Transjugular Intrahepatic Portosystemic Shunts (TIPS): A Decade Later

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Abstract
Since the introduction of transjugular intrahepatic portosystemic shunt (TIPS) 10 years ago, it has been used increasingly in the management of portal hypertension and its complications. TIPS is now considered the procedure of choice for management of refractory variceal bleeding. Its role in the management of refractory ascites, hepatic hydrothorax, hepatorenal syndrome, and hepatopulmonary syndrome still awaits further prospective studies. The two main complications of TIPS are hepatic encephalopathy and shunt malfunction. Generally, TIPS stenosis or occlusion is a major drawback requiring routine surveillance of TIPS with doppler ultrasound. Venography with balloon dilation of the stent or placement of serial or parallel stents may be required in some cases. Promising modalities of preventing TIPS malfunction (e.g., brachytherapy, covered stents, or anti-platelet derived growth factor) are currently being investigated.

Transjugular intrahepatic portosystemic shunt or TIPS is a percutaneously created shunt through the liver parenchyma connecting the right or left portal vein to one of the three main hepatic veins (See Fig. 1). A TIPS functions to decompress the portal circulation in patients with portal hypertension. The shunt functions in the same manner physiologically as a side-to-side surgical portacaval shunt. It is used increasingly in patients with portal hypertension to treat such complications as variceal bleeding, refractory ascites, and hepatic hydrothorax. This procedure has also been successfully used in the pediatric population. This explosion in the use of TIPS in patients with liver disease and portal hypertension can be attributed to two advantages it has over surgical shunts. TIPS placement can be accomplished without the use of general anesthesia and major abdominal operation, which is poorly tolerated by cirrhotic patients; furthermore, in experienced hands, TIPS does not alter the extrahepatic vascular anatomy in patients who are transplant candidates. TIPS has also been reported to improve quality of life.

FIG. 1. TIPS stent in place.
Portal hypertension is defined as a portal vein pressure that is greater than 10 mmHg (normal 5-10 mmHg) or a hepatic venous pressure gradient (HVPG) of >5 mmHg. Portal hypertension occurs because there is increased resistance to portal blood flow. Increased blood flow from splanchnic circulation also contributes to this increase in portal vein pressures. Complications of portal hypertension include variceal bleeding, ascites, hepatic hydrothorax, hepatopulmonary syndrome, hepatorenal syndrome, and hepatic encephalopathy. Except for hepatic encephalopathy, management for most of these complications has been focused on lowering portal vein pressures (or HVPG) that can be achieved by use of medications or by creation of surgical shunts. The advent of TIPS has offered an alternative to these traditional strategies. Optimal treatment of patients with portal hypertension will ultimately depend on the severity of liver disease and the transplant potential of the patient.

HISTORY

In 1969, Rosch et al. introduced a new method of percutaneously creating a shunt between the hepatic and portal veins to decompress the portal venous system (Fig. 2). They later reported the use of this technique in a larger group of animals using different types of stents to keep the tract open. Silastic or teflon tubing or silicone-coated coil springs were used to bridge the shunt through the liver parenchyma. The procedure was also performed on human cadavers. Migration of stents and shunt occlusion were problems encountered during the early phase of TIPS development. Balloon angioplasty used to create larger tract diameters was introduced in the 1970s. The first clinical application of TIPS was in a patient with variceal bleeding reported by Colapinto et al. in 1982. Balloon expandable stents came into use for the first time in 1985 in dogs with experimentally induced portal hypertension. They were able to achieve longer primary and primary-assisted patencies of up to 9 months. Self-expanding metallic stents were first reported in 1987 and the first clinical use of metallic stents was reported by Rossle et al. in 1989 using the Palmaz stent.

TECHNIQUE

Pre-TIPS Placement Preparation

A doppler ultrasound is performed to assess the size and patency of portal and hepatic venous systems. Intravenous antibiotics are given on call during the procedure. First generation cephalosporins are generally used although some radiologists prefer broad-spectrum antibiotics. Coagulopathy is very common in these patients and some authors recommend correction if platelets are <60,000 and international normalized ratio (INR) is >1.8. Paracentesis is performed in patients with tense ascites.

