Transjugular Intrahepatic Portosystemic Shunt in the Management of Refractory Ascites

Guadalupe Garcia-Tsao, M.D.[1]

ABSTRACT

The purpose of this article is to describe the pathophysiological basis for the use of transjugular intrahepatic portosystemic shunt (TIPS) in patients with cirrhosis and refractory ascites, the short- and long-term hemodynamic, biochemical, and hormonal changes after TIPS, and the results of controlled trials of TIPS in cirrhotic patients with refractory ascites. TIPS placement is associated with normalization of sinusoidal pressure and a significant improvement in urinary sodium excretion that correlates with suppression of plasma renin activity (indicative of an improvement in effective arterial blood volume). Although effective in preventing the recurrence of ascites, the efficacy of TIPS is offset by an increase in the incidence of severe hepatic encephalopathy, a high incidence of shunt dysfunction, and a higher cost without an overall survival benefit, which should be reevaluated in light of polytetrafluoroethylene-covered stents. TIPS placement is currently indicated in selected cirrhotic patients with refractory ascites who require more than two to three large-volume paracenteses per month.

KEYWORDS: Refractory ascites, cirrhosis, transjugular intrahepatic portosystemic shunt, large-volume paracentesis

Objectives: Upon completion of this article, the reader should understand (1) the pathophysiological bases for the use of TIPS in refractory ascites, (2) its results in relation to other therapies, and (3) its limitations as well as current recommendations for the use of TIPS in patients with refractory ascites.

Accreditation: Tufts University School of Medicine (TUSM) is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Credit: TUSM designates this educational activity for a maximum of 1 Category 1 credit toward the AMA Physicians Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

PATHOPHYSIOLOGY OF CIRRHOTIC ASCITES

In cirrhosis, two main mechanisms are responsible for ascites formation: sinusoidal hypertension and sodium retention.

Sinusoidal Hypertension

Sinusoidal hypertension results from hepatic venous outflow block. In cirrhosis, this block is both structural, secondary to regenerative nodules and fibrosis, and functional, due to increased intrahepatic vascular tone and

Transjugular Intrahepatic Portosystemic Shunts: An Update; Editors in Chief, Brian Funaki, M.D., Peter R. Mueller, M.D.; Guest Editor, Hector Ferral, M.D. *Seminars in Interventional Radiology*, volume 22, number 4, 2005. Address for correspondence and reprint requests: Guadalupe Garcia-Tsao, M.D., Section of Digestive Diseases, Yale University School of Medicine, One Gilbert Street, TAC, Room #S241B, New Haven, CT 06510. [1]Professor of Medicine, Yale University School of Medicine, and VA-CT Healthcare System, New Haven, Connecticut. 0739-9529,p;2005,22,04,278,286, ftx,en;sir328x.

hyperresponsiveness to vasoconstrictors that, in cirrhotic rats with ascites, occurs mostly in the postsinusoidal area.[1] It has been shown that ascites is present only in patients in whom the hepatic venous pressure gradient (which reflects sinusoidal pressure) is above 12 mm Hg.[2,3] In fact, two recent studies show that the development of ascites is significantly lower in patients in whom the hepatic venous pressure gradient decreases either below 12 mm Hg or more than 20% from baseline values.[4,5]

Sodium Retention

The most likely explanation for sodium retention is a decrease in effective arterial blood volume secondary to splanchnic and peripheral vasodilatation that leads to the activation of sodium-retaining neurohumoral systems (renin-angiotensin and aldosterone) and plasma volume expansion.[6] Without replenishment of the intravascular space, that is, without plasma volume expansion, leakage of fluid into the peritoneal cavity would be a self-limited process.

REFRACTORY ASCITES AND RATIONALE FOR TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT USE

In the majority of cases, cirrhotic ascites responds to the use of diuretics, which act by increasing urinary sodium excretion, thereby producing a negative sodium balance. Refractory ascites, present in 10 to 20% of cirrhotic patients with ascites, assumes either diuretic-resistant ascites (ascites that is not eliminated even with maximal diuretic therapy) or diuretic-intractable ascites (ascites that is not eliminated because maximal doses of diuretics cannot be attained given the development of diuretic-induced complications such as hepatic encephalopathy, renal and/or electrolyte abnormalities).[7] In the majority of patients (80%), refractory ascites is of the diuretic-intractable type. The development of refractory ascites denotes a more advanced liver disease with further vasodilatation and activation of neurohumoral systems and a higher mortality.[8] Therefore, these patients should be considered for liver transplantation.

