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MINI REVIEW

TIPS for management of portal-hypertension-related complications in patients with cirrhosis

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KEYWORDS
Transjugular intrahepatic portosystemic shunt;
Cirrhosis;
Ascites;
Variceal bleeding

Summary Portal hypertension is primarily due to liver cirrhosis, and is responsible for complications that include variceal bleeding, ascites and hepatorenal syndrome. The transjugular intrahepatic portosystemic shunt (TIPS) is a low-resistance channel between the portal vein and the hepatic vein, created by interventional radiology, that aims to reduce portal pressure. TIPS is a potential treatment for severe portal-hypertension-related complications, including esophageal and gastric variceal bleeding. TIPS is currently indicated as salvage therapy in this setting when patients fail to respond to standard endoscopic and medical treatment. More recently, early TIPS has been shown to be effective in decreasing risk of rebleeding after variceal

Abbreviations: FHVP, Free Hepatic Vein Pressure; HE, Hepatic Encephalopathy; HVPG, Hepatic Venous Pressure Gradient; HRS, Hepatorenal Syndrome; LT, Liver Transplantation; LVP, Large-Volume Paracentesis; MELD, Model For End-Stage Liver Disease; PT, Prothrombin Time; PSPG, Porto-Systemic Pressure Gradient; PVT, Portal Vein Thrombosis; RCT, Randomized Controlled Trials; TIPS, Transjugular Intrahepatic Portosystemic Shunt; WHVP, Wedged Hepatic Vein Pressure; EBL, endoscopic band ligation; ICU, intensive care unit; CSPH, clinically significant portal hypertension.

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hemorrhage and mortality in Child-Pugh B patients with active hemorrhage at endoscopy, and in Child-Pugh C patients. TIPS is also an efficient treatment for refractory ascites and hepatic hydrothorax. In contrast, the role of TIPS in the hepatorenal syndrome has not been precisely defined. The aim of this review was to specifically describe the current role of TIPS in management of portal hypertension in patients with cirrhosis.

Introduction

Portal hypertension is responsible for variceal bleeding, ascites and hepatorenal syndrome (HRS), which significantly contribute to morbidity in patients with cirrhosis and strongly impair their prognosis. The transjugular intrahepatic portosystemic shunt (TIPS) was developed at the beginning of the nineties to reduce portal pressure and to treat complications of portal hypertension after failure of medical therapy. Initial results were impaired by technical difficulties, procedure-related complications and treatment of unselected patients at high risk of complications. Moreover, the main drawback of the initially used uncovered shunt was the risk of thrombosis and stenosis during follow-up, leading to recurrence of portal hypertension.

However, use of a covered stent has reduced this risk of stenosis and thrombosis, with a sustained effect on portal hypertension and its related complications. Moreover, recent studies have defined a target population possibly benefitting from TIPS, with limited risk of complications related to the procedure in cases of variceal bleeding and refractory ascites.

The aim of this review was to evaluate the current role of TIPS in management of portal hypertension in patients with cirrhosis.

Definition and consequences of portal hypertension

Definition of portal hypertension

The starting point of portal hypertension is an increase in outflow resistance located at any point in liver circulation (presinusoidal, sinusoidal and postsinusoidal). In western countries, over 90% of portal hypertension is due to sinusoidal obstruction related to cirrhosis [1]. Portal hypertension is defined as an increase in the trans-hepatic pressure gradient (known as the porto-systemic pressure gradient [PSPG]) between liver inflow and outflow pressure, which is obtained by the difference between portal venous pressure and inferior vena cava pressure. In clinical practice, the presence of portal hypertension is generally evaluated using a transjugular approach, by measurement of the hepatic venous pressure gradient (HVPG) obtained by subtracting free hepatic vein pressure (FHVP) from wedged hepatic vein pressure (WHVP) according to the following formula: HVPG = WHVP-FHVP. HVPG is the indirect measurement of the PSPG, but can only be assessed in intrahepatic-intrasinusoidal portal hypertension such as cirrhosis without portal vein thrombosis. HVPG > 5 mmHg defines sinusoidal portal hypertension; when HVPG is greater than 10 mmHg, i.e. clinically significant portal hypertension [CSPH], clinical manifestations such as varices, variceal bleeding and/or ascites may occur [1].

Pathophysiology and consequences

Intrahepatic obstruction due to cirrhosis induces production of several vasodilatators, including nitric oxide, that promote portal hypertension and splanchnic vasodilatation, consequently reducing effective arterial blood volume. In compensated cirrhosis, cardiac output is able to counterbalance the reduction in systemic vascular resistance. Portal hypertension leads to collateral formation and/or opening of pre-existing porto-systemic shunts, causing potential complications such as variceal bleeding or portal hypertensive gastropathy. At a late stage, cardiac output is unable to counteract peripheral vasodilatation; thus, effective arterial blood volume declines and leads to stimulation of compensatory neurohormonal vasoconstrictor systems (renin angiotensin system, sympathetic nervous system) and to production of arginine vasopressin. It induces sodium and water retention as well as vasoconstriction of renal, cerebral and peripheral vascular beds. Sodium and water retention foster the occurrence of ascites, hydrothorax and hyponatremia. In kidneys, production of prostaglandins is unable to counterbalance the effects of vasoconstrictor systems, inducing a decline in renal blood flow and development of HRS [2,3].