Procedure
The procedure is usually performed with conscious sedation. Patients who have massive bleeding and are hemodynamically unstable with a Blakemore tube in place require intubation and mechanical ventilation for better airway management. The right internal jugular vein approach is preferred because it provides a straight path into the infrahepatic inferior vena cava (IVC). Alternative approaches that can be used are right external jugular vein, left internal jugular vein, or femoral vein approach. Using the Seldinger technique, an angiographic catheter is advanced into the infrahepatic IVC and pressures are measured. The sheath is then advanced into the right hepatic vein and both free hepatic vein pressure and wedged hepatic vein pressure are measured. A wedged hepatic venogram is performed with either iodinated contrast or CO₂ for portal vein localization. Other methods of portal vein localization have been described. A puncture needle is then advanced to access the portal vein. Once puncture of the portal vein is achieved, the needle is removed and a guidewire is advanced to the superior mesenteric vein or splenic vein. Portal pressures are measured and a portal venogram is performed. An angioplasty balloon is advanced to dilate the transhepatic tract. A bridging expandable stent is deployed and then dilated to 8-12 mm. Parallel stents may be used. Embolization of varices can be done through the TIPS, especially in cases where dilation of the stent to 12 mm still does not reduce the portosystemic gradient to less than 12 mmHg or 20% below the baseline. An ultrasound is performed within 24 hours to assess patency of the stent.

CONTRAINDICATIONS AND INDICATIONS

Careful preprocedural evaluation must be performed in every patient referred for TIPS placement. In certain groups of patients, TIPS placement should not be attempted. The absolute and relative contraindications are listed in Table 1. There are other instances where TIPS seems to be a promising modality, but data to support the use of TIPS in these instances is still lacking. Clinicians who are making decisions regarding TIPS placement should take into consideration the expertise and facilities available locally. TIPS placement generally requires a multidisciplinary team consisting of hepatologists, hepatobiliary surgeons, and interventional radiologists. This review will discuss the evidence supporting the accepted and promising indications for TIPS at the present time.

### TABLE 1. Contraindications to TIPS placement

<table>
<thead>
<tr>
<th>Absolute</th>
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<tbody>
<tr>
<td>Right-sided heart failure</td>
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<tr>
<td>Polycystic liver disease</td>
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<tr>
<td>Severe hepatic failure, unless active variceal bleeding or fulminant Budd-Chiari syndrome was the inciting event</td>
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<tr>
<td>Cavernoous portal vein thrombosis</td>
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<tr>
<th>Relative</th>
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<tbody>
<tr>
<td>Active intrahepatic or systemic infection</td>
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<tr>
<td>Severe hepatic encephalopathy poorly controlled by medical therapy</td>
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<tr>
<td>Non-cavernomatous portal vein thrombosis</td>
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<tr>
<td>Biliary obstruction</td>
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TIPS, transjugular intrahepatic portosystemic shunt.
TABLE 2. Indications for TIPS placement

<table>
<thead>
<tr>
<th>Accepted</th>
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<tbody>
<tr>
<td>Acute variceal bleeding that cannot be successfully controlled with pharmacological and endoscopic treatment or are not amenable to endoscopic treatment (e.g., portal hypertensive gastropathy, gastric varices, or ectopic gastrointestinal varices)</td>
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<tr>
<td>Recurrent variceal bleeding in Child’s class C patients who are refractory or intolerant of conventional medical management including sclerotherapy and pharmacological therapy</td>
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<tr>
<th>Promising</th>
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<tr>
<td>Refractory ascites</td>
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<tr>
<td>Refractory hepatic hydrothorax</td>
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<tr>
<td>Hepatorenal syndrome</td>
</tr>
<tr>
<td>Budd-Chiari syndrome and veno-occlusive disease</td>
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<table>
<thead>
<tr>
<th>Not indicated</th>
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<tbody>
<tr>
<td>Initial therapy of acute variceal hemorrhage</td>
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<tr>
<td>Initial therapy to prevent recurrent variceal hemorrhage after a 1st variceal bleed</td>
</tr>
<tr>
<td>Prevention of recurrent variceal bleeding refractory to conventional treatment in Child’s class A or B patients</td>
</tr>
<tr>
<td>Prevention of 1st variceal bleed</td>
</tr>
<tr>
<td>Prior to liver transplantation to decrease intraoperative morbidity</td>
</tr>
<tr>
<td>Hepatopulmonary syndrome</td>
</tr>
</tbody>
</table>

TIPS, transjugular intrahepatic portosystemic shunt.

**VARICEAL BLEEDING AND TIPS**

One of the complications of portal hypertension is variceal bleeding. A hepatic venous pressure gradient or portosystemic gradient of >12 mmHg is generally regarded as the cut-off point for an increased likelihood for variceal bleeding; therefore, therapy is instituted with the goal of reducing this gradient to <12 mmHg or to at least 20% from the baseline HVPG. Management of variceal bleeding consists of three different phases: Prevention of the first variceal bleed (primary prophylaxis), management of active variceal bleed, and prevention of recurrent variceal bleed (secondary prophylaxis). TIPS, because of its favorable effects on portosystemic gradient, is used increasingly in variceal bleeding, specifically in the management of active variceal bleeding and in the secondary prophylaxis of variceal bleed.

