

# Are TIPS tops in the treatment of portal hypertension? A review on the use and misuse of transjugular intrahepatic portosystemic shunts

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RK Sterling, AJ Sanyal. Are TIPS tops in the treatment of portal hypertension? A review on the use and misuse of transjugular intrahepatic portosystemic shunts. *Can J Gastroenterol* 2000;14(Suppl D):122D-128D. Complications of portal hypertension are the Achilles heel of end-stage liver disease. Although initially developed in the 1960s, transjugular intrahepatic portosystemic shunts (TIPS) have recently gained popularity for decompressing the portal vein in patients with portal hypertension. The main indications for TIPS are the treatment of variceal hemorrhage unresponsive to endoscopic treatment and refractory ascites. Although several other applications for TIPS have been reported, they have not been tested in controlled trials. TIPS are not appropriate as initial therapy for variceal hemorrhage and ascites. Due to the virtually universal development of TIPS stenosis in the majority of patients, careful monitoring of stent patency is required. Several complications of TIPS are recognized, some of which are potentially fatal. Consequently, careful patient selection for TIPS is of paramount importance. Until further clinical trials become available, TIPS should be considered as a therapeutic option for the treatment of refractory variceal hemorrhage and refractory ascites in selected patients.

**Key Words:** Ascites; Portal hypertension; Transjugular intrahepatic portosystemic shunts; Variceal hemorrhage

## Les shunts portosystémiques transjugulaires intrahépatiques conviennent-ils au traitement de l'hypertension portale? Revue de leur utilisation à bon ou à mauvais escient.

**RÉSUMÉ :** Les complications de l'hypertension portale sont le talon d'Achille de l'insuffisance hépatique terminale. Bien que mis au point dès les années 1960, les shunts portosystémiques transjugulaires intrahépatiques (SPTI) ont récemment gagné en popularité pour la décompression de la veine porte chez les patients qui souffrent d'hypertension portale. Les principales indications des SPTI sont le traitement de l'hémorragie variqueuse qui ne répond pas aux manœuvres endoscopiques et l'ascite rebelle. Bien que plusieurs autres applications des SPTI aient été signalées, elles n'ont pas fait l'objet d'essais contrôlés. Les SPTI ne conviennent pas d'emblée aux hémorragies variqueuses et à l'ascite. En raison de leur sténose quasi-inévitable chez la majorité des patients, il faut surveiller étroitement la perméabilité des SPTI. Plusieurs complications des SPTI sont connues; certaines sont fatales. Par conséquent il faut sans contredit procéder à une sélection attentive des patients candidats à un SPTI. Tant qu'on ne disposera pas d'autres essais cliniques, les SPTI doivent être envisagés comme option thérapeutique pour le traitement des hémorragies variqueuses et de l'ascite rebelles, chez des patients triés sur le volet.

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Complications from portal hypertension are the major cause of morbidity and mortality in patients with end-stage liver disease. Treatment of recurrent portal hypertensive bleeding or refractory ascites has been limited to surgical shunts to decompress the portal system. Transjugular intrahepatic portosystemic shunts (TIPS) are a major addition to the therapeutic armamentarium against portal hypertension. TIPS are created by making an intrahepatic tract between the hepatic and portal vein using angiographic techniques via a transjugular approach, resulting in a low-resistance, side to side portosystemic shunt. TIPS do not need to be created under general anesthesia nor do they require major surgery and, therefore, have become popular in clinical practice. However, the expanding use of TIPS has also led to its misuse in some circumstances, sometimes with dire consequences for the patient. The present article reviews the accepted indications and contraindications for TIPS, the spectrum of complications associated with TIPS and the natural history of portal hypertension following the creation of TIPS.