Indications for TIPS related to portal hypertension

Variceal bleeding

Gastrointestinal bleeding is a common complication of portal hypertension, and its management is currently well defined by Baveno VI recommendations (Fig. 1) [1]. This protocol combines antibiotic prophylaxis, vasoactive drugs for up to five days (terlipressin, somatostatin, octreotide) and endoscopic therapy according to the origin of bleeding: endoscopic band ligation (EBL) for acute esophageal variceal bleeding and tissue adhesion glue injection (N-butyl-cyanoacrylate) for gastric varices and gastro-esophageal varices type 2 that extend beyond the cardia. TIPS may be indicated for uncontrolled bleeding despite adequate medical and endoscopic therapy (salvage TIPS), but also as secondary prophylaxis in selected patients at high risk of rebleeding (early TIPS). Moreover, TIPS can be proposed for patients with recurrent variceal bleeding despite adequate

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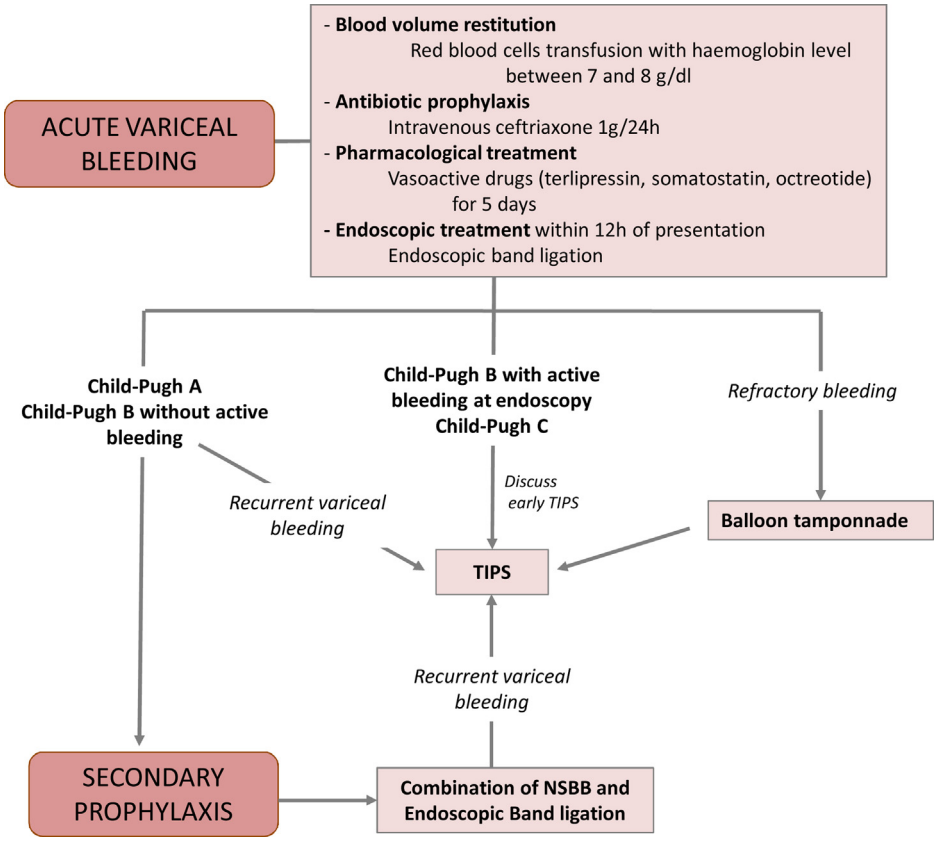

Figure 1 Management of varices due to portal hypertension in cirrhotic patients. Figure sums up the main recommendations of the Baveno VI consensus concerning treatment of varices in cirrhotic patients with portal hypertension. NSSB: non selective beta blockers.

secondary prophylaxis by EBL and beta-blockers (Fig. 1). Data available in the literature mainly included patients with esophageal varices bleeding. Nevertheless, several retrospective studies suggested that, for the same indications, a similar benefit was observed after TIPS for gastric variceal bleeding [4–6]. To date, no data on a potential impact of TIPS in primary prophylaxis for esophageal or gastric variceal bleeding is available, and currently, TIPS is not recommended in this situation [1].

