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Patient Selection in Transjugular Intrahepatic Portosystemic Shunt (TIPS) for Refractory Ascites and Associated Conditions

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Abstract

Purpose of Review This review summarizes the key developments and latest evidence for transjugular intrahepatic portosystemic shunt (TIPS) for the indications of refractory ascites and related conditions, as well as factors that should be taken into consideration with regard to patient selection.

Recent Findings Recent evidence from randomized controlled studies has suggested that the early institution of TIPS in well-selected patients with refractory ascites may confer a survival benefit. Increasing evidence is also mounting on the potential role of TIPS in improving and reversing hepatorenal syndrome.

Summary TIPS has conventionally been sought as a second-line treatment for refractory ascites. Recent evidence has suggested a potential survival benefit with early TIPS in well-compensated patients for this indication; this may lead to a paradigm shift for TIPS to be considered as primary therapy in well-selected "low-risk" patients. In hepatorenal syndrome, while evidence on TIPS is limited, multiple studies have shown a serendipitous improvement to renal function in both type 1 and 2 hepatorenal syndrome following TIPS.

Keywords Transjugular intrahepatic portosystemic shunt · Refractory ascites · Hepatic hydrothorax · Hepatorenal syndrome

Abbreviations

AASLD	American Association for the Study of Liver
AKI-HRS	Acute kidney injury–hepatorenal syndrome
CP	Childs-Pugh
CKD-HRS	Chronic kidney disease–hepatorenal syndrome
HE	Hepatic encephalopathy
HRS	Hepato-renal syndrome
LVP	Large-volume paracentesis
MELD	Model for end-stage liver disease
RCT	Randomized controlled trial
TIPS	Transjugular intrahepatic portosystemic shunt

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Introduction

Transjugular intrahepatic portosystemic shunt (TIPS) is an effective management strategy for treating portal hypertension and its complications, used most frequently in the context of cirrhotic liver disease. The American Association for the Study of the Liver (AASLD) last published guidelines regarding TIPS in January 2010 [1] though a wealth of new studies has surfaced since, providing additional evidence regarding the utility of this important treatment option.

The main indications for TIPS, as supported by multiple randomized controlled trials, are the management of variceal bleeding and refractory ascites. This review focuses on considerations towards patient selection for TIPS for the indication of refractory ascites and related conditions.

Refractory Ascites

The risk of mortality once refractory ascites has developed is high and frequently quoted as 50% at 1 year [2]. Though large-volume paracentesis (LVP) in itself has not been associated with improved survival [3], it would seem from clinical

experience that despite the onset of refractory ascites, given the known risks of hepatic encephalopathy (HE) and perhaps from a cost-saving perspective [4], TIPS is often considered at a later stage and as a "last resort," arbitrarily considered only when LVP is required very frequently, for example, at more than once every 2 weeks. TIPS is, however, very effective in controlling refractory ascites and does significantly decrease requirements for LVP [5]. It is noteworthy that in the context of randomized control trials, refractory ascites has been often defined by the International Ascites Club criteria [6, 7], which does not incorporate the frequency of LVP as a criterion.

Evidence for the Use of TIPS vs LVP

Up until recently, multiple randomized controlled trials (RCTs) further analyzed by meta-analysis had failed to demonstrate a survival benefit with TIPS compared with LVP [5, 8, 9] for the indication of refractory ascites, with one study even showing increased mortality with TIPS [10]. Incidence of HE tended to be higher in the TIPS groups though ability to improve ascites was unequivocal. However, bare TIPS stents were utilized in these studies, and as displayed in the meta-analysis by Deltenre et al. [5] which included five RCTs [4, 10–13], the patient cohorts tended to have more compromised liver function as indicated by mean Child-Pugh (CP) scores of 9.1–9.4 and mean baseline bilirubin levels of 29–35 μmol/L. An updated meta-analysis including the same studies but with the addition of a 6th RCT [14] has however concluded that TIPS significantly improves the transplant-free survival in patients with refractory ascites though increases the risk of HE [15].

