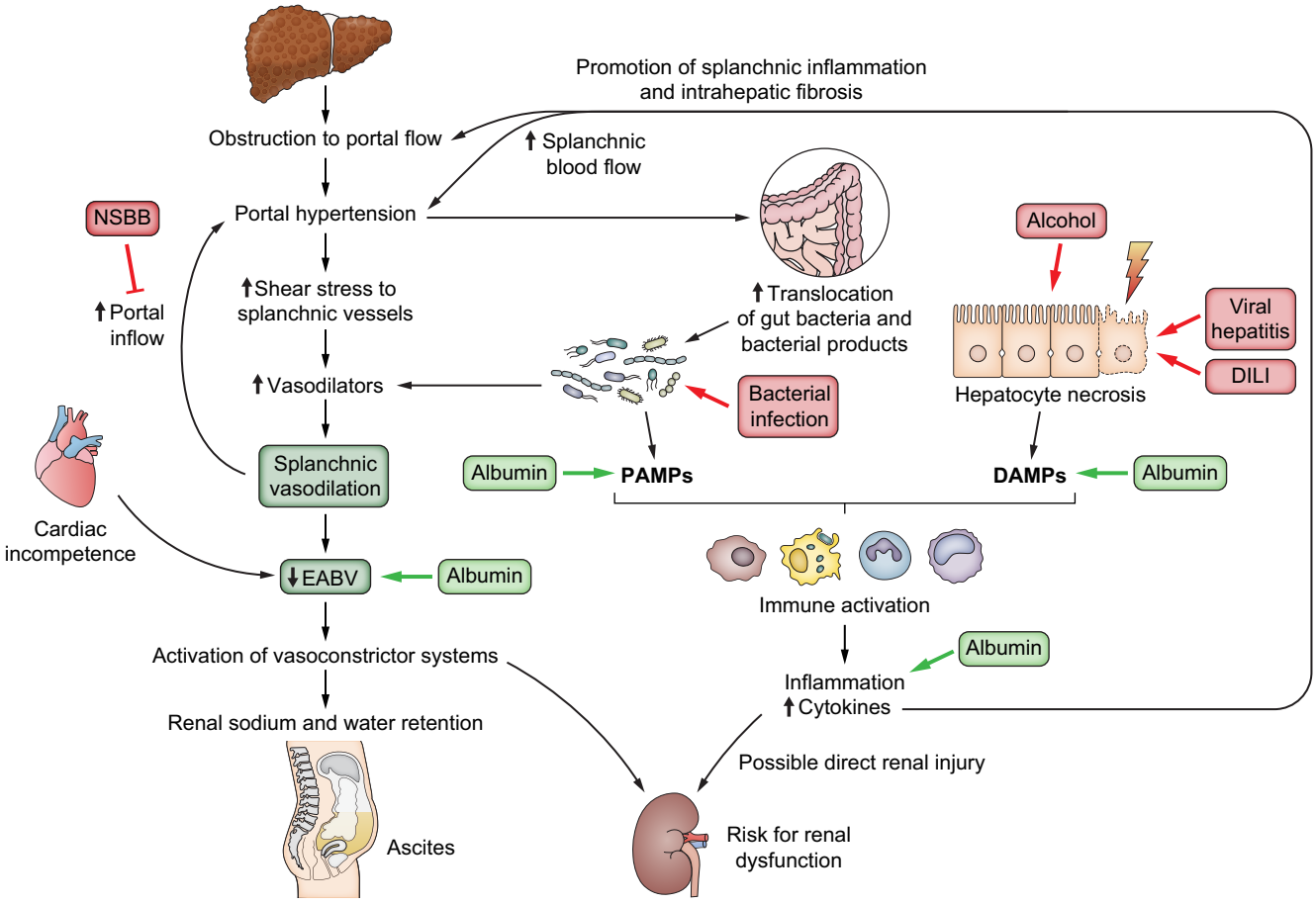

Fig. 1. Pathophysiology of ascites formation and where interventions could be applied to disrupt the development or progression of ascites. DAMP, damage-associated molecular pattern; DILI, drug-induced liver injury; EABV, effective arterial blood volume; NSBBs, non-selective beta-blockers; PAMP, pathogen-associated molecular pattern.