### CLINICAL APPLICATIONS FOR TIPS

TIPS are primarily used to treat the principal consequences of portal hypertension – variceal hemorrhage and ascites (Table 1). Approximately one-third of patients with varices experience active variceal hemorrhage. Bleeding is often severe and, in approximately 25% of patients, may rapidly lead to exsanguination without specific intervention (1). Those with Child class C cirrhosis and actively spurting varices are most likely to continue to bleed despite therapy, with at least 50% requiring additional urgent life-saving intervention to stop the hemorrhage (2). After the bleeding is stopped, if left untreated, hemorrhage recurs in more than 70% of individuals (3). This risk is greatest in the first 48 h after the initial bleeding stops and gradually subsides thereafter over the next six weeks (4). Patients aged 60 years or older with large varices, renal failure and severe initial bleeding defined by a hemoglobin concentration of less than 8 g/dL at admission are particularly at risk for early rebleeding. All deaths that occur within six weeks of an episode of active hemorrhage are considered to be bleeding-related deaths (5). Causes of early mortality include severe initial hemorrhage, recurrent bleeding, progressive liver failure and hepatic encephalopathy despite cessation of bleeding, and complications of the bleed such as infections, aspiration pneumonia and renal failure.

The goals of treatment of active variceal hemorrhage are to stop initial bleeding quickly, prevent recurrent bleeding and bleeding-related complications, and minimize treatment-associated morbidity and mortality. Endoscopic sclerotherapy or band ligation can be performed at the bedside, achieve hemostasis in 80% to 90% of subjects (6-8), decrease early rebleeding and improve short term survival. Pharmacological treatment is equally (9) or somewhat less effective (7) but more widely available and can be started in the emergency room. Consequently, endoscopic and/or pharmacological treatment are considered first-line therapy for

**TABLE 1**  
**Clinical applications for transjugular intrahepatic portosystemic shunts**

Accepted indications (established in controlled trials)
Active variceal hemorrhage despite emergency endoscopic and/or pharmacological treatment
Recurrent variceal hemorrhage despite adequate endoscopic treatment
Potential indications (efficacy proven but not adequately compared with that of existing therapies)
Bleeding isolated gastric fundic varices
Refractory ascites
Experimental indications (efficacy not established in large scale trials)
Bleeding portal gastropathy
Budd-Chiari syndrome
Veno-occlusive disease
Hepatorenal syndrome
Hepatic hydrothorax
Bleeding ectopic varices
Protein-losing enteropathy due to portal hypertension

active variceal hemorrhage. The creation of TIPS involves moving an unstable patient to the angiography suite and often cannot be done immediately. Moreover, it is associated with a long list of complications (10). Therefore, TIPS cannot be considered first-line treatment of active variceal hemorrhage from esophageal varices.

Approximately 10% to 20% of patients fail to stop bleeding with endoscopic and/or pharmacological treatment (6-8,11). Some patients rebleed in the first few days after the index bleed stops. A second attempt to control hemorrhage with endoscopic treatment is sometimes effective and is often recommended (12). However, if two attempts to control active hemorrhage fail, the risk of mortality rises exponentially (13-15). It is important to differentiate failure of endoscopic treatment for variceal hemorrhage from complications of endoscopic therapy (ie, sclerotherapy-induced ulcers) with respect to rebleeding because further treatment options may differ. We consider the recurrence of variceal hemorrhage, despite at least two sessions of endoscopic treatment performed no more than two weeks apart, to be failure of endoscopic treatment. While emergency surgery is extremely effective in stopping hemorrhage and preventing rebleeding, it is associated with a mortality rate of approximately 50% (13,16,17) due to liver failure and complications of surgery, despite achievement of effective hemostasis. Patients with severe hemorrhage, tense ascites, deep coma, aspiration pneumonia, renal failure or sepsis are at highest risk (greater than 90%) of dying after emergency surgery (16,18). Therefore, it has been recommended that such patients should not undergo operation (16).