This 6th RCT performed by Narahara et al. [14] was focused on the utility of TIPS in patients who had refractory ascites with "good hepatic and renal function," with CP < 11 as an inclusion criterion. Thirty patients were recruited in each arm. In the TIPS arm, though mean CP scores were 8.9, mean MELD scores were 9.6 and mean baseline bilirubin 1.3 mg/dL (22 μmol/l). Patients had refractory ascites for about 4 months prior to randomization. Results showed that TIPS was clearly superior in controlling ascites, and there was a significant survival benefit when comparing the cumulative probability of survival in the TIPS cohort at 1, 2, and 3 years as compared to the LVP arm (80%, 64%, 58% vs 49%, 25%, 19%). Though severe HE was significantly higher in the TIPS arm, all cases could be managed conservatively without any significant difference in survival between those who did and did not develop post-TIPS HE. Bare TIPS stents were utilized in this study, and hence, shunt dysfunction was reported at 87% in the TIPS arm.

Most recently, a randomized controlled trial conducted in four French centers comparing covered-TIPS with repeated LVP in 62 patients (CP ≤ 11) revealed that the group with covered-TIPS had improved 1-year transplant-free survival (93% vs 52%) with no significant difference in number of severe HE episodes, while significantly decreasing LVP requirements [16••]. Of note, though the intended study population was for patients who required at least two LVPs within a minimal interval of 3 weeks, patients who required > 6 LVPs within the previous 3 months were excluded. This selection criterion seems somewhat odd but may indicate that the study investigators were interested in looking into patients who were fairly "early on" in their course of refractory ascites. In addition, these criteria would potentially limit cross-over to TIPS in the LVP arm, since TIPS is considered standard therapy for RA in many centers. Patients who were expected to receive transplants in the next 6 months were also excluded. Looking further at the patient cohorts, though the mean CP score in both arms was 9, these were patients with mean bilirubin of 18 μmol/L and fairly low mean MELD scores of 12–13. Nonetheless, despite perhaps having more well-compensated patients, transplant-free survival in the LVP arm was similar to that reported in other meta-analysis while transplant-free survival in the TIPS arm was higher than that of recently reported studies (93% vs 77–80%) [13, 14], leading the authors to conclude that the survival benefit in the TIPS arm was mainly due to the use of covered stents.

Criteria for Patient Selection

While MELD was developed to prognosticate short-term mortality post-TIPS [17], the isolated use of bilirubin as a surrogate of liver function in the setting of TIPS for refractory ascites may be more appropriate as compared to MELD; this is due to the incorporation of creatinine within MELD. The close relationship between refractory ascites and renal function is further elaborated in the next sections. Briefly, however, TIPS has the potential to reverse hepatorenal syndrome [18, 19], and moreover, creatinine in the setting of refractory ascites may be fluctuant and artificially elevated depending on diuretic dosage. Serum bilirubin, reflecting the degree of liver failure, might hence be the best selection criteria to optimize the balance of harms and benefits achieved by TIPS as compared with LVP. Indeed, in the meta-analysis by D'Amico et al. [20] (all bare stents), meta-regression analysis showed that lower mean serum bilirubin was independently associated with a survival gain with TIPS as compared with LVP. This is further supported with the addition of newer trials (summarized in Table 1 and Fig. 1). Other studies have also previously suggested a bilirubin cutoff of 3 mg/dL (51 μmol/L) as predictor for mortality post-TIPS [11, 21, 22].

In summary, findings from the latest two RCTs [14, 16••] as well as from the most recently performed meta-analysis [15] would support the novel use of TIPS as preferred *primary* therapy in highly selected "low-risk" patients with refractory ascites. Patient selection (of not so sick patients) might be the key to improved survival with TIPS for the indication of

Table 1 Odds ratio of mortality in seven RCTs comparing TIPS vs LVP for refractory ascites