Salvage TIPS

In the 1990s, patients with acute bleeding secondary to portal hypertension received endoscopic treatment with sclerotherapy in association with vasoactive drugs, allowing hemorrhage control in 80-90% of cases [7–11]. In patients with persistent bleeding despite optimal medical and endoscopic treatment, the prognosis was poor, with a mortality rate of over 90% in Child-Pugh B and C patients [12]. In this context, standard treatment was the use of balloon tamponade as a bridge treatment, followed by surgery (i.e. esophageal transection or portosystemic diversion) [13,14]. These surgical treatments were effective in decreasing portal hypertension, but were associated with high mortality (ranging from 50% to 90%) [15–17]. Moreover, subsequent liver transplantation (LT) was more difficult to perform because of anatomical changes induced by the surgery [17]. In order to improve the outcome of these patients, a percutaneous technique of portosystemic shunt, referred to as TIPS, was then developed and described for the first time in animal models by Rosch et al. in 1969 [18]. Colapinto et al. performed the first clinical trial in humans in 1982 [19], and the first study on salvage TIPS was published in 1993 [20]. In that study, emergency TIPS was associated with immediate control of bleeding in all 20 patients who received uncovered TIPS, while 30% later had early bleeding recurrence in the first 5 days, and 10% had delayed bleeding due to recurrence of portal hypertension secondary to occlusion or TIPS stenosis (the main complication of uncovered stents). Forty-day mortality was 60%; among the 12 patients with Child-Pugh C score at inclusion, only 1 was alive at the end of follow-up. Main causes of death were liver failure and sepsis; no deaths were related to recurrent bleeding [20]. Subsequently, new retrospective single-center cohort studies (19 to 144 patients included) primarily using uncovered stents were published (Table 1) [20–32]. Thirty-day mortality varied between 10.5% and 42% according to the study [21–25,27–30], and bleeding recurrence was reported in 11 to 25% of patients [20–22,24–27,29–32]. Leading causes of death were hepatic, renal or multivisceral failure and sepsis, particularly pneumonitis [20–32]. Predictors of mortality were identified, i.e. use of balloon tamponade, orotracheal intubation and intensive care unit (ICU) stay, presence of hepatic encephalopathy (HE) or ascites, use of catecholamines, presence of sepsis, prothrombin time (PT), bilirubin, albumin, ALT, leukocytes, platelets and serum creatinine levels prior to insertion of TIPS [23–32].

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Table 1 Retrospective studies of salvage TIPS for variceal bleeding.

Reference	Number of patients	Type of stent	Child-Pugh score	Median follow-up	Mortality rates	Bleeding recurrence	Encephalopathy	Predictive factors (before TIPS) of death in multivariate analysis
Mc Cormick et al. BJS Open 1994 [20]	20	Uncovered	Child-Pugh A (5%), B (35%) and C (60%)	10 months	60% at 40 days	10%	MD	MD
Le Moine et al. Scand J Gastroenterol 1994 [21]	24	Uncovered	Child-Pugh A (12%), B (52%) and C (36%)	5 months	17% at 30 days	25%	17%	MD
Jalan et al. Am J Gastroenterol 1995 [22]	19	Uncovered	MD	MD	42% at 30 days	16%	25%	MD
Rubin et al. Am J Gastroenterol 1995 [23]	49	Uncovered	MD	8,4 months	39% at 30 days	MD	MD	PT, bilirubin, albumin, ALAT Orotracheal intubation Vasopressin, balloon tamponade Child-Pugh and APACHE II score
Sanyal et al. Gastroenterology 1996 [24]	30	Uncovered	Child-Pugh A (3%), B (23%) and C (73%)	30,7 months	37% at 30 days 40% at 45 days	13%	27%	Orotracheal intubation Encephalopathy grade IV
Banares et al. Am J Gastroenterol 1998 [25]	56	Uncovered	Child-Pugh A (19%), B(39%) and C (41%)	MD	28% at 30 days	14%	MD	Encephalopathy Ascites Albumin
Patch et al. J Hepatol 1998 [26]	54	Uncovered	Child-Pugh A (9%), B (37%) and C (54%)	5,7 months	48% at 45 days	20%	MD	Ascites Leucocytes, platelets, PT, creatinine Orotracheal intubation
Azoulay et al. J Hepatol 2001 [27]	58	Uncovered	Median Child-Pugh score: 10,6 ± 2	16 months	29% at 30 days 35% at 60 days	7%	MD	Sepsis Vasoactive drugs Balloon tamponade
Tzeng et al. Korean J Radiol 2009 [28]	107	Uncovered	MD	12 months	28% at 30 days 35% at 60 days	MD	MD	Child-Pugh score > C11 -MELD > 20

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Table 1 (*Continued*)

Reference	Number of patients	Type of stent	Child-Pugh score	Median follow-up	Mortality rates	Bleeding recurrence	Encephalopathy	Predictive factors (before TIPS) of death in multivariate analysis
Gazerra et al. Radiol Med 2012 [29]	85	Uncovered	MD	MD	26% at 30 days	7.3%	15.8%	Child-Pugh C score Creatinine, PT
Casadaban et al. Ann Hepatol 2015 [30]	101	Uncovered (40%)	Child-Pugh A (2%), B (46%) and C (52%)	MD	31% at 30 days	21%	MD	MELD score Alcoholic cirrhosis
Maimone et al. Dig Dis Sci 2018 [31]	144	Uncovered (56%)	Child-Pugh A (8%), B (38%) and C (54%)	117 days	36% at 45 days	29%	MD	Child-Pugh score MELD score Length of intensive care unit stay before TIPS Ascites
Zhu et al. J Gastrointestin Surg 2019 [32]	57	Uncovered (5.3%)	Child-Pugh A (9%), B (62%) and C (29%)	17.3 months	10.5% at 45 days	20%	33.3%	Orotracheal intubation and intensive care unit stay

MD: missing data; PT: prothrombin time; TIPS: transjugular intrahepatic shunt.

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Clinico-biological scoring systems associated with mortality were Child-Pugh score, APACHE II and model for end-stage liver disease (MELD) [23,28]. As these studies mainly involved uncovered stents and sclerotherapy, new series are needed to evaluate the outcome of patients in the area of EBL, covered stents and resuscitation measures in cirrhotic patients.