incidence of ascites (p = 0.042), which was only seen in patients in whom HVPG was reduced by >10% or to <10 mmHg. There was also a significant improvement in survival with carvedilol use. NSBBs may also have other non-haemodynamic benefits, *e.g.* reducing inflammation.[13] Based on these results, the Baveno VII consensus conference[15] has recommended the long-term use of carvedilol in patients with compensated cirrhosis. When HVPG measurements are not available, and based on available data, Baveno VII has recommended that a combination of liver stiffness of >15 kPa using transient elastography, and a platelet count of <150x10^9/L indicate CSPH. Therefore, prophylactic carvedilol is recommended in patients who meet these criteria.[14] In the 40-60% of patients in whom the Baveno VII criteria cannot definitively rule in CSPH, either spleen stiffness of ≥40 kPa[15] or von Willebrand factor antigen-to-platelet ratio of ≥2.5[16] can be used alongside the Baveno VII criteria to rule in the presence of CSPH, thereby permitting the prophylactic use of NSBBs in patients who meet these criteria.

Non-diuretic treatments of ascites

Once ascites becomes visible, the prognosis worsens to 50% survival at 1 year. Therefore, while patients with ascites traverse through this natural history, other non-diuretic treatment options have been assessed.

The use of albumin

Both the quantity of albumin produced and its quality are reduced in patients with cirrhosis. Therefore, albumin infusions, which can attenuate systemic inflammation and improve circulatory dysfunction,[17] have been used in different settings in patients with cirrhosis and ascites. The ANSWER study was a multicentre Italian randomised study in 440 outpatients with uncomplicated ascites who were receiving moderate doses of diuretics.[18] Patients received either standard medical treatment (SMT) or SMT plus long-term albumin, initially 40 g twice weekly for 2 weeks, and thereafter 40 g weekly. Over the course of 18 months, survival was significantly improved in those receiving SMT plus albumin (p = 0.0285), with a 38% reduction in the mortality hazard ratio. Further analysis of the data showed that a serum albumin concentration of 40 g/L at 1 month was the best discriminant value for long-term survival.[19]

Similar results were obtained in another Italian study in patients with refractory ascites, which showed that weekly albumin infusions of 20 g over the course of 24 months were associated with a significant reduction in mortality (p = 0.032).[20] Furthermore, there were significant reductions in hospital admissions for the indications of overt hepatic encephalopathy (HE), ascites and infections. However, in a cohort of outpatients with cirrhosis and ascites awaiting a liver transplant, the use of midodrine, at a median dose of 23 mg per day, and albumin at a dose of 40 g every 2 weeks for 1 year, was not shown to improve survival compared to SMT.[21] These discrepant results (Table 1) may be related to differences in the patient populations assessed, and different study designs. The ongoing multinational PRECIOSA study will hopefully resolve controversies around the potential benefits of long-term albumin infusions in patients with cirrhosis and ascites. It is likely that albumin use will have to be individualised, with the dose, frequency and duration of albumin infusion dependent on the patient's clinical state.[22] Other practical issues such as the costs and manpower required to deliver such a treatment will need to be considered even if it proves to be clinically beneficial.

The potential of sodium glucose co-transporter 2 inhibitors

Sodium glucose co-transporter 2 (SGLT2) inhibitors are a new class of drugs that inhibit the sodium glucose co-transporter located at the proximal renal tubule, thereby blocking the reabsorption of both glucose and sodium at that site (Fig. 2). Sodium delivery from the proximal renal tubule to the macula densa is therefore increased, thereby reducing renin secretion and renin activity at the juxtaglomerular apparatus. Therefore, theoretically, SGLT2 inhibitors could be used to reduce sodium reabsorption and protect the kidneys.[23] There are case reports of SGLT2 inhibitors improving ascites in patients with non-alcoholic steatohepatitis-related cirrhosis and type 2

Table 1. Comparison of clinical trials that evaluated the effectiveness of albumin in patients with decompensated cirrhosis.