	Number randomized	Mean follow-up period (months) (TIPS/LVP)	Odds ratio mortality	Mean bilirubin (mg/dL) (SD) (TIPS/LVP)	Mean Child–Pugh score (TIPS/LVP)	Mean MELD (TIPS/LVP)
Lebrec (1996) [10]	25	7.5/12.4	4.50 (0.84–24.18)	2.04 (0.5)/1.57 (0.2)	9.3 (0.6)/9.2 (0.6)	
Rossle (2000) [11]	60	45/44	0.37 (0.13–1.10)	1.8 (1.2)/1.8 (1.0)	9.1 (1.9)/8.7 (1.2)	
Gines (2002) [4]	70	9.5/10.8	1.26 (0.49–3.23)	2.0 (0.2)/2.4 (0.3)	9.3 (0.2)/9.2 (0.3)	
Sanyal (2003) [12]	109	41/38	1.16 (0.54–2.51)	1.9 (1.2)/1.9 (1.4)	9.2 (1.2)/9.3 (1.3)	
Salerno (2004) [13]	66	21/15	0.42 (0.16–1.13)	1.7 (0.15)/1.8 (0.24)	9.4 (0.2)/9.4 (0.2)	11.1 (0.8)/11.1 (0.9)
Narahara (2011) [14]	60	27.6/13	0.56 (0.19–1.62)	1.3 (0.7)/1.4 (0.7)	8.9 (1.0)/8.9 (1.0)	9.6 (3.6)/10.6 (4.5)
Bureau (2017) [16]	62	11.6/10.5	0.41 (0.07–2.32)	1.04 (0.74)/1.02 (0.96)	9.1 (1.4)/9.0 (1.6)	12.1 (3.5)/13.1 (3.9)

refractory ascites. Nevertheless, even in relatively "higher-risk" patients, TIPS as a bridge towards liver transplant is likely to improve the quality of life for patients with refractory ascites [23] and remains an important treatment strategy even in the absence of a proven survival benefit.

Non-response to TIPS

It is important to note that TIPS significantly reduces requirements for LVP but may not completely obliterate the need for it. Ascites reaccumulation despite TIPS is common [5, 15]. Hence, most patients may still benefit from continued, albeit reduced doses of diuretic therapy. It may take months for diuretic requirement to decrease [24]. As well, the natriuretic effect from TIPS may be delayed by increased age and prior impaired renal function pre-TIPS [25], and the TIPS stent may take up to 6 weeks to passively expand to full diameter [26], with the full effect of TIPS hence taking some time to manifest. These considerations are important before deciding to do further dilation of TIPS, which might be unnecessary and increase the risk of HE. TIPS stent dysfunction is also an important factor to consider if patients lose response or redevelop persistent ascites despite TIPS. With the now conventional use of covered metal stents, stent dysfunction due to occlusion or stenosis is far less common, though this still occurs [27]. Still, since TIPS induces a marked increase in cardiac output (and therefore in splanchnic blood flow), the maximum diameter of the shunt (10 mm) might be insufficient to reduce portal pressure effectively to target levels. In these cases, if blood pressure is robust, addition of non-selective beta-blockers might achieve the desired target reduction in portal pressure [28]. Finally, with the propensity for TIPS to induce cardiac complications such as pulmonary hypertension and cardiac overload over time [29], reevaluation of the patient's cardiac function with basic echocardiography should also be considered if ascites is persistent, particularly if peripheral edema has also developed.

TIPS Contraindications and Complications

In the context of competing effective therapies (such as in the case of refractory ascites and the availability of LVP), patient selection becomes especially important. In this section, we address the potential contraindications and complications of TIPS, to aid in guiding patient selection.

Contraindications

Absolute contraindications to TIPS are few, and over the years, several relative contraindications have been overcome by evolution of the TIPS technique (e.g., complete portal vein thrombosis); these are presented in Table 2.