In initial uncontrolled studies (19,20), TIPS was shown to stop effectively variceal hemorrhage that was refractory to endoscopic treatment. One study focused on the role of TIPS in patients who were actively bleeding and who were consid-

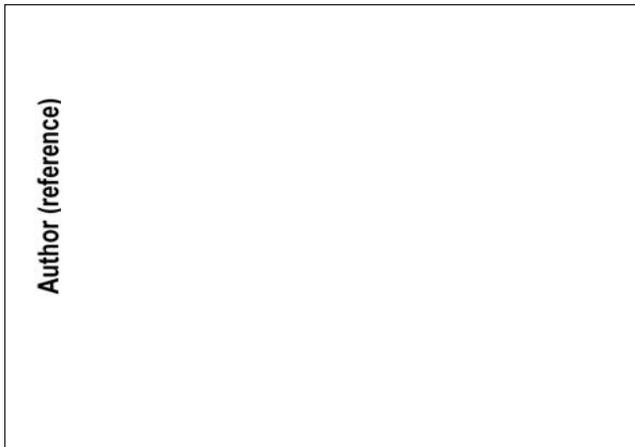


Figure 1) Comparison of transjugular intrahepatic portosystemic shunts (TIPS) and endoscopic sclerotherapy (EST) for the prevention of recurrent variceal hemorrhage. Effect on rebleeding

ered to be at high risk of dying after emergency surgery (21). In this trial of a subset of patients with an expected survival of approximately 10% (18), TIPS were successfully placed in 29 of 30 patients, and hemostasis was achieved in all patients, with a six-week rate of survival of 60% (21). In those without pulmonary aspiration, a survival rate of 90% was obtained at six weeks. These data have been corroborated by other investigators (22-25). Consequently, careful attention should be given to airway protection, with elective intubation. Unfortunately, once multiorgan failure develops, the majority of patients die, regardless of treatment (26). Therefore, TIPS should be considered early in the treatment of patients who fail endoscopic and medical therapy before the onset of complications such as aspiration, sepsis or renal failure. Based on available data, TIPS can be recommended for uncontrolled esophageal variceal hemorrhage that is unresponsive to emergent endoscopic and/or pharmacological treatment in patients who are poor risk candidates for urgent surgery.

The role of TIPS in the management of active hemorrhage not controlled by first-line endoscopic and or pharmacological therapy in patients who are otherwise good surgical candidates (Child's class A cirrhosis and absence of complications of bleeding) is controversial. A single clinical trial comparing TIPS with small diameter prosthetic H-graft (27) is difficult to interpret because of the high rate of rebleeding in the group who received TIPS compared with that reported in the literature. Large scale, multicentre trials are needed to answer this question. Until then, local expertise will dictate the optimal choice of therapy for these patients.

Several randomized, clinical trials comparing TIPS with endoscopic treatment for the prevention of rebleeding have been published (28-31). The individual trials are difficult to compare because of the varying patient populations, treatments and study designs. Despite this heterogeneity, rebleeding rates were reduced in patients undergoing TIPS compared with rebleeding rates in those undergoing sclerotherapy in most (29-31) but not all (28) studies (Figure 1).

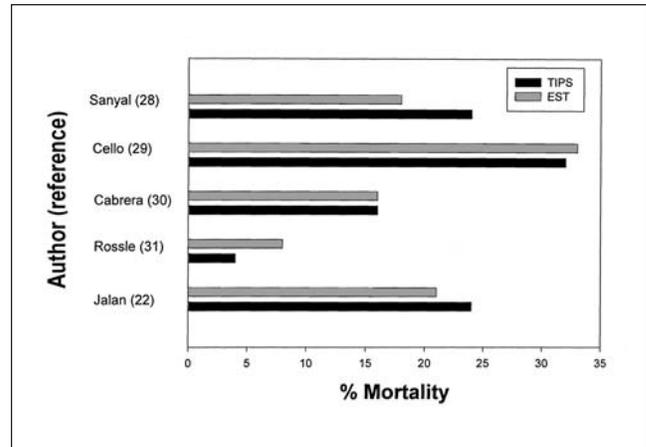


Figure 2) Comparison of transjugular intrahepatic portosystemic shunts (TIPS) and endoscopic sclerotherapy (EST) for the prevention of recurrent variceal hemorrhage. Effect on mortality

The discrepancy in the latter study is due to the relatively lower rebleeding rate in patients undergoing sclerotherapy rather than to a higher rebleeding rate in the TIPS arm (28). The superiority of TIPS for preventing rebleeding did not, however, translate into improved survival. Virtually all studies found a higher rate of mortality in patients undergoing TIPS (Figure 2). The risk of encephalopathy was also significantly higher in patients undergoing TIPS. Advanced age, liver failure, shunt diameter and history of encephalopathy before receiving TIPS were risk factors for worsening encephalopathy after receiving TIPS (32,33). Therefore, TIPS cannot be recommended as first-line therapy over endoscopic treatment for the prevention of recurrent variceal hemorrhage.