Study/first author name	Country	Study population	Design	n	Dose	Treatment duration	Results
ANSWER	Italy	Patients with diuretic responsive ascites	Multicentre, randomised, open label trial of albumin *vs.* SMT	Albumin = 218 SMT = 213	Albumin = 40 g 2x weekly for 2 weeks, then 40 g weekly	18 months	Survival at 18 months: Albumin = 77% Control = 66% p= 0.028
MACHT	Spain	Patients on liver transplant waiting list	Multicentre, randomised, placebo-controlled trial of albumin + midodrine *vs.* placebo	Albumin = 87 Placebo = 86	Midodrine median dose = 23 mg/day; albumin = 40 g every 2 weeks	12 months	No difference in rates of complications or survival
Di Pascoli *et al.*	Italy	Patients with refractory ascites	Single-centre, non-randomised, open label trial of albumin *vs.* SMT	Albumin = 45 SMT = 25	Albumin = 20 g 2x per week	24 months	Reduction in hospitalisation (p = 0.008); reduction in mortality (p = 0.032)
PRECIOSA (ongoing)	Worldwide	Patients with decompensated cirrhosis and ascites	Multicentre, randomised, open label trial of albumin *vs.* SMT	Total: 410	1.5 g albumin/kg of body weight every 10 days	1 year	Pending

SMT, standard medical treatment.

diabetes.[24,25] This opens a potential new opportunity for better management of sodium and fluid retention in patients who have type 2 diabetes,[26] but carefully designed trials are needed – such studies will also need to clarify whether the doses to be used will be titrated to diabetic control or sodium excretion. Thorough pharmacokinetic studies, especially in patients with advanced liver dysfunction, are also needed as SGLT2 inhibitors are metabolised by the liver.

Newer approaches to the use of TIPS in the management of ascites

TIPS is a recognised treatment for refractory ascites in cirrhosis for appropriately selected patients.[27] Its role in improving survival in patients with refractory ascites is also established.[28] However, the insertion of TIPS is associated with complications, especially the risks of developing HE, liver failure or cardiac failure. The following are various aspects of TIPS management that have provided new findings to improve patient outcomes (Table 2).

Cardiac assessment pre-TIPS

As TIPS insertion returns a significant splanchnic volume to the central circulation, profound haemodynamic changes occur immediately after TIPS insertion.[29] Since some patients with decompensated cirrhosis have cardiac dysfunction as part of the cirrhotic cardiomyopathy syndrome,[30] careful cardiac assessment pre-TIPS is recommended to reduce the likelihood of cardiac decompensation post-TIPS. However, this is not uniformly practised. In a French study that included 100 patients who underwent detailed cardiac investigations pre-TIPS, the incidence of cardiac decompensation post-TIPS was 20%, and this occurred in patients who had evidence of cardiac dysfunction pre-TIPS, including B-type natriuretic peptide (BNP) levels of >40 pg/ml, or N-terminal proBNP (NT-proBNP) levels of >125 pg/ml, a prolonged corrected QT interval by the Frederica method on electrocardiography, increased E/A and E/e' and left atrial dilatation on 2-dimensional echocardiogram.[31] Furthermore, aortic stenosis was strongly associated with cardiac mortality. In another study, Modha and colleagues also showed a tight correlation between the pre-TIPS right atrial pressure and the onset of symptomatic heart failure after TIPS placement.[32]

Current guidelines from various academic societies recommend evaluation of cardiac history, clinical examination, 12-lead electrocardiography, NT-proBNP, 2-dimensional echocardiography, and a cardiology consultation if indicated.[33–35] The Italians suggest that TIPS is contraindicated in patients with a mean pulmonary artery pressure of >45 mmHg or a systolic pulmonary pressure of >50 mmHg on echocardiography, especially if confirmed on angiography.[35] Therefore, it is becoming clear that clinicians are increasingly concerned about cardiac dysfunction pre-TIPS negatively impacting on post-TIPS outcomes. Until there are uniform guidelines about cardiac investigations pre-TIPS, it would be prudent to ascertain that the patient has normal BNP or NT-proBNP, and no abnormalities on 12-lead electrocardiography and echocardiography prior to TIPS insertion.[36]