Use of salvage TIPS is currently recommended in cases of persistent bleeding and severe rebleeding during the first five days after combined pharmacological and endoscopic therapy for esophageal varices and/or gastro-esophageal varices according to the Baveno VI consensus workshop [1]. Balloon tamponade or, more recently, the esophageal stent, can be used as a bridge to TIPS in refractory variceal bleeding [33].

Early TIPS in patients with high risk of bleeding recurrence

In case of acute variceal bleeding, some predictive factors of failure to control bleeding and mortality were identified as, for example, increased portal pressure and severity of underlying liver disease, suggesting that more effective therapy could be suitable for selected patients [34—43].

Monescillo et al. studied 52 patients considered at high risk of bleeding recurrence due to HVPG $\geq$ 20 mmHg. These patients were randomized into two groups (TIPS placement within the first 24 h of the bleeding episode versus no TIPS in addition to somatostatin plus sclerotherapy as standard of care). Six-week (11 versus 31%, $P = 0.02$) and one-year (31 versus 65%, $P = 0.01$) mortality were significantly lower in the group treated with TIPS [44].

The concept of early-TIPS was then proposed by Garcia-Pagan et al. in 2010 in a multicenter randomized controlled trial (RCT) involving 63 patients at high risk of bleeding recurrence (defined as Child-Pugh B with active bleeding at endoscopy and Child-Pugh C) randomized in two groups (medical treatment, EBL and covered TIPS within the first 72 h of the bleeding episode versus medical treatment and EBL alone). In the group that underwent TIPS placement, only one patient presented bleeding recurrence, compared to 14 patients in the group without TIPS (3 versus 45%, $P = 0.001$). Overall survival at one year was higher in the early TIPS group than in the control group (86 versus 61%, $P < 0.001$). It is noteworthy that Child-Pugh C patients included in this study were at Child-Pugh C13 maximum without severe renal failure [45]. Following this RCT, beneficial effects of use of early TIPS in high-risk patients were confirmed in various observational studies, especially in Child-Pugh C patients [46—50]. Some controversies remain regarding Child-Pugh B patients with active bleeding; in fact, the study of Hernandez-Gea et al. did not show improvement in survival with early TIPS in this specific population of patients [50]. Nevertheless, in a real-life study conducted at 58 centers in France, only 22 of 326 eligible high-risk patients underwent early TIPS placement (6.7%). This low rate was explained by the lack of access to the TIPS procedure in several centers, or because their physicians did not believe in the benefit of early TIPS placement for these patients [49]. The same trend was observed in a recent multicenter international observational study. Among 671 patients who presented early-TIPS placement criteria without TIPS contraindications, only 66 received early TIPS treatment (10%). However, the 1-year mortality rate was significantly lower in the group of Child-Pugh C patients treated with TIPS (22%) compared to that treated with endoscopic and medical treatment only (47%, $P = 0.002$) [50].

Consequently, in light of these results, and according to the Baveno VI consensus, early-covered TIPS within 72 h (ideally < 24 h) must be considered in patients at high risk of treatment failure (Child-Pugh class C < 14 points or Child-Pugh class B with active bleeding) after successful pharmacological and endoscopic therapy for esophageal varices and/or gastro-esophageal varices [1]. Nevertheless, further studies on the role of early TIPS in patients with severe liver failure (Child-Pugh C14 or more), or with renal failure, are warranted.

Secondary prophylaxis

Use of TIPS may also be proposed as secondary prophylaxis after bleeding control. Indeed, despite application of optimal medical and endoscopic treatments, some patients will present rebleeding. A meta-analysis published in 2008 that included 12 RCT showed a significant decrease in variceal rebleeding (OR = 0.32, 95% CI [0.24—0.43], $P < 0.00001$) and death due to rebleeding (OR = 0.35, 95% CI [0.18—0.67], $P = 0.002$) after TIPS placement in secondary prophylaxis, compared to EBL or sclerotherapy alone [51]. Later, two RCT analyzed the impact of covered TIPS after a first episode of variceal bleeding, by comparing TIPS placement to EBL associated with medical treatment (beta-blockers) in unselected Child-Pugh A to C patients [52,53]. Lower rebleeding rates were observed in the two studies in patients treated by TIPS (0 versus 29%, $P = 0.001$ for Holster et al. [52] and 7 versus 26%, $P = 0.002$ for Sauerbruch et al. [53]). However, no differences in terms of survival were observed, and TIPS was associated with higher rates of HE (35 versus 14% at 1 year, $P = 0.035$ for Holster et al. [52] and 18 versus 8% at 2 years, $P = 0.05$, for Sauerbruch et al. [53]). Similar data were reported in secondary prophylaxis following gastro-esophageal variceal bleeding in Child-Pugh A to C, and bleeding recurrence was less frequent without impacting mortality [4—6].

TIPS in patients with portal vein thrombosis

Portal vein thrombosis (PVT) is a common complication of cirrhosis, due to the hypercoagulable state, static portal blood flow and endothelial injury. The incidence of PVT may vary from 10 to 23% in patients with cirrhosis, and can lead to variceal bleeding even in Child-Pugh A patients [54,55].