TIPS are appropriate therapy for bleeding esophageal varices in patients who fail endoscopic and/or medical management. They may be used as an alternative to surgical shunts, especially in those who are poor candidates for urgent surgery. In patients with decompensated cirrhosis who are otherwise appropriate candidates, TIPS are particularly useful as a bridge to liver transplantation.

The response of bleeding gastric varices to endoscopic treatment depends on their location. Gastric varices, in continuity with esophageal varices along the lesser curvature, respond to endoscopic therapy in the same manner as esophageal varices (34). However, patients with bleeding from gastric varices – in continuity with esophageal varices along the greater curve, or in isolation in the fundus or elsewhere in the stomach – do not respond as well to endoscopic treatment. Isolated gastric varices in the fundus of the stomach are of special interest because they are often associated with spontaneous collaterals from the splenic vein, which feeds the varices and eventually drains into the left renal vein (35). In patients with spontaneous collaterals, hemorrhage often occurs at lower portal pressures than those with esophageal varices (36).

The initial treatment of bleeding fundic varices is pharmacological. Endoscopic treatment is often ineffective and

sometimes harmful. Clinical trials have shown that TIPS can effectively lower portal pressures and stop hemorrhage from bleeding gastric fundal varices (21,24). However, because of spontaneous splenorenal collaterals in some patients, flow through the collateral veins and varices often persist after TIPS, even when an adequate shunt is created (35). Therefore, where surgical expertise is available, surgical ligation of the splenorenal collateral vein and portal decompression are the definitive treatments of choice. When surgical expertise is unavailable or the patient is deemed to be too ill for surgery, TIPS may provide an effective, albeit short term treatment for bleeding gastric varices.

Several caveats must be remembered to obtain the best outcomes after TIPS. Because a 'window of opportunity' exists in each patient when salvage therapy is effective, candidates for TIPS must be identified in a timely manner. Needless to say, persisting with repeated endoscopic and medical attempts to stop bleeding may result in the development of sepsis, renal failure and pulmonary compromise. Once pulmonary aspiration occurs, mortality increases steeply (21,26). If active bleeding continues despite medical and endoscopic therapy, balloon tamponade can be used as a temporizing measure to allow the patient to be moved to the angiography suite for TIPS placement in a relatively stable condition. Finally, while embolization of the left gastric vein is often performed along with creation of the TIPS, it is rarely necessary (21), and adds both time and expense to the procedure. Embolization is recommended if bleeding persists despite successful portal decompression by TIPS.

Ascites is the most common complication of cirrhosis (37). Its development usually heralds a progressive deterioration in the patient's condition, with a 50% two-year survival rate (38). When ascites becomes refractory to medical management, the prognosis worsens further, and more than 50% of subjects die within six months (39). The majority of patients with mild to moderate ascites respond to sodium restriction, diuretics and occasional paracentesis. TIPS does not offer any significant advantage over standard treatment in such cases and, therefore, TIPS cannot be recommended as first-line therapy for mild to moderate ascites. When ascites becomes refractory to diuretics, the need for repeated large volume paracentesis increases. This is associated with more frequent hospitalizations, more patient discomfort, malnutrition and increased risks of other complications of cirrhosis such as spontaneous bacterial peritonitis. TIPS correct sinusoidal hypertension. Therefore, the creation of TIPS is a rational therapy for patients with refractory ascites.