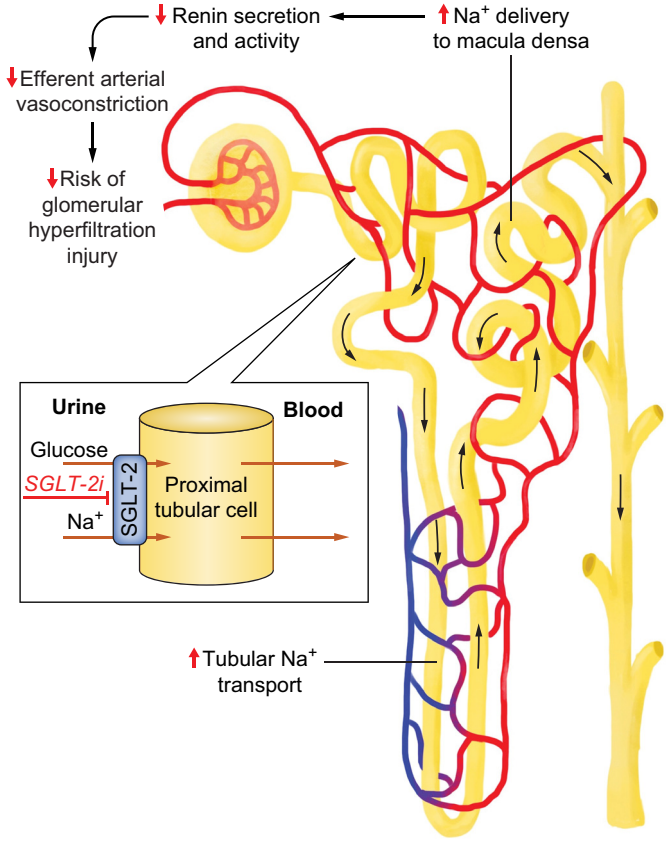

Fig. 2. Mechanism of action of SGLT-2*i* in reducing sodium and glucose reabsorption at the proximal renal tubule and potential renal protective effect. SGLT-2, sodium glucose co-transporter 2; SGLT-2*i*, sodium glucose co-transporter 2 inhibitor.

Under-dilation of a nominal 10 mm-diameter TIPS

Various investigators have demonstrated that deliberate under-dilation of the stent at the time of TIPS insertion can reduce the risk of post-TIPS HE.[37,38] The newly designed controlled expansion (CX) version of the poly-tetra-fluoroethylene (PTFE) stent, when under-dilated, provides a fixed degree of stent distension without further passive distension with time, thereby preventing a further reduction in portal pressure that could increase the risk of HE. In one prospective non-randomised study, the incidence of HE in patients who had their standard PTFE

Table 2. New Information on the use of TIPS in the management of ascites.

Phase of care	New information
Patient selection	Integrated MELD model - combines patient's age, pre-TIPS serum sodium concentration and MELD score[42] Freiberg index of post-TIPS survival (FIPS) score - combines patient's age, serum bilirubin, creatinine and albumin[43]
Pre-TIPS	Cardiac investigations to prevent post-TIPS cardiac failure[31,35] - BNP <40 pg/ml - NT-proBNP: <125 pg/ml - Absence of prolonged QT interval on ECG by Frederica method - Normal 2D echocardiogram - Mean pulmonary artery pressure >45 mmHg
During TIPS insertion	Under-dilate TIPS to 8 mmHg using controlled expansion stent[37,38]
Post-TIPS	Pre-emptive use of rifaximin[39]

BNP, B-type natriuretic peptide; MELD, model of end-stage liver disease; NT-proBNP, N-terminal pro BNP; TIPS, transjugular intrahepatic portosystemic shunt.

stent deliberately under-dilated to 6 mm was 27%, compared to 54% in patients whose stent was dilated to 8-10 mm, without any negative impact on variceal bleeding or ascites recurrence or on the incidence of stent thrombosis.[37] In another prospective case-controlled study, 47 patients who received a CX-PTFE stent were matched one-to-one to patients who received a standard nominal 10 mm PTFE stent, both under-dilated to 8 mm. Another control group of patients (n = 20) received a PTFE stent that was fully dilated to 10 mm.[43] Those patients who received the under-dilated CX-PTFE stents had significantly lower incidence of HE (23% *vs.* 51%), LVP requirement (11% *vs.* 21%) and incidence of heart failure (2% *vs.* 15%) compared to those who received a standard under-dilated PTFE stent (all p <0.05). Furthermore, 1-year survival was best amongst patients who received the under-dilated CX-PTFE stent (85%), compared to those who had an under-dilated standard PTFE stent (70%) and to those who received a fully dilated standard PTFE stent (55%) (p = 0.008).