**Uncontrolled Acute Variceal Bleed**

Currently, first line of management for acute variceal bleeding is endoscopic variceal band ligation or endoscopic sclerotherapy. Adjunctive management include vasopressin plus nitroglycerin, somatostatin, octreotide, or terlipressin. However, endoscopic therapy in combination with pharmacologic therapy fails to achieve hemostasis in 10%-20% of all cases. Standard therapy for medically and endoscopically uncontrolled acute variceal bleeding is balloon tamponade followed by either devascularization or surgical portosystemic shunting. However, both of these surgical interventions are associated with high mortality rates in the emergency setting. In addition, most of these patients are often considered unfit to undergo surgery. TIPS, because it is less invasive and non-operative, is used increasingly in these patients.

Six uncontrolled studies have been published that evaluated the efficacy of TIPS for acute variceal bleeding refractory to endoscopic management. One study compared TIPS to esophageal transection in a nonrandomized fashion.
TABLE 3. TIPS for active variceal bleeding refractory to endoscopic treatment

TIPS can be successfully placed in almost all patients with uncontrolled active variceal bleeding. Undetected portal vein thrombosis was the reason for technical failure in one study.32 In most studies, cessation of variceal bleeding was achieved in all patients with successful TIPS placement.31,32,35 It should be noted that a majority of patients who underwent TIPS in these studies had Child’s C cirrhosis (37%-73%).

The lack of randomized comparative trials between TIPS and surgery makes it difficult to make firm recommendations for patients who are good surgical candidates with uncontrolled active variceal bleeding. In the only study that compared TIPS with esophageal transection, significantly lower rebleeding and mortality rates were noted in the patients treated with TIPS.31 This study, however, was retrospective and the treatment groups were followed over different time periods.

TIPS has largely replaced surgery in patients who are poor surgical risks either because they have advanced liver disease (Child’s B and C cirrhosis) or have multiple other medical problems. Sanyal et al.32 reported complete hemostasis in all patients with successful TIPS placement (Table 3). Patients enrolled in this study were all deemed unfit to undergo surgical decompression.32

Prevention of Recurrent Variceal Bleeding

After a first episode of variceal bleed, there is a high risk of rebleeding. Current recommendations for the prevention of recurrent variceal bleeding after an initial episode of variceal bleeding include combination endoscopic and pharmacologic therapy.6,28,29 These interventions have been shown to decrease rebleeding and mortality rates 6,28 Endoscopic variceal band ligation (EVBL) was found to be more effective than endoscopic sclerotherapy (EST) in addition to having the advantage of requiring fewer sessions to variceal obliteration and having fewer complications related to the procedure.41 The advent of TIPS has provided another option in the armamentarium that clinicians have in the prevention of variceal rebleeding. In seven uncontrolled series of patients undergoing TIPS for variceal bleeding, technical success with TIPS placement was very high.42-48 Rebleeding rates were comparable to those achieved by surgical shunts and were better than EST.28,49

The role of TIPS vis a vis conventional treatment (EST or EVBL plus beta-blockers) in the prevention of variceal rebleeding has been investigated in 11 randomized controlled trials.50-60 The results from these studies are summarized in the Table 4.

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>Child C, %</th>
<th>Technical success, %</th>
<th>Initial hemostasis, %</th>
<th>Rebled, %</th>
<th>Survival (30-day), %</th>
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<tr>
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<td>73</td>
<td>97</td>
<td>100</td>
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</tbody>
</table>

*Only 4 patients actually underwent emergent salvage TIPS.
†With comparison group consisting of patients who underwent surgical decompression.
N/R, not reported; TIPS, transjugular intrahepatic portosystemic shunt.
TABLE 4. Randomized controlled trials comparing TIPS with conventional treatment (endoscopy with or without propranolol) in the prevention of variceal bleeding

Eight trials compared TIPS with EST and three compared TIPS with EVBL. All of the studies except one showed that TIPS decreases the variceal rebleeding rate compared with endoscopic treatment alone or in combination with propranolol (Fig. 3). One year survival rates in all studies except two are similar between patients treated with TIPS and those treated with endoscopy (Fig. 4). This is probably due to both the small sample sizes of the studies and the fact that these studies were designed with rebleeding and not mortality as an endpoint. In addition, a proportion of patients randomized to endoscopic treatment were crossed over to TIPS after endoscopic treatment failure. These patients probably survived because their death from variceal rebleeding was prevented by salvage TIPS; however, they are analyzed in an intention to treat fashion under the endoscopy treatment group.61 In the only study that showed a survival advantage for TIPS, patients who underwent EST and had variceal rebleeding died before undergoing salvage TIPS.57

The only study that did not show a difference in rebleeding in favor of TIPS had a very low variceal rebleeding rate in the patients treated with EST (2% vs. 50% in other studies). The time to randomization in this study was longer than that of the other ten trials. An important factor in determining rebleeding and survival outcomes in clinical trials on variceal bleeding is the time from the last variceal bleed to randomization.62 The longer time to randomization in this study may have influenced its outcomes as patients who were at higher risk of rebleeding may have already been excluded even before randomization.61 This point is supported by the findings of Merli et al. who found that the earlier treatment of patients after a bleed TIPS was more effective than compared with endoscopy in those treated much later after control of a variceal bleed.53