Secondary prophylaxis after variceal bleeding

Secondary prophylaxis in cirrhotic patients with PVT usually consists of EBL combined with non-selective beta-blockers and, when necessary, anticoagulation when confronted with increased risk of rebleeding. PVT has been associated with higher risk of variceal relapse and rebleeding in patients who underwent EBL. In two recent RCT in which patients with cirrhosis, PVT and a history of variceal bleeding (49 patients with 94% of Child-Pugh A-B for Lv et al. [56], 73 patients with 67% of Child-Pugh A-B for Luo et al. [57]) were randomly assigned 1:1 to the TIPS group or EBL plus

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propranolol group in association with anticoagulation, TIPS was associated with a lower variceal rebleeding rate (25% versus 50% at 2 years for Lv et al. [56] and 22%, versus 57% at 2 years, $P = 0.002$ for Luo et al. [57]) and a higher portal recanalization rate (95% versus 70%, $P = 0.03$ for Lv et al. [56] and 65% versus 19%, for Luo et al. [57]). No statistically significant difference was observed in survival (75% versus 84%, $P = 0.31$ for Lv et al. [56] and 83% versus 57.2%, $P = 0.23$ for Luo et al. [57]), nor in the occurrence of HE between the 2 groups. Interestingly, similar results were observed in cases of cavernous transformation of the portal vein, with lower rates of rebleeding but without improving survival, in patients who underwent TIPS placement compared to EBL plus propranolol [58]. Consequently, in patients with cirrhosis and PVT, TIPS is a satisfactory alternative for preventing variceal rebleeding and improving PVT recanalization; however, future studies addressing optimal selection criteria for TIPS in this population are needed.

Portal vein thrombosis persistent despite anticoagulation

TIPS placement has also been associated with regression/disappearance of pre-existing portal thrombosis and could be used for PVT recanalization allowing successful liver transplantation. In 70 patients with PVT (thrombosis occupying over 50% of light in 56% of patients) who underwent TIPS for portal hypertension complications (refractory ascites, hydrothorax and variceal bleeding), 57% showed complete regression of thrombosis, 30% partial regression, and only 13% showed no improvement. None of these patients received thrombolysis or anticoagulation in pre- or postprocedures. In that study, predictors of a complete response included the presence of recent thrombosis, non-extensive or incomplete thrombosis and the absence of esophageal varices. Only two patients presented thrombotic recurrence during follow-up [59]. In the study of Thornburg et al., 55 out of 61 patients with PVT (56% of fully occlusive PVT) maintained successful recanalization during the 19.2 months of follow-up, and 24 of them underwent successful LT with physiologic porto-portal anastomosis [60]. In patients with complete chronic portal vein thrombosis or cavernoma, the classical technique of TIPS insertion is often difficult or impossible to carry out. However, a new radiological approach that includes TIPS following portal vein recanalization using trans-splenic access was shown to be a safe and effective option for these patients [60,61].

Ascites and hydrothorax

Refractory ascites

Refractory ascites is a common complication of cirrhosis associated with a poor prognosis (50% survival at one year) [62]. For these patients, LT should always be considered; unfortunately, patients have frequent contraindications such as comorbidities. Moreover, patients with refractory ascites frequently have low MELD scores that may delay accessibility to LT, with high mortality on waiting lists. In such situations, TIPS would appear to be a satisfactory alternative treatment. Several RCT compared uncovered TIPS to large-volume paracentesis (LVP) [63–68] (Table 2). In those studies, TIPS was associated with a significant reduction in ascites recurrence and paracentesis, but also with a higher rate of HE and TIPS dysfunction. However, its impact on survival remains controversial, as shown by the different meta-analyses available [69–73]. Indeed, some studies did not consider transplant-free survival, and most studies used uncovered stents. New data on transplant-free survival and the occurrence of HE using covered TIPS are needed. Interestingly, some series showed that TIPS in cases of refractory ascites was associated with an increase in muscle mass and a decrease in fat mass, suggesting a positive impact on the nutritional status of patients prior to LT [74–76].

Recurrent ascites

Recurrent ascites refers to patient with ascites who have not reached the stage of refractory ascites defined by ''ascites that cannot be mobilized or the early recurrence of ascites after LVP, which cannot be satisfactorily prevented by medical therapy'' [77]. Recently, Bureau et al. conducted a multicentric RCT in 62 patients with recurrent ascites (Child-Pugh score <12 and serum creatinine < 250 μmol/L) using a covered stent (29 treated by covered TIPS and 33 by LVP and albumin). At one year, transplant-free survival was increased in the covered-TIPS group compared to LVP associated with albumin (93% versus 52%, $P = 0.003$). No significant difference in the occurrence of HE was observed between the two groups. During follow-up, a higher proportion of the LVP group presented portal-hypertension-related bleeding (18% versus 0%, $P = 0.01$) and hernia-related complications (18% versus 0%, $P = 0.01$) compared to the covered-TIPS group [78].

Hepatic hydrothorax

Cirrhosis is also associated with the occurrence of pleural ascites (hepatic hydrothorax) in 0.4 to 12.2% of patients. Hepatic hydrothorax is unilateral in most cases, and is frequently localized in the right lung (80%) [79]. Standard treatment includes diuretics and thoracentesis. To date, no RCT exists comparing standard treatment to TIPS, and published series were retrospective, and limited by the small numbers of patients analyzed. Improvement, along with a reduced need for thoracentesis, was observed in 40–75% of patients treated by TIPS after a median follow-up of 10 months; mortality at one month was 5 to 30% and a MELD score < 15 was associated with better survival [80–86]. Despite weak evidence, TIPS might be proposed to patients with refractory hepatic hydrothorax and a low MELD score but, like refractory ascites, LT should be considered in case of refractory hydrothorax, especially if liver function worsens after the procedure [77].