Several uncontrolled series have evaluated the efficacy and safety of TIPS in patients with refractory ascites (40-45). Although these studies were not controlled and had differing definitions of refractoriness of ascites, they did show that ascites resolved or became amenable to medical management in 70% to 90% of patients after receiving TIPS. However, this improvement in ascites was offset by a failure to improve survival (41% to 90%) and the development of severe, and sometimes crippling, encephalopathy in 35% to 50% of patients after receiving TIPS. In two randomized, controlled

trials of TIPS compared with large volume paracentesis, patients who had TIPS had either lower (46) or similar (47) rates of survival compared with patients treated medically. Therefore, TIPS appear to be effective in improving ascites in some patients who are refractory to medical management. However, because of the high rates of encephalopathy and mortality, especially in patients with advanced liver disease (Child's class C), TIPS cannot be routinely recommended as therapy for patients with refractory ascites. In patients with preserved liver function, the recommendation for TIPS must be individualized, and it must be recognized that liver failure, encephalopathy and death may develop after the procedure.

There are several caveats when using TIPS for ascites. Severe ascites pushes the liver cephalad, making the angle of the TIPS needle catheter difficult to negotiate through the hepatic vein into the liver to access the portal vein. Consequently, it is recommended that large volume paracentesis be performed on the day before the procedure (48). The relatively ascites-free state induced by paracentesis also makes it easier for the patient to lie flat for the duration of the procedure. The degree of portal decompression required to achieve an ascites-free state is controversial. Although ascites should not form if the portosystemic gradient is less than 8 mmHg (49), it is difficult to achieve this gradient with a single stent 10 mm in diameter. While further decompression may be obtained by dilating the stent to 12 mm diameter, the benefits of a lower portosystemic gradient are offset by increasing rates and severity of encephalopathy. It is also worth noting that ascites resolved in most patients in published studies despite post-TIPS portosystemic pressure gradients of 10 to 14 mmHg. Therefore, we recommend that the initial shunt diameter not exceed 10 mm. Finally, it is important to remember that TIPS do not correct the salt-retentive state associated with ascites development. Consequently, sodium should be restricted. The need for diuretics often decreases after creation of TIPS. Therefore, careful monitoring is required to avoid dehydration and prerenal azotemia.

TIPS have been used in the treatment of additional severe complications of portal hypertension, including portal gastropathy, Budd-Chiari syndrome, veno-occlusive disease, hepatorenal syndrome, hepatic hydrothorax, bleeding ectopic varices, portal colopathy and protein-losing enteropathy due to portal hypertension (Table 1). However, because the efficacies of these complications of portal hypertension have not been established in large scale trials, the use of TIPS remains experimental in these conditions.

Although TIPS seem attractive for the treatment for many complications of portal hypertension, they are not a panacea. Although there are isolated anecdotal reports on the use of TIPS for the treatment of pulmonary hypertension and/or hepatopulmonary syndrome, the results are not predictable. Similarly, hypersplenism and thrombocytopenia associated with portal hypertension from cirrhosis do not correct after creation of TIPS. There are no controlled data on the use of TIPS for primary prophylaxis of variceal hemorrhage, in the treatment of prehepatic portal hypertension (ie, portal vein thrombosis) or in the treatment of portal hy-

**TABLE 2**  
**Causes of recurrent portal hypertension and bleeding after transjugular intrahepatic portosystemic shunts**

Continued esophageal variceal hemorrhage
Stent dysfunction
Stenosis
Thrombosis
Retraction
Chinking
Displacement
Hemobilia
Persistent gastric varices
Associated with spontaneous splenorenal collaterals
Associated with massive splenomegaly

**TABLE 3**  
**The importance of Doppler sonography is dependent on the flow cutoff value used**

Parameter	Sensitivity	Specificity
<50 cm/s	78	99
<70 cm/s	89	83
<80 cm/s	92	60
<100 cm/s	98	4

portal hypertension associated with polycystic liver disease or Caroli's disease. Therefore, TIPS should not be used in these situations.

**COMPLICATIONS AND NATURAL HISTORY FOLLOWING CREATION OF TIPS**

The appropriate use of TIPS involves not only identification of suitable patients for the procedure, but also management after its placement. If patients are followed long enough (34,50), recurrent portal hypertension occurs in most patients over time. The causes of recurrent portal hypertension (Table 2) include stenosis or thrombosis of the TIPS, stent chinking, retraction of the stent into the parenchymal tract and development of severe right-sided heart failure with reflection of systemic venous pressures into the portal tree. TIPS thrombosis occurs in up to 5% of cases and usually develops within days to weeks after placement (34). Although some advocate the use of anticoagulants routinely after creation of TIPS (51), the use of routine anticoagulation cannot be justified based on the clinical literature available.