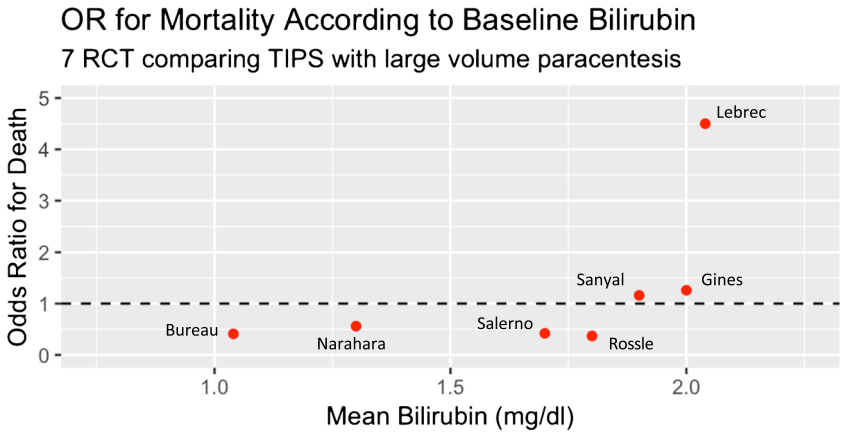

Fig. 1 Odds ratios of mortality from seven RCTs in refractory ascites plotted against mean baseline bilirubin

Complications of TIPS

Complications arising from TIPS may be classified into procedural vs non-procedural and are well documented (Table 3) [30, 31].

HE

HE is a well-recognized complication of TIPS and may be de novo or worsened post-TIPS. As reported in several of the trials mentioned above, incidence of HE is often higher in the patients who received TIPS, with post-TIPS HE reported at over 30% [32]. In a systematic review by Bai et al. of over 30 studies, pre-TIPS HE was the most significant predictor of post-TIPS HE though CP class and age were also found to be common risk factors for post-TIPS HE [33].

While success of TIPS is determined by appropriate placement of stent and sufficient reduction of the portosystemic pressure gradient (PPG), in most instances aiming for a reduction to < 12 mmHg, this being shown to reduce rebleeding rates in acute variceal bleeding [1, 34, 35], decrease of PPG to < 8 mmHg may be associated with increased mortality [36], and lowering of PPG to < 10 mmHg is a predictor for the development of HE [37].

In a recent prospective non-randomized study by Schepis et al. [38••], the authors sought to investigate whether "underdilation" of TIPS (where conventionally TIPS is dilated to either 8 mm or 10 mm) could reduce post-TIPS incidence of HE. Indication for TIPS included previous variceal bleeding and refractory ascites. Comparing patients who had underdilation of TIPS to 6 mm and those with conventional dilation to ≥ 8 mm, decrease of PSG to < 12 mmHg was less frequently achieved in those with under-dilated TIPS, but there was no significant difference to clinical efficacy. Importantly, underdilation of TIPS was associated with significant reduction of post-TIPS HE, this likely related also to the gentler reduction in PSG with under-dilation. The authors hence suggest that dilation of TIPS to 6 mm be the proposed initial option for patients who have risk factors for post-TIPS HE. This would require further validation before becoming standard of care.

Deterioration of Liver Function Post-TIPS

Due to the effective shunting away of blood from the portal vein and reduced portal perfusion of the liver, liver decompensation may occur post-TIPS manifesting with jaundice, worsened coagulopathy, encephalopathy, and ascites and has been reported to occur in 6% in one series [39]. Though in this series post-TIPS decompensation was treated by shunt reduction, mortality was still about 50% at 6 months and increased INR after TIPS reduction was reported as the most important prognostic variable for early death.

Table 2 Contraindications to TIPS

Absolute	Relative
Severe pulmonary hypertension	Unrelieved biliary obstruction
Congestive cardiac failure	Central hepatoma
Uncontrolled systemic infection	Severe coagulopathy/ thrombocytopenia
Uncontrollable severe hepatic encephalopathy	Cardiac diastolic dysfunction
	Unfavorable vascular anatomy
	Inability to lie flat

Table 3 Complications of TIPS

Procedural related	Non-procedural related
Endotipsitis (mostly seen with bare metal stents)	Mortality
Perforation of other viscus/liver capsule/bile ducts (biliary fistula)	Hepatic encephalopathy
Arrhthymias during RA traversement	Worsening of hepatic function/decompensation
Hemorrhage	Hepatic ischemia/infarction
Early stent occlusion and thrombosis	Hemolysis
Damage to hepatic vasculature	Right-sided cardiac dysfunction
TIPS maldeployment	TIPS stent migration
Anesthetic risks	Late stent stenosis/occlusion
Radiation skin burn	
Renal dysfunction from contrast	

Other Considerations with Patient Selection

Age

Age has been found to be another significant predictor of HE post-TIPS [33] and though not represented in the current guidelines, in our personal practice, we would be extremely hesitant to perform TIPS on those > 65 years. Age > 55 has also been found to be a prognostic factor for mortality post-TIPS [40].