These encouraging results suggest that it would be advisable to avoid fully dilating a 10 mm stent for ascites treatment until larger RCTs can confirm these results.

Management of HE post-TIPS

Although the use of an under-dilated TIPS can reduce the risk of HE, other factors, such as older age, advanced liver disease (Child-Pugh class C, or MELD score >18), sarcopenia, previous history of spontaneous HE, higher pre-TIP serum creatinine, or hyponatremia[36] can also predispose the patient to post-TIPS HE. Therefore, the practice is to offer treatment for HE pre-emptively after TIPS insertion. A recent RCT found that prophylactic rifaximin, 600 mg twice daily starting 14 days pre-TIPS without lactulose, was able to reduce the incidence of overt HE to 34% *vs.* 53% in the placebo group (p = 0.012).[39] There was no difference in the other adverse events or in transplant-free survival. The authors emphasised that since most of their patients (86%) had alcohol-related liver disease, their results might only be applicable to this population. In a retrospective multicentre German study including 233 patients, the use of lactulose alone had no prophylactic effects; lactulose plus rifaximin could prevent recurrent but not *de novo* HE. The addition of L-ornithine-L-aspartate did not enhance the prophylactic effects of lactulose plus rifaximin against HE recurrence.[40] A Dutch and Belgium RCT is currently underway, planning to recruit 238 patients over the course of 3 years, to assess the efficacy of lactulose 25 ml plus rifaximin 550 mg or placebo, all twice daily, starting 72 h pre-TIPS, in the prevention of post-TIPS HE (The PEARL trial) in patients without prior overt HE.[41] The primary endpoint is overt HE within 90 days after TIPS insertion. If the results of this latest RCT prove to be positive, then it will establish lactulose and rifaximin as standard of care prophylaxis against overt HE in patients receiving TIPS.

The prediction of survival post-TIPS

Post-TIPS survival is mainly influenced by age and severity of liver disease. A recent study from China assessed 10 predictive models for survival in 280 patients with recurrent or refractory ascites. The authors found that an integrated MELD model, (= MELD + [0.3 × (age, years)] − [0.7 × (Na, mmol/L) + 100]) provided the best discriminant function for the prediction of post-TIPS survival.[42] The 2-year transplant-free survival rates were 71%, 57% and 26% in patients with an integrated MELD score of <32, between 32 and 38, and >38, respectively. In another study from Germany, the Freiberg index of post-TIPS survival (FIPS) score ([1.43 × ($\log_{10}$ bilirubin, mg/dl)] - [1.71 × (1/creatinine, mg/dl)] + [0.02 × (age, years)] - [0.02 × (albumin, g/L)] + 0.81)[43] was able to identify patients at high risk for mortality after TIPS, significantly better than the MELD score, MELD-sodium score, Child-Pugh score or the bilirubin/platelet score.[44] However, the study has been criticised for using random samples to generate the training and validation sets from the same cohort of patients, and the lack of "optimism correction" made the FIPS appear to have better discriminatory power.[45] In an external validation amongst Chinese patients with predominantly hepatitis B infection, the Child-Pugh score performed better in stratifying patients into high/low risk groups, whereas the FIPS score was able to predict individual patient outcome in patients who were in Child-Pugh classes A and B.[46]

Therefore, these scores still require refinement before they can be used for their discriminative power in the prediction of post-TIPS survival. A note of caution may be added regarding the use of these prognostic scores for post-TIPS outcomes. They are only prognostic and not predictive biomarkers, *i.e.* they do not provide information on the individual benefit of TIPS.

TIPS placement at the stage of recurrent ascites

It has been suggested that TIPS should be inserted before the stage of refractory ascites in patients with cirrhosis to reduce the likelihood of post-TIPS complications. A multicentre French study randomised 62 patients with cirrhosis (predominantly alcohol-related) and recurrent ascites defined as the need for at least three LVPs within 12 months at intervals of >4 weeks to receive either a PTFE stent or repeat LVPs with albumin infusions.[47] During the follow-up of 12 months, patients in the TIPS group had significantly better ascites control, which was associated with a significantly improved 1-year survival of 93% compared to 52% for the LVP plus albumin group (p = 0.003), with no increase in post-TIPS HE incidence in the TIPS group. This study has not been replicated, and therefore, PTFE stents cannot be recommended as standard of care yet for patients with recurrent ascites.