![FIG. 3. Rebleeding rates between TIPS and endoscopic therapy from the randomized controlled trials on the prevention of variceal rebleeding. * p < 0.05](image)

![FIG. 4. One-year survival of patients undergoing TIPS or endoscopic therapy from the randomized controlled trials on the prevention of variceal rebleeding. * p < 0.05](image)
New or worsening hepatic encephalopathy was seen in significantly more patients treated with TIPS than with EST or EVBL (Fig. 5). The incidence of new or worsened hepatic encephalopathy ranged from 16%-55% (Table 4). Most of these episodes were easily controlled by dietary protein restriction and lactulose. A few cases of medically refractory cases of hepatic encephalopathy required revision of the stent and placement of a smaller stent. TIPS malfunction was fairly common but was associated with the clinical consequence of variceal rebleeding in only a few cases. Variceal rebleeding, however, in the TIPS group was almost always related to either TIPS occlusion or stenosis.

These studies show that TIPS is more effective than conventional treatment for the prevention of variceal rebleeding. However, because (1) EST or EVBL is more widely available than TIPS, (2) hepatic encephalopathy is more common with TIPS, and (3) survival is not improved by TIPS, TIPS cannot be recommended over EST or EVBL as the first line of treatment in the prevention of variceal rebleeding. It is, however, a very attractive option in medically refractory recurrent variceal bleeding.

Prevention of Recurrent Variceal Bleeding Despite Adequate Pharmacologic and Endoscopic Treatment

Recurrent bleeding despite adequate pharmacologic and endoscopic treatment generally requires variceal decompression. TIPS has provided an alternative to surgical shunts in the treatment of these patients. Surgical shunts have been the preferred treatment in patients with relatively preserved liver function (Child-Pugh class A or B), mainly because they are less prone to occlusion or stenosis and are highly effective in the prevention of rebleeding. TIPS has largely supplanted surgical shunts in the more critically ill patients who are poor surgical risks.

There is only one randomized controlled trial that compares TIPS with surgical shunts in the management of recurrent variceal bleeding after failing nonoperative treatment. Forty patients underwent TIPS and forty underwent 8 mm H-graft portocaval shunt (HGPCS) placement. Results show that, with at least one year of follow-up, patients undergoing TIPS had more episodes of variceal rebleeding than those who receive HGPCS placement. The incidence of hepatic encephalopathy (HE) was similar in both groups. Mortality rate was not significantly different between treatment groups. There are, however, several issues with this study. (1) Randomization was done by pairs; therefore it is unclear if true randomization occurred. This may account for the significant difference in the number of patients undergoing "urgent" shunting (28% TIPS vs. 8% HGPCS, p < 0.05). (2) Follow-up was short, with a mean of one year. (3) The use of general anesthesia in all patients undergoing TIPS is unusual and raises the issue of the technical expertise of the interventional radiologists. (4) It is unclear from the study how long it took to randomize the patients from the last episode of variceal bleeding and how many previous variceal bleeding episodes the patients each group had. This study has not settled the issue of how variceal decompression should be achieved in medically refractory variceal bleeding, but it emphasizes the need for further studies in this area.

Currently, surgical decompression is recommended for medically refractory variceal bleeding in good surgical risk patients and in patients with preserved liver function (Child's class A or B). TIPS is the accepted treatment for those who are not surgical candidates and who have severe liver dysfunction (Child's class C). A multicenter study comparing distal splenorenal shunt with TIPS for medically refractory variceal bleeding in patients with well-preserved liver function is currently underway.

TIPS AND REFRACTORY ASCITES, HEPATIC HYDROTHORAX, AND HEPATORENAL SYNDROME

Refractory Ascites
In the large series of patients in whom TIPS was performed for variceal bleeding, a substantial number of patients had either a concomitant resolution of their ascites or had improved ascites control. This is likely due to the fact that TIPS acts as a side-to-side portacaval shunt and, by reducing sinusoidal hypertension, has a positive impact on ascites. The use of TIPS in all patient with ascites, however, is not warranted because of the morbidity associated with TIPS, e.g., encephalopathy, shunt malfunction, or potential worsening of liver function. Its use in refractory ascites (defined as ascites that cannot be mobilized or the recurrence of which cannot be satisfactorily prevented by medical therapy) deserves consideration.

The improvement in ascites after TIPS placement is paralleled by an increased natriuresis. Natriuresis occurs because TIPS placement decreases plasma levels of renin and aldosterone and increases creatinine clearance. These humoral and renal hemodynamic changes are thought to occur in association with the reduction in sinusoidal pressure after TIPS placement. In fact, the serum ascites-albumin gradient narrows shortly after TIPS placement.