Cardiac Function

Post-TIPS, cardiac output and right atrial pressures may increase by 50% and 100%, respectively [41]. In the presence of obvious pre-morbid conditions such as significant pulmonary hypertension or overt cardiac failure, TIPS would be unsafe. However, in those with borderline cardiac dysfunction, it remains to be seen whether TIPS may have long-term deleterious effect on cardiac function. A recent 5-year follow-up of TIPS patients compared with cirrhotic controls reported an increase in cardiac overload and development of pulmonary hypertension [29]. Additionally, it is still unclear as to whether diastolic dysfunction has any impact on mortality post-TIPS [42, 43] and presently is not a contraindication to TIPS.

TIPS for Refractory Ascites: Special Cases

Refractory Hepatic Hydrothorax

Hepatic hydrothorax is used to describe a pleural effusion (usually on the right) that has resulted from ascites that has tracked into the pleural space due to a diaphragmatic defect [44]. In patients with hepatic hydrothorax, diuretic treatment tends to be less effective and associated with more complications as compared to patients with ascites, likely due to the much smaller surface of pleural membrane available for fluid reabsorption, as compared with the large peritoneal surface. Up to 6% of cirrhotic patients with ascites may develop hepatic hydrothorax though about 10% of patients with hepatic hydrothorax have neither clinically nor radiologically detected ascites [45]. Patients with refractory hepatic hydrothorax hence constitute a subgroup of patients with refractory ascites though TIPS studies for the latter do not tend to differentiate those with concomitant hydrothorax. Due to the rapid reaccumulation and experience of dyspnea that can occur with relatively small volumes of pleural fluid, patients with refractory hepatic hydrothorax may require frequent repeated procedures. It is not recommended that large-bore chest tubes be placed in hepatic hydrothorax due to high morbidity and mortality and risk of hastened deterioration [46–48].

Studies to date looking specifically at outcomes with TIPS in hepatic hydrothorax have been limited mainly to case reports and case series retrospective in nature. There have been no controlled trials performed. A cumulative meta-analysis published by Dital et al. of 6 retrospective studies (latest study published in 2009) [49], which included 198 patients with hepatic hydrothorax, found that overall mortality post-TIPS was 50% during mean follow-up of 10 months (45-day mortality was 18%). It was unclear which studies had utilized covered stents. Incidence of HE was 12%. Eighty percent of patients had response to the treatment. Fifty-seven percent of the patients were CP C and < 1% were CP A. Predictors of mortality included older age, severity of liver disease, elevated creatinine, and those with persistent hydrothorax.

In a more recent study by Young et al. [50], 32 patients undergoing TIPS for refractory hepatic hydrothorax were compared with 115 patients who underwent TIPS for refractory ascites. Patients were followed for over 900 days. Ninety-day mortality was 12.5% in the cohort with hepatic hydrothorax (30-day mortality 3%) compared with 6% in those with refractory ascites, though this difference was not statistically significant. In this study, the mortality rates with regard to TIPS for hepatic hydrothorax seem much improved to that as reported in the meta-analysis by Dital et al., which reported

a 45-day mortality of 18% [49], although mean CP score of this cohort was also lower at 9.4, and all TIPS stents placed were covered stents.

At present, TIPS is recommended as a second-line consideration in those with refractory hepatic hydrothorax although we believe the interval between thoracocentesis ought to guide earlier institution of this therapy.

The Use of TIPS in Patients with Functional Kidney Dysfunction

CKD-HRS

Type 2 HRS (now known as chronic kidney disease (CKD)-HRS) refers to the gradual worsening of renal function in a cirrhotic patient mainly occurring in the context of refractory ascites [6]. Type 2 HRS is a manifestation of the severe hemodynamic dysregulation and compensatory mechanisms that have occurred resulting in splanchnic vasodilatation, hyperdynamic cardiac output, hypovolemia of the effective circulation, vasoconstriction of the renal vasculature, activation of the renin–angiotensin–aldosterone system, and retention of excess free water causing ascites and hyponatremia [51].