Hepatorenal syndrome (HRS)

HRS is a functional kidney injury explained by a decrease in renal blood flow with histologically normal kidneys, occurring in patients with decompensated cirrhosis. No specific diagnostic biomarkers have been validated, and diagnosis is currently based on the conjunction of several criteria:

- exclusion of other causes of renal impairment;
- no improvement after diuretic withdrawal and volume expansion with albumin and;
- advanced liver failure [77,86].

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Table 2 Randomized controlled trial of TIPS for refractory and recurrent ascites compared to large volume paracentesis.

Reference	Number of patients	Median follow-up	Survival	Hepatic encephalopathy	Ascites recurrence
Refractory ascites					
Lebrec D, et al. J Hepatol 2006 [63] (uncovered stent)	25 patients 17 Child-Pugh B 8 Child-Pugh C 13 randomized for TIPS 12 randomized for LVP	MD	2 year survival 29% in TIPS group 60% in LVP group ($P = 0.03$)	23% in TIPS group 0% in LVP group	73% in TIPS group 82% in LVP group (P = NS)
Rossle M, et al. NEJM 2000 [64] (uncovered stent)	60 patients 42 Child-Pugh B 18 Child-Pugh C 29 randomized for TIPS 31 randomized for LVP	10 months	2 year TFS 58% in TIPS group 32% in LVP group	58% in TIPS group 48% in LVP group (P = NS)	21% in TIPS group 76% in LVP group ($P = 0.006$)
Ginès P, et al. Gastroenterology 2002 [63] (uncovered stent)	70 patients 28 Child-Pugh B 42 Child-Pugh C 35 randomized for TIPS 35 randomized for LVP	10 months	2 year TFS 26% in TIPS group 30% in LVP group ($p = 0.51$)	77% in TIPS group 66% in LVP group ($P = 0.29$)	49% in TIPS group 83% in LVP group ($P = 0.003$)
Sanyal AJ, et al. Gastroenterology 2003 [66] (uncovered stent)	109 patients 52 randomized for TIPS 57 randomized for LVP	MD	Median TFS 20 months in TIPS group 12 months in LVP group ($P = 0.77$)	38% in TIPS group 21% in LVP group ($P = 0.058$)	42% in TIPS group 84% in LVP group ($P < 0.001$)
Salerno F, et al. Hepatology 2004 [67] (uncovered stent)	66 patients 16 Child-Pugh B 50 Child-Pugh C 33 randomized for TIPS 33 randomized for LVP	18 months	2 year TFS 59% in TIPS group 29% in LVP group ($P = 0.021$)	61% in TIPS group 39% in LVP group (P = NS)	39% in TIPS group 97% in LVP group ($P < 0.001$)
Narahara Y, et al. J Gastroenterol 2011 [68] (uncovered stent)	60 patients 40 Child-Pugh B 20 Child-Pugh C 30 randomized for TIPS 30 randomized for LVP	28 months	2 year TFS 64% in TIPS group 35% in LVP group ($P < 0.005$)	20% in TIPS group 5% in LVP group ($P < 0.001$)	33% in TIPS group 73% in LVP group ($P < 0.005$)
Recurrent ascites					
Bureau C, et al. Gastroenterology 2017 [78] (covered stent)	62 patients 41 Child-Pugh B 21 Child-Pugh C 29 randomized for TIPS 33 randomized for LVP	12 months	1 year TFS 93% in TIPS group 52% in LVP group ($P = 0.003$)	34% in TIPS group 33% in LVP group (P = NS)	At 1 year 1 in TIPS group 10 in LVP group ($P < 0.001$)

LVP: large volume paracentesis; MD: missing data; TFS: transplant-free survival; TIPS: transjugular intrahepatic shunt

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Type 1 HRS is a rapidly progressive acute kidney injury of less than two weeks, and is often associated with precipitating factors. Type 2 HRS evolves slowly over several months, usually in patients with refractory ascites. Median survival times of HRS-1 and HRS-2 are about 2 weeks and 4-6 months, respectively. A combination of vasoconstrictor therapy by terlipressin and albumin expansion is the first-line treatment for HRS-1, but LT remains the best therapy for HRS-1 and HRS-2 [77,87]. Use of TIPS as a treatment for HRS was proposed following the observation of improvement in renal function in patients who received TIPS for refractory ascites. However, no RCT has investigated the role of TIPS for this indication, and only retrospective studies are currently available.

Type 1 SHR

One of the first studies reporting the impact of TIPS on type 1 HRS described 10 patients who responded to a combination of albumin, midodrine and octreotide, with a decrease in creatinine levels < 133 μmol/L for at least 3 days. TIPS was performed in 5 of these patients, resulting in improved renal function persistent at one year in 4 of them [88]. Another study demonstrated improvement in renal function in six of seven patients with type 1 HRS treated by TIPS [89]. Testino et al. performed TIPS in nine patients with type 1 HRS and acute alcohol-related hepatitis; this resulted in decreased serum creatinine (5.2 ± 0.9 mg/dL to 1.6 ± 0.6 mg/dL by 30 days) and blood urea nitrogen and increased urine output [90]. However, many patients with type 1 SHR also have severe liver failure, contraindicating TIPS, and only LT remains possible in most of these patients [76,86].