TIPS has been evaluated in refractory ascites in several uncontrolled series of patients. These studies, summarized in Table 5, illustrate three important points regarding the role of TIPS in refractory ascites.

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
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†With comparison group consisting of patients who underwent surgical devascularization.
N/R, not reported; TIPS, transjugular intrahepatic portosystemic shunt.

1. TIPS can be effective in refractory ascites, eliminating the need for paracentesis in 50%-92% of patients or decreasing the required doses of diuretics.

2. TIPS is associated with significant rate of hepatic encephalopathy (12%-50%).

3. TIPS for refractory ascites does not improve survival. Survival rates at one year (33%-76%) remain essentially similar to the rates reported for repeated paracentesis and peritoneovenous shunts for refractory ascites.

There were no consistent clinical or biochemical predictors of response of refractory ascites to TIPS prior to TIPS; however, nonresponders were generally older, had more severe liver disease, or had organic renal disease. It has been suggested that a low pre-TIPS shunt fraction that increases after TIPS placement may predict good response of refractory ascites to TIPS.

To date, there are only two small randomized controlled trials comparing TIPS and repeated paracentesis for refractory ascites—one published and another in abstract form. Lebrec et al. found that TIPS was more effective than paracentesis in managing refractory ascites in a group consisting of patients with Child's class B and C cirrhosis. This result was duplicated by Ochs et al. Survival rates were similar in Child's class B patients who underwent either TIPS or paracentesis. Child's class C patients who received TIPS, however, had a significantly lower survival rate than their counterparts who had repeated paracentesis. Child's C patients also had a poorer survival rate in one other series that used TIPS to treat refractory ascites.

Based on the available data, TIPS is a reasonable alternative to conventional treatment in patients with refractory ascites but requires critical deliberation in patients with Child's C cirrhosis, advanced age, or renal failure. Larger randomized, controlled trials are needed to identify subgroups of patients with refractory ascites that respond best to TIPS. A multicenter trial comparing TIPS and large volume paracentesis is currently underway.

**Refractory Hepatic Hydrothorax**

Hepatic hydrothorax is considered refractory when thoracentesis needs to be performed at least weekly in spite of adequate medical therapy (e.g., sodium restriction and diuretics). There are few safe and effective therapeutic options for patients with refractory hepatic hydrothorax. The only definitive treatment is liver transplantation. Although combined chemical pleurodesis and peritoneovenous shunts can control hydrothorax, their associated
complications preclude their use in many patients. TIPS has been reported to cause resolution of hepatic hydrothorax with or without accompanying ascites.

The use of TIPS in the treatment of refractory hepatic hydrothorax has been studied in three small uncontrolled series. Resolution of hepatic hydrothorax or fewer requirements for thoracentesis was seen in 58%-100% of patients. The mortality rate, however, remained high at 27%-58%. Although one study found improvement in the Child-Pugh score after TIPS in a group of patients with mainly alcoholic cirrhosis, another study showed that patients who had TIPS placed for refractory hepatic hydrothorax either died or required transplantation on follow-up. Although TIPS can be effective in the management of refractory hepatic hydrothorax, its use may have to be limited to patients already on the transplant list. There were no pre-TIPS predictors of a good response to TIPS for hepatic hydrothorax.

Hepatorenal Syndrome

Liver transplantation is the only available treatment for patients with hepatorenal syndrome (HRS). TIPS, with its beneficial effects on renal hemodynamics and neurohumoral systems, has been used in a limited number of patients with both Type I (rapid decline in renal function) and Type II (fairly stable renal dysfunction) hepatorenal syndrome. Patients with HRS who have TIPS placed have increased natriuresis with improvement in creatinine clearance and urine output. They have been reported to survive for up to 470 days. Although some patients experienced worsening renal function immediately after TIPS secondary to the dye load, this was only transient as their renal function eventually improved on follow-up. The use of CO2 for wedged venography may mitigate this problem with dye toxicity. There is a need to undertake studies that will evaluate the use of TIPS in a randomized and controlled fashion in the treatment of hepatorenal syndrome. The lack of effective alternative treatment modalities and the almost universally fatal outcome of HRS without intervention make TIPS an attractive option in the treatment of HRS in nontransplant candidates and as a bridge to liver transplantation in those who are.

TIPS AND BUDD-CHIARI SYNDROME AND VENO-OCLUSIVE DISEASE

The goal of treatment in Budd-Chiari syndrome is liver decompression to prevent further hepatocyte necrosis and deterioration of liver function from sinusoidal congestion. The hemodynamic goal in the treatment of Budd-Chiari syndrome, when there is ongoing necrosis, is to use the portal vein as the outflow tract from the sinusoids. The use of TIPS placement to bridge the portal vein and the intrahepatic vena cava or hepatic vein has been successfully performed in these patients. TIPS placement has been reported to decrease the sinusoidal pressure and reverse Budd-Chiari syndrome. Although Blum et al. found no benefit in two patients, TIPS has been known to improve liver function in patients with fulminant hepatic failure from Budd-Chiari syndrome and thus serve as a bridge to subsequent liver transplantation in these severely ill patients.