The most important cause of recurrent portal hypertension after creation of TIPS is shunt stenosis (52), which develops in 50% to 60% of patients within six months and 70% to 90% of patients within one year. Shunt stenosis is responsible for 20% to 30% of rebleeding after creation of TIPS, and results from ingrowth of tissue from the surrounding liver into the TIPS to produce a pseudointimal lining that impinges on the shunt lumen and eventually occludes the

**TABLE 4**  
**Complications associated with transjugular intrahepatic portosystemic shunts (TIPS)**

Related to technique
Neck hematoma
Cardiac arrhythmia
Perihepatic hematoma
Rupture of liver capsule
Extrahepatic puncture of portal vein
Arteriportal fistula
Portobiliary fistula
Related to portosystemic shunting
Hepatic encephalopathy
Increased susceptibility to bacteremia
Liver failure
Unique complications
TIPS-associated hemolysis
TIPSitis (infection of stent)

TIPS (53). It is easily treated in most cases by dilation of the stenosis, with placement of additional stents to reinforce the dilated segment (34,50). While the ideal regimen for following patients with TIPS to assess shunt patency remains to be defined (54-57), two common ways include Doppler sonography performed at three- to six-month intervals and angiography at six- to 12-month intervals (34). The accuracy of Doppler sonography is dependent on several factors, including the experience of the ultrasonographer, location used for flow measurements (hepatic venous, midstent or portal vein side of the TIPS) and the cutoff value used to determine stenosis (Table 3) (58).

The correct use of TIPS also requires an appreciation of the spectrum of complications that can occur after creation of TIPS (Table 4). Complications are divided into those that are technique-related, those due to portosystemic shunting of blood away from functioning hepatocytes and unique complications that occur after creation of TIPS (10). Intraabdominal hemorrhage is the most important and potentially fatal complication that may occur during the procedure or shortly thereafter, and results from inadvertent puncture of the liver capsule at the hepatic vein or extrahepatic puncture of the portal vein. Portosystemic encephalopathy occurs in approximately 30% of patients after creation of TIPS and is related to increasing age of the patient, shunt diameter, advanced liver failure and prior history of encephalopathy. TIPS-induced liver failure leading to death has been reported without transplantation (59). Hemolysis occurs in 10% of patients after TIPS (60). Fortunately, it is usually mild and resolves spontaneously within eight to 12 weeks. Blood is shunted away from the remaining functioning portion of the liver, a major component of the reticuloendothelial system, after creation of TIPS. As a consequence, the patients has increased susceptibility to bacterial infections (61). Finally, as with any prosthetic de-

vice, infection of the stent (TIPSitis) has been reported (62).

### CONCLUSIONS

Are TIPS tops in the treatment of portal hypertension? Current recommendations based on available clinical trials support the use of TIPS in patients who fail endoscopic and pharmacological treatment for esophageal variceal bleeding (63). Attention to airway protection and temporary stabilization by balloon tamponade can facilitate the TIPS procedure and may improve survival. TIPS are also indicated for those with recurrent variceal hemorrhage despite at least two sessions of adequate endoscopic treatment. Data are controversial on the use of TIPS in the treatment of refractory ascites. TIPS are best reserved for patients who do not have advanced liver failure. It is not known whether TIPS

are better than conventional medical treatment for refractory ascites in patients with Child's class A or B cirrhosis. A large multicentre, international, randomized, prospective trial (North American Study for the Treatment of Refractory Ascites [NASTRA]) is underway to address this question. TIPS may be useful in selected patients with ectopic varices, Budd-Chiari syndrome, veno-occlusive disease or hepatorenal syndrome.

TIPS should not be used as an alternative for liver transplantation in patients with advanced hepatic decompensation (Child's class B and C). TIPS can, however, be particularly useful as a bridge to liver transplantation in selected patients with complications of portal hypertension. With careful patient selection and follow-up, TIPS will continue to play an important role in the treatment of portal hypertension.

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