Type 2 SHR

Improvement in renal function has been observed in patients with type 2 HRS and refractory ascites treated by TIPS while awaiting LT. Consequently, it could be used as a bridge to transplantation in type 2 HRS patients with refractory ascites by improving renal function before transplantation [91—94]. In a recent meta-analysis that included 9 studies, 1-year survival rates were 47% in type 1 HRS and 64% in type 2 HRS after TIPS [95]. Overall, LT may be considered in all patients with HRS and, due to the limited data available, no strong recommendations exist concerning TIPS in patients with HRS type 1 or 2 [77,87].

Use of TIPS prior to extrahepatic surgery in patients with cirrhosis

Portal hypertension patients undergoing extrahepatic abdominal surgery are at high risk of complications such as liver failure, ascites, bacterial infection and peri-operative bleeding, with a mortality rate ranging from 10 to 57% [96]. TIPS before surgery was proposed so as to reduce the degree of portal hypertension. To date, few studies have evaluated pre-operative TIPS for extrahepatic abdominal surgery in the setting of portal hypertension. The available observational studies on extrahepatic surgery considered only a limited number of patients, without a control group [97—101]. Two retrospective controlled studies were performed comparing outcome of cirrhotic patients who underwent TIPS prior to abdominal surgery with cirrhotic patients without TIPS. No significant difference was observed in post-operative complications, 1-month or 1-year mortality. However, patients who underwent TIPS placement presented higher Child-Pugh scores, and PSPG was not measured in all subjects in the control group; thus, we cannot eliminate a difference in the severity of portal hypertension between the 2 groups [102,103]. Due to the lack of strong data, we cannot conclude that TIPS reduces morbidity or mortality after abdominal surgery. Further studies are needed to decipher the role of TIPS so as to increase the feasibility of surgery.

Complications and related contraindications

Complications related to creation of a portal systemic shunt

Liver failure

Due to a decrease in liver perfusion secondary to creation of a portal systemic shunt and portal flow diversion, liver failure may rapidly occur after TIPS, and emergency recalibration of TIPS might be considered [104,105]. Consequently, the possibility of LT should be discussed before each TIPS procedure.

Since TIPS may increase risk of liver failure, it is essential to carefully select patients. In various studies, hyponatremia, serum concentration of bilirubin, creatinine and prothrombin time, as well as pre-TIPS encephalopathy, were associated with higher mortality [106—114], and the MELD score was better than the Child-Pugh score in predicting 3-month survival of patients undergoing TIPS [114]. Current American Association for the study of liver diseases (AASLD) guidelines recommend that TIPS be placed only in the absence of other options if MELD is higher than 15—18 or serum bilirubin > 4 mg/dL [115]. In case of refractory ascites, the combination of total bilirubin over 50 μmol/L with a platelet count below 75,000/mm^3 was also associated with increased mortality in patients with refractory ascites treated by TIPS [116]. The European Association for the Study of the Liver (EASL) suggests eventual use of TIPS in refractory ascites in the absence of severe liver failure (serum bilirubin > 5 mg/dL, INR ≥ 2, Child-Pugh score > 11, current HE ≥ grade 2 or chronic HE) [77]. In patients with severe hepatocellular insufficiency, LT should be considered as first-line treatment. However, in case of refractory variceal bleeding, risk of liver failure after TIPS must be counterbalanced by the absence of alternative therapeutic treatments and high risk of early death without treatment [1].

Hepatic encephalopathy

EH is the most frequent complication related to the creation of a portal systemic shunt; it occurs in about 10 to 50% of patients, and is of great concern to physicians [115,117].

Nevertheless, as exposed in this review, TIPS placement remains the best option for treating numerous complications of decompensated cirrhosis. Moreover, when cirrhosis is decompensated, the natural history of the disease will be impaired by HE, even in the absence of TIPS placement. Predisposing factors in HE have been identified, such as

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past history of HE, minimal HE, sarcopenia, high creatinine levels, low serum sodium value, age > 60 years and high Child-Pugh score [118—120].

Nevertheless, HE is not an absolute contraindication for TIPS placement, and the risk/benefit balance should be discussed in each situation. In urgent situations such as acute variceal bleeding, HE or a history of HE does not appear to be a contraindication; indeed, treatment of life-threatening complications remains the priority. In non-urgent situation, TIPS placement is contraindicated when HE is uncontrollable [115]. Previous spontaneous episodes of HE without a triggering factor, or episodes that required oro-tracheal intubation and mechanical ventilation, are frequently considered as a contra-indication to TIPS. Nevertheless, strong heterogeneity in patient selection was observed regarding HE. Indeed, in most studies, excluded patients presented a recurrent history of HE or a history of overt HE, without distinguishing the number of episodes or whether these outbreaks were related to a triggering factor. Recently, it has been shown that use of a covered stent compared to a bare stent reduces the risk of developing HE as well as the diameter of the stent [121,122,105].