TIPS has also been used to treat complications of portal hypertension in patients with veno-occlusive disease, either as a complication of chemotherapy or bone marrow transplantation. TIPS was successfully placed in a series of six patients with veno-occlusive disease after bone marrow transplantation. There was no benefit seen in three patients as they died immediately after TIPS placement. Two patients had improvement but subsequently succumbed to multiorgan failure and recurrent lymphoma. Only one patient had sustained clinical improvement with a follow-up of 36 weeks.

OTHER USES FOR TIPS

TIPS has been used in a number of other conditions including hepatopulmonary syndrome, gastric varices, ectopic intestinal varices, stomal varices, and variceal bleeding in the setting of hepatocellular carcinoma. Due to the lack of extensive data, these are not discussed further.

COMPLICATIONS OF TIPS

TIPS placement has a reported procedure-related morbidity rate of 10% and a procedure-related mortality rate of 2%. There are many reported complications of TIPS. Table 6 outlines these complications categorized according to their severity and time of onset. The discussion of all of the complications is beyond the scope of this review and the reader is referred to two excellent reviews on TIPS complications. Emphasis will be given to a discussion of the two most common chronic complications of TIPS, namely shunt malfunction and hepatic encephalopathy.
### TABLE 6. Complications of TIPS

<table>
<thead>
<tr>
<th>Minor complications</th>
<th>Major complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Puncture site hematoma and/or pain; cardiac dysrhythmias; fever; reactions to contrast media; transient hemolytic anemia; fluoroscopy-induced radiodermatitis</td>
<td>Intraoperative hemorrhage; hemobilia; *cholangitis; cardiopulmonary failure from sudden hemodynamic changes; shunt thrombosis; stent dislodgment or migration; hepatic encephalopathy; progressive liver failure</td>
</tr>
<tr>
<td></td>
<td>Early</td>
</tr>
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<td>Infecive “endopatosis”—bacterial or fungal infection of TIPS; shunt stenosis; hepatic encephalopathy; portal vein thrombosis; progressive liver failure</td>
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**TIPS, transjugular intrahepatic portosystemic shunt.**

### TIPS AND HEPATIC ENCEPHALOPATHY

Hepatic encephalopathy is one of the long-term complications of TIPS placement. It is difficult to determine the true incidence of post-TIPS hepatic encephalopathy from the literature. This can be explained by a number of reasons. The definition of hepatic encephalopathy and the method of making the diagnosis of hepatic encephalopathy varies from study to study. Some authors report only new or worsened hepatic encephalopathy whereas others report all cases of hepatic encephalopathy after TIPS placement. Moreover, most patients are prophylactically placed on lactulose, a fact that can lead to underestimation of the true incidence of hepatic encephalopathy. The trials that compared TIPS with endoscopic treatment for the prevention of variceal bleeding showed an incidence of post-TIPS encephalopathy of 23%-55%, which was significantly higher than the incidence of HE after endoscopic treatment. Larger prospective series report an incidence of new or worsened hepatic encephalopathy of 13%-44%.

The pathogenesis of post-TIPS hepatic encephalopathy is multifactorial, mainly related to either decreased portal flow due to the diversion of portal flow through the TIPS and away from the liver or increased bioavailability of gut-derived toxins. Arterial ammonia was noted to increase significantly after TIPS placement and remained elevated despite improvement in hepatic encephalopathy. Although precipitating factors can be occasionally identified and hepatic encephalopathy reversed by their treatment, a majority of the episodes of hepatic encephalopathy occur without an identifiable precipitating factor. Post-TIPS hepatic encephalopathy has an onset early after TIPS placement and some authors have noted fewer episodes of hepatic encephalopathy on long-term follow-up. This late improvement in mental status may be the result of aggressive medical treatment, progressive shunt stenosis, or cerebral adaptation to shunted neurotoxins derived from the intestines.

A number of studies have tried to identify pre-TIPS factors that predict the onset of hepatic encephalopathy after TIPS placement. The most consistent finding has been the presence of pre-TIPS hepatic encephalopathy. Other factors identified are severity of liver disease, advanced age, nonalcoholic liver cirrhosis, low albumin, female gender, low post-TIPS portosystemic gradient, and pre-TIPS subclinical hepatic encephalopathy.