Three studies have specifically investigated use of TIPS in type 2 HRS: in a small prospective Italian study, 10 patients (CP 10–12) with type 2 HRS on the waiting list for liver transplant underwent TIPS for type 2 HRS and experienced significant renal function improvement post-TIPS [52]. In a further prospective study looking at 31 patients with HRS (including both types 1 and 2), renal function improved within 2 weeks of TIPS with creatinine clearance improving from 18 to 48 ml/min and stabilizing thereafter; in patients who were on hemodialysis pre-TIPS, 4 of 7 were able to come off hemodialysis. In those who did not receive TIPS, renal function worsened progressively [19]. In a small prospective study intending to compare the effect of TIPS in those with type 2 HRS and those with organic renal disease, 11 patients with type 2 HRS and refractory ascites were treated with terlipressin and albumin for 7 days with subsequent placement of TIPS in 9 of these 11 patients. There was significant improvement to serum creatinine, plasma aldosterone levels, and 24-h urinary volume at 1-month post-TIPS [53]. All who had improved on terlipressin had subsequent response to TIPS whereas of the three patients who did not respond to terlipressin, two received TIPS but only one experienced improvement to renal function post-TIPS [53]. We speculate that the responsiveness of renal function to terlipressin in type 2 HRS may allude to responsiveness to TIPS.

Other studies have shown positive effects of TIPS on creatinine: in a retrospective cohort-matched study in an American center comparing TIPS to LVP for refractory ascites, renal function in those with pre-TIPS eGFR < 60 ml/min/1.73 m^2 had significant improvement to eGFR at 90 days post-TIPS though no difference was seen for those with eGFR > 60 ml/min [54]. A retrospective series of 129 patients from a single American center who underwent TIPS for multiple indications revealed that those with pre-TIPS creatinine > 1.2 mg/dL (106 μmol/L) had post-TIPS improvement to their creatinine levels and those with the worst renal function had improvement to their MELD scores post-TIPS though MELD increased in patients with normal renal function [55]. In a controlled study of TIPS versus LVP for refractory ascites, TIPS appeared to be protective against the development of HRS [4].

AKI-HRS

In patients with AKI-HRS (previously known as type 1 HRS) [56], the most effective therapy is with the use of albumin and terlipressin which is the current first-line recommended treatment [57–59]. On the other hand, TIPS has been shown to be effective in improving renal function though its effect on survival remains unclear [60, 61•].

In a prospective observational study by Wong et al. [18], 14 patients with type 1 HRS were treated with midodrine + octreotide + albumin and those who had a stable reduction in creatinine to < 135 μmol/L for 3 days after 7 days of treatment and who had no contraindications, received a TIPS (n = 5). In those who received TIPS, glomerular filtration rate continued to improve and had nearly normalized by 12 months post-TIPS. However, in three of five patients who responded to medical treatment but did not receive a TIPS, creatinine had also nearly normalized at 1 month after enrollment, and in the remaining two patients who received liver transplant within 1 month after enrollment, serum creatinine had remained normal at time of liver transplant. Hence, though TIPS resulted in a sustained improvement in renal function and "complete reversal" of type 1 HRS (which was supported also by evidence of improved renal hemodynamics from 6 months), from this study, it is difficult to draw any conclusions on whether TIPS is superior to medical therapy alone (with midodrine + octreotide + albumin) in the treatment of type 1 HRS.

Hence, the role of TIPS in HRS (particularly type 1 HRS) remains undefined although TIPS has certainly shown serendipitous advantageous impact on renal function in type 2 HRS as elaborated above.

Conclusion

In conclusion, there is increasing evidence to support the earlier use of TIPS in selected patients with refractory ascites, which apart from potential beneficial impact on renal function,

may also improve survival. In the context of type 1 HRS, which carries a high mortality, more studies are required to investigate the potential role of TIPS in reversing this condition.

Compliance with Ethical Standards

Conflict of Interest Juan Gonzalez-Abraldes reports lecture fees from GILEAD, Ferring, and Lupin, as well as consulting from GILEAD, Pfizer, and Theravance outside the submitted work. Beverley Kok declares no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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