To prevent the occurrence of HE, one RCT compared a placebo versus lactulose versus rifaximin administered within the first month after TIPS placement in 75 patients, but no difference in HE was observed between the different groups (respectively, 32%, 36% and 32%, $P = 0.97$) [123]. Other methods have been studied, such as L-ornithine-L-aspartate or albumin perfusion but they did not reduce overt HE occurrence [124,125]. To date, there is no evidence for use of prophylaxis. In case of overt HE after TIPS placement, medical treatment consists of lactulose as a first line and rifaximin in association with lactulose as a second line. In case of failure of medical treatment, recalibration of TIPS (reduction in diameter) by interventional radiology should be performed. If symptoms persist, complete occlusion of the shunt should be considered [126]. However, a reduction in diameter or occlusion of the shunt might increase the risk of recurrence of complications of portal hypertension. Finally, liver transplantation should be considered in case of persistent HE.

Heart failure

Pre-existing systolic or diastolic dysfunction may lead to the occurrence of acute pulmonary edema after TIPS insertion. Selection of patients via screening of systolic and diastolic dysfunction using cardiac ultrasonography is helpful in reducing the occurrence of this complication. Severe systolic dysfunction (ejection fraction < 40—50%) contraindicates TIPS due to risk of acute pulmonary edema. In the case of echocardiographic pulmonary systolic arterial pressure PAPs > 45—50 mmHg, right heart catheterization should be performed in order to accurately diagnose the presence of pulmonary hypertension (defined by mean pulmonary pressure over 25 mmHg). This would confirm primary pulmonary portal hypertension (pre-capillary pulmonary hypertension classified as low, moderate or severe) and exclude post-capillary pulmonary hypertension [115].

Diastolic dysfunction as a contraindication for TIPS is more controversial. An $E/A \leq 1$ (ratio allowing detection of cardiac diastolic dysfunction with E: maximum speed of rapid protodiastolic filling and A: maximum filling speed due to auricular contraction in telediastole) was associated with excess mortality after TIPS insertion (HR = 4.7, 95% CI: 1.1—20.2; $P = 0.035$) [127], but only 7% of deaths after TIPS were due to cardiac failure in patients with $E/A \leq 1$, while 46% of deaths were secondary to liver failure. In another study, 22 patients with an E/A ratio greater than 1 were alive one year after TIPS, while six of the ten patients with an $E/A \leq 1$ had died, and the presence of diastolic dysfunction was an independent predictor of mortality (RR = 8.9, 95% CI: 1.9—41.5, p = 0.005) [128]. Nevertheless, these observations have been recently questioned by the fact that few or no patients with $E/A \leq 1$ at echocardiography develop cardiac failure after TIPS [129,130]. Consequently, the E/A ratio does not seem to be the most accurate parameter for adequately predicting cardiac failure in TIPS candidates; it might be considered as a hallmark of more advanced chronic liver disease rather than as a parameter of risk for cardiac-related complications after TIPS. Additional studies are needed.

Complications related to the stent

Other complications, related to the stent itself, may be observed. These include rapid occurrence of thrombosis after TIPS placement, or even several weeks or months later. Stenosis is a later complication also diagnosed by ultrasound. The occurrence of thrombosis or stenosis of TIPS can lead to the reappearance of portal hypertension and its complications, but the development of covered stents has reduced this type of stent-related complication. Anticoagulation can be discussed for patients with PVT, particularly in case of superior mesenteric vein thrombus (associated with recanalization failure), but is not mandatory before the procedure [131]. Infections have been described in up to 20% of patients following the procedure, with rare occurrence of intraluminal septic thrombosis of TIPS in 1.3% of cases. Although antibiotic prophylaxis is currently not formally recommended, it is often practiced [115,132—134]. Overall, uncontrolled sepsis (such as uncontrolled bacteremia or spontaneous bacterial peritonitis) is a contraindication in a non-urgent indication such as refractory ascites, but should not be an absolute contraindication when confronted with a life-threatening situation such as uncontrolled variceal bleeding.

Complications related to the TIPS procedure

The TIPS procedure exposes patients to complications that include liver hematoma and hemoperitoneum (1 to 2% of procedures), but also hemobilia (due to accidental creation of a fistula between arterial or venous branches and the biliary tree). Consequently, unrelieved biliary obstruction and multiple hepatic cysts are contraindications for the TIPS procedure. However, a small hepatocellular carcinoma lying outside the TIPS path does not constitute a contraindication to TIPS. Conversely, advanced hepatocellular carcinoma is an absolute contraindication because of risk of bleeding during TIPS insertion, risk of tumor seeding and limited survival in patients with advanced HCC [115]. Systematic assessment of coagulation before the procedure should be performed,

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but the threshold value for transfusing platelet concentrates and plasma is currently unknown in this situation.

Conclusion

Improvement in radiological techniques, use of covered stents and more accurate selection of patients have improved results of TIPS in treatment of portal hypertension. For variceal bleeding, TIPS is currently validated in refractory bleeding and in prevention of bleeding in patients at high risk of rebleeding (Child-Pugh B with active hemorrhage at endoscopy and Child-Pugh C patients). However, accessibility of early TIPS must be more satisfactorily implemented in clinical practice. Several unmet needs require additional investigation, including the role of TIPS in treatment of HRS and in preparation for abdominal surgery. Moreover, the high rate of encephalopathy after TIPS warrants further studies aimed at identifying prophylactic strategies and novel curative approaches. Finally, liver transplantation should be discussed in each patient for whom TIPS is under consideration.

Disclosure of interest

The authors declare that they have no competing interest.

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