Precipitant-induced post-TIPS hepatic encephalopathy is easily managed by eliminating the precipitating factor. Protein restriction and lactulose are mainstays in the management of post-TIPS hepatic encephalopathy. Antibiotics such as vancomycin or metronidazole may be added if needed. In a minority of patients, the mental status changes are refractory to aggressive medical management. These patients may require shunt modification, in the form of shunt reduction or total shunt occlusion. Embolization of esophagogastric varices can be performed at the time of shunt revision. In patients with recurrent shunt dysfunction, refractory encephalopathy, or refractory bleeding, liver transplantation may be an option.

### TIPS MALFUNCTION
One of the main limitations of TIPS has been the high incidence of shunt malfunction. Shunt malfunction is often asymptomatic. It is associated with a clinical consequence in only about one-fourth of cases, either in the form of variceal rebleeding or recurrence of ascites. However, nearly all reported cases of recurrent variceal bleeding after TIPS have been associated with shunt malfunction.

Shunt malfunction is defined as symptomatic or asymptomatic occlusion or stenosis (>50% diameter narrowing) that should be associated with a portosystemic gradient greater than 12 mmHg. Some authors consider stenosis to be hemodynamically significant if the portosystemic gradient is greater than 15 mmHg or greater than a 20% increase from the immediate post-TIPS gradient if the portosystemic gradient is <15 mmHg. There is a wide range of shunt malfunction rates reported in the literature from 17%-50% within six months to 23%-87% within the first year. Differences in the definition of shunt malfunction, the manner in which surveillance is conducted, and the length and frequency of follow-up account for this wide variation in the reported rates of shunt malfunction. Saxon et al. have suggested that the guidelines for stent patency established for endovascular procedures be used in the studies that evaluate TIPS patency. Primary patency includes only TIPS that are patent without intervention. Primary assisted patency includes TIPS that are primarily patent and those that are patent after a stenosis has been revised. Patency does not include stents that have occluded. Secondary patency includes all patent stents even those that have occluded and been re-opened. Primary, primary assisted, and secondary patency rates from several large series on TIPS are presented in Table 7.

Shunt malfunction, either stenosis or occlusion, has been divided into early and delayed shunt malfunction based on the time of onset of the shunt malfunction. Early shunt malfunction occurs within 30 days of the TIPS procedure and is most likely due to thrombosis of the intraparenchymal tract of the TIPS. Technical errors, such as inadequate stent length and stent retraction, may lead to thrombosis, but most cases of early shunt malfunction remain unexplained. Bile duct injury and subsequent bile leak has been implicated as a cause of shunt thrombosis. Mucus in bile, not bile itself, is thought to be the thrombogenic factor. Other authors have advanced the idea that patients who develop shunt thrombosis have increased thrombogenicity.

Delayed shunt malfunction occurs after 30 days of TIPS procedure. Pseudointimal hyperplasia causing a narrowing or stenosis of the lumen of the shunt either at the hepatic venous end or within the parenchymal tract is the most common cause of delayed shunt malfunction. Hepatic vein stenosis, or Type 2 stenosis, is more common than parenchymal tract stenosis, or Type 1, stenosis in most studies. The pathogenesis of pseudointimal hyperplasia is not known, but the end result is exuberant myofibroblast proliferation and deposition of an extracellular matrix composed mostly of collagen. Factors that have been suggested to cause this exaggerated healing response include platelet aggregation with release of platelet derived growth factor, bile leak with mucin causing thrombosis which is later replaced by granulation tissue, and hemodynamic factors especially at the hepatic venous end.

TIPS Surveillance

Ultrasound has been the screening procedure of choice for TIPS patency. A baseline ultrasound is performed 24 hours after TIPS placement to assess patency, to establish baseline flow measurements, and to evaluate for possible procedural complications such as hematomas, hepatic infarction, or hemoperitoneum. Subsequent sonographic screening is suggested at six weeks, three months, six months, and every six months thereafter.

The absence of flow in the TIPS stent on ultrasound is very useful in detecting shunt thrombosis. Sonographic criteria that suggest hemodynamically significant TIPS stenosis include decreased mean portal flow velocity, decreased peak flow velocity in the midshunt, and reversal of flow direction in the intrahepatic portal vein branches from hepatofugal to hepatopetal.
The most important sonographic criteria for TIPS stenosis has been peak midshunt or intrastent velocity. A value of <50-60 cm/s has been quoted to predict hemodynamically significant stenosis with a sensitivity of 86%-100% and a specificity of 54%-98%. Two studies however showed that a peak midshunt velocity of <50-60 cm/s had a low sensitivity of 25%-35% indicating that it is a poor screening parameter for stenosis. A combination of two or several sonographic criteria may be the optimal method of screening for shunt stenosis. Casado et al. found a low sensitivity for single sonographic criteria with 42% for peak flow velocity <50 cm/s, 65% for reversal of intrahepatic blood flow, and 70% for mean portal flow velocity < 19 cm/s. A combination of at least two of these criteria results in a higher sensitivity of 91%.