The automated low flow ascites pump (alfapump)

The alfapump is a programmable and rechargeable subcutaneous device that continuously pumps a small volume of ascites from the peritoneal cavity and discharges it into the bladder, from there it is discharged as urine (Fig. 3), for approximately 16 h each day during waking hours. The rate of ascites discharge can be adjusted according to the patient's dietary sodium consumption, including being able to do a pump paracentesis of up to 4 L should the patient accumulate a significant volume of ascites. Therefore, the management of ascites is individualised. Regular albumin infusions are not required with the use of the alfapump system.

An RCT,[48] several prospective[49–53] and retrospective[54] studies, as well as a meta-analysis,[55] have shown that the alfapump system is effective in controlling ascites, thereby reducing the required frequency and volume of needle paracenteses. The initial study showed that the infection rate was high.[49] The use of prophylactic antibiotics has reduced its occurrence. Other adverse events reported have included pump malfunction and catheter dislodgement, which have diminished with better pump and catheter design. As the alfapump system provides a slow continuous low volume paracentesis, some patients still experience haemodynamic disturbances with activation of vasoconstrictor systems, as shown in a physiological study.[56]

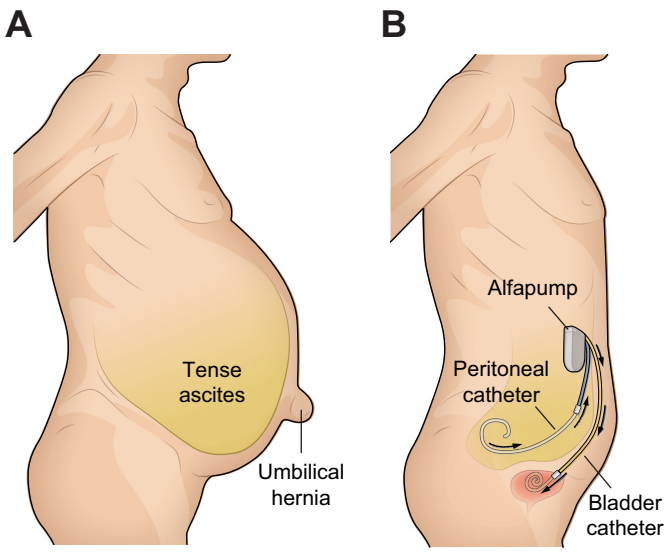

Fig. 3. Depiction of patient with tense ascites and alfapump *in situ*. (A) Patients with cirrhosis and tense ascites, (B) alfapump *in situ* with peritoneal catheter removing ascites from peritoneal cavity and discharging via the bladder catheter into the bladder, to be removed as urine (Figure provided by Sequana Medical Inc with permission).

Therefore, it is prudent to monitor the renal function regularly in these patients and give albumin should acute kidney injury (AKI) occur. As a corollary, it would not be advisable to implant an alfapump into patients who have background renal dysfunction (serum creatinine >132 μmol/L [>1.5 mg/dl] or an estimated glomerular filtration rate <30 ml/min/1.72 m^2).[57] Other contra-indications to alfapump implantation include loculated ascites, untreatable bladder neck obstruction, recent intra-abdominal surgery, history of bladder cancer, previous solid organ transplantation, bilirubin of >85 μmol/L (5 mg/dl) and life expectancy of less than 3 months.[57] Clearance of bacterial peritonitis or urinary tract infection for 6 months is recommended before implanting the device. In malnourished patients with minimal subcutaneous fat in the abdominal wall, it is advisable to wear some form of padding over the implanted device, as constant rubbing of the device against clothing will lead to erosion of the pump through the skin, which will necessitate pump removal.