Venography is the gold standard for the diagnosis of shunt occlusion or stenosis. This should be performed whenever a screening sonography suggests stenosis or whenever the patient has documented recurrence of variceal bleeding even in the face of a normal ultrasound study. Because we still do not have the optimal screening method and variceal rebleeding carries a significant mortality rate, venography is suggested by some authorities to be performed at six month intervals for at least three years.

The role of endoscopy in TIPS surveillance is not known. Sanyal et al. found that recurrence of varices on endoscopy after initial disappearance after TIPS is associated with recurrent portal hypertension in all cases and therefore needs venography. They also found that endoscopy was more sensitive in the detection of recurrent portal hypertension than ultrasound in the group of patients with documented initial disappearance of varices. Endoscopy should be the first test to determine the etiology of the gastrointestinal bleed and to institute endoscopic treatment if appropriate in a patient who presents with upper gastrointestinal bleeding and who has a TIPS in place.

Treatment of TIPS Malfunction

Once TIPS malfunction is detected, therapeutic interventional procedures can be performed at the time of the venogram. Recanalization may be attempted percutaneously in shunt thrombosis or a parallel stent may be placed if recanalization is not possible. For TIPS stenosis, either angioplasty or further stent placement may be performed. Surgical shunt is an option in those patients who cannot be corrected percutaneously.

Prevention of TIPS Malfunction

Anticoagulation with heparin or phenprocoumon and antplatelet therapy have not been shown to prevent thrombosis or to improve TIPS patency. Recently, Siegenerstetter et al. studied a platelet derived growth factor inhibitor (trapidil) in combination with ticlopidine given for six months and found a significantly reduced stenosis rate, specifically at the hepatic venous end at one year compared to those who did not receive the treatment. There was, however, a 20% dropout rate from the treatment group either from non-compliance or from side effects. This treatment is promising but requires further investigation.

The possible role of bile leak in the pathogenesis of TIPS malfunction has stimulated efforts to decrease the likelihood of bile leak with the use of "covered" stents. Covering the stents would prevent bile from getting into the lumen of the stent and has been shown in animals using polytetrafluoroethylene (PTFE)-covered stents to improve patency. The use of PTFE-covered stents in patients with recurrent TIPS stenosis have improved short-term patency rates. Long term follow-up of these patients is not available and the use of covered stents as the initial TIPS stents deployed to prevent shunt malfunction has not been evaluated.

Whatever the inciting event is for pseudointimal hyperplasia in TIPS stents, the end result is myofibroblastic proliferation and collagen deposition. This process is akin to neointimal proliferation in restenosis in coronary artery stenting. Brachytherapy has been shown to decrease neointimal proliferation in animal models of restenosis. Teirstein et al. have shown that brachytherapy after redilatation decreases restenosis in patients who have had prior coronary restenosis. Although a TIPS stent traverses a non-vascular tract, except at both ends, the similarity of the histology and pathogenesis of pseudointimal hyperplasia to that of neointimal hyperplasia in endovascular stents makes brachytherapy an attractive option in the prevention of stenosis or restenosis in TIPS. There is a need to study the application of brachytherapy in the prevention of TIPS malfunction from pseudointimal hyperplasia.

**SUMMARY**

Since its introduction ten years ago, TIPS has gone from being a novelty to being an important therapeutic modality of portal hypertension. It is the procedure of choice in refractory active variceal bleeding and refractory recurrent variceal bleeding in poor surgical risk patients. Its role in good surgical risk patients with refractory recurrent variceal bleeding still needs to be defined. The use of TIPS in the other complications of portal hypertension (e.g., prevention of recurrent variceal bleed after the index bleed, refractory ascites, hepatic hydrothorax, hepatorenal syndrome) remains to be determined and awaits further study. Hepatic encephalopathy is increased after TIPS placement but is easily controlled with medical therapy in most patients. Shunt malfunction is the main limitation...
of TIPS and is usually asymptomatic. However, recurrence of variceal bleeding in approximately 20% of patients and of ascites after TIPS placement is almost always associated with shunt malfunction. Intensive follow-up after TIPS placement is necessary for early detection of shunt malfunction and immediate intervention. Ultrasound is the current screening procedure of choice. Venography is the gold standard and should be performed every time a clinical event suggests recurrent portal hypertension (e.g., variceal bleeding or ascites). Research is urgently needed to find ways to prevent stenosis or occlusion of TIPS stents. Promising modalities include covered stents, anti-platelet derived growth factor, brachytherapy, or a combination of the above.

Acknowledgments: The authors thank Drs. J. Michael Henderson and Kevin Mullen for their thoughtful review of the manuscript.

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Key Words: Transjugular intrahepatic portosystemic shunt; Portal hypertension; Variceal bleeding; Shunt malfunction; Refractory ascites

**IMAGE GALLERY**

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