To date, the studies have indicated improved mobility and better quality of life in patients who have gained control of their ascites,[53,58] allowing various abdominal hernias to be repaired, further enhancing patient well-being.[59] Survival with the alfapump system has not been specifically assessed in any of the studies published so far. In a recent meta-analysis, survival has been shown to be at least the same as for patients who undergo regular LVP.[60] In a prospective study that records the real-world experience of long-term (24-month) alfapump use in 106 patients not eligible for TIPS insertion, the median survival was 10.1 months.[61] There were 108 surgical interventions in 72 patients (60 device- or catheter-related interventions and 48 pump explants). Pump explants were performed in preparation for liver transplant in 13 patients, because of ascites elimination resulting from treatment of the underling aetiology in five patients, because of infection in 23 patients, and for other reasons in seven patients. Finally, there were seven cases of AKI, occurring a median of 160 days (range 12 to 605 days) after implantation, with AKI directly contributing to the deaths of two patients.[61]

Therefore, careful selection of patients is necessary to gain the most out of the alfapump system. In patients without co-morbid conditions that can compromise short-to medium term survival, alfapump implantation is an attractive alternative to repeat LVP. Currently, there are several ongoing trials that will address the cost effectiveness of the alfapump system and the optimal candidates for this device.[62]

The potential of metabolomics to predict complications of ascites

The field of metabolomics involves the study of metabolite profiles and their association with certain clinical conditions. With respect to clinical applications for patients with ascites, metabolomics is still in its infancy. However, in the future, one could envision being able to use a patient's metabolomic profile to predict their likely response to treatment, thereby enabling the development of an individualised treatment plan and ultimately helping to improve outcomes.

Metabolomic profile for response to NSBBs

In a Spanish study that included 66 patients with CSPH, as determined by HVPG measurements,[63] 41 (62%) patients had a haemodynamic response to acute intravenous propranolol, defined as a >10% drop in their HVPG. Several metabolites belonging to glycerophospholipid and non-esterified fatty acid chemical groups seemed to differentiate between the NSBB responders and non-responders. At multivariate analysis, a model including a phosphatidylcholine and a free fatty acid (eicosadienoic acid) performed well for the prediction of HVPG response. This combination was able to correctly identify 74% of responders. Given that the use of NSBBs is increasingly accepted as the standard of care for delaying the appearance of ascites in cirrhosis, it would be useful to identify NSBB responders and devise other ascites prevention strategies for non-responders. This will also have to be compared with other non-invasive tests of NSBB response.[64]

Metabolomics biomarkers for assessing AKI risk in decompensated cirrhosis

In a multicentre North American study in patients admitted with cirrhosis and ascites, those who had a high likelihood of developing AKI had increased levels of molecules associated with activation of the tryptophan-kynurenine and the trans-sulfuration pathways in both the serum and the urine.[65] This confirms a previous finding that an elevated quinolinic acid/tryptophan ratio is predictive of AKI development amongst critically ill patients.[66] The trans-sulfuration pathway is known to produce cysteine and methionine by-products, which are known uremic toxins. Therefore, finding elevated levels of these metabolites will allow us to better identify patients with ascites who are more likely to develop AKI and thus require closer monitoring. The study of these metabolites may also help guide the development of renal protective strategies.[67])

Conclusion

A better understanding of the pathogenetic mechanisms leading to ascites formation has helped guide therapeutic strategies, *i.e.* the pre-emptive use of NSBBs to reduce portal pressure and hence delay the appearance of ascites, the use of albumin to increase the effective arterial blood volume and to reduce the extent of inflammation, or SGLT2 inhibitors to block renal sodium excretion. Refinements in the application of TIPS and the

use of alfapump for the treatment of refractory ascites are measures that could improve patients' quality of life and potentially survival. New omics techniques will add further tools to individualise ascites treatment and ultimately improve patient outcomes, though these approaches will require validation in large multicentre trials.

Abbreviations

AKI, acute kidney injury; BNP, B-type natriuretic peptide; CSPH, clinically significant portal hypertension; CX, controlled expansion; FIPS, Freiberg index of post-TIPS survival; HE, hepatic encephalopathy; HVPG, hepatic venous pressure gradient; LVP, large volume paracentesis; MELD, model for end-stage liver disease; NSBBs, non-selective beta blockers; NT-proBNP, N-terminal pro BNP; PTFE, poly-tetra- fluoroethylene; RCT, randomised-controlled trial; SGLT2, sodium glucose co-transporter 2; SMT, standard medical treatment; TIPS, transjugular intrahepatic porto-systemic shunt.

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Supplementary data

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