Large-volume paracentesis (LVP) is the most commonly used method to treat refractory ascites.[9] It is a local therapy that does not modify any of the mechanisms that lead to ascites formation. Therefore, recurrence of ascites is practically universal, unless there is an improvement in liver disease (e.g., resolution of alcoholic hepatitis). Additionally, LVP has been associated with the postparacentesis circulatory dysfunction, an entity defined by an increase in plasma renin activity, that leads to faster reaccumulation of ascites, a higher susceptibility to develop renal dysfunction, and a higher mortality.[10,11] The incidence of postparacentesis circulatory dysfunction is lowest (but not absent) when LVP is associated with the concomitant administration of intravenous albumin infusion and when quantities lower than 4 to 5 L are extracted.[10] Albumin infusion has the objective of increasing effective arterial volume but its effect is transient. The need for repeated procedures, requiring albumin infusion, increases the cost of LVP, potentially increasing its morbidity, and without a survival benefit.[12,13]

There is a need for better therapies for refractory ascites that should ideally act on the pathophysiological mechanisms that lead to ascites formation, namely sinusoidal hypertension and reduced effective arterial blood volume.

Surgical portosystemic shunts decrease the development of ascites.[14] Although an end-to-side portocaval shunt decreases ascites by decreasing blood flow into the sinusoids (thereby decreasing sinusoidal pressure) and by decompressing splanchnic capillaries, it can also lead to greater ascites formation, particularly in patients with advanced cirrhosis in whom the hepatic venous outflow block is such that the portal vein becomes the outflow tract. Conversely, the side-to-side portocaval shunt (and the mesocaval shunt), by connecting the side of the portal vein (or the mesenteric vein) to the low-pressure inferior vena cava, effectively decompresses not only the splanchnic capillaries but also the sinusoids.[15] When comparing end-to-side versus side-to-side portocaval shunts, both experimentally[16] and in cirrhotic patients,[15] side-to-side portocaval shunting results in less ascites formation and less ascites reaccumulation. However, given a high operative morbidity and mortality in this patient population and a high rate of severe hepatic encephalopathy,[17] the surgical side-to-side portocaval shunt is practically never used for the treatment of refractory ascites.

The transjugular intrahepatic portosystemic shunt (TIPS) is a nonsurgical procedure by which an intrahepatic artificial communication between the portal and the hepatic vein is created, effectively acting as a side-to-side portocaval shunt as it decompresses the hepatic sinusoids. Therefore TIPS should be as effective as a surgical side-to-side portocaval shunt in treating ascites without the morbidity and mortality associated with major surgery.

In addition to decompressing sinusoids, TIPS has theoretical advantages in the treatment of refractory ascites because by connecting the portal vein with a systemic vein, the blood volume that is sequestered in the splanchnic circulation is transferred to the systemic circulation, increasing effective arterial blood volume and sodium excretion.

By reversing the mechanisms responsible for the formation of ascites, TIPS should be effective not only in resolving ascites but also in preventing its recurrence, thereby constituting a more definitive treatment for

ascites than LVP + albumin and, by preventing other complications of portal hypertension and ascites, such as variceal hemorrhage, hepatorenal syndrome, and spontaneous bacterial peritonitis, it could have a beneficial effect on survival. On the other hand, TIPS has been shown to lead to the development of liver failure and/or hepatic encephalopathy as a result of the diversion of blood away from the liver and into the systemic circulation, and various randomized trials of TIPS for variceal hemorrhage have identified hepatic encephalopathy and shunt dysfunction as long-term complications of TIPS, with no survival benefit.[18]

EFFECTS OF TIPS ON HEMODYNAMICS AND SODIUM-RETAINING MECHANISMS IN CIRRHOTIC PATIENTS WITH REFRACTORY ASCITES

Immediately after TIPS, there is an increase in cardiac output and a decrease in systemic vascular resistance (already decreased in these patients), without significant changes in mean arterial pressure.[19,20] These changes persist for 2 weeks[21,22] to 1 month after TIPS,[19,20] but are no longer present 3 months or more after TIPS insertion.[19,20,22] The increase in cardiac index is most probably the result of an increase in venous return secondary to shunting of blood sequestered in the splanchnic circulation into the systemic circulation through the newly created shunt. The decrease in systemic vascular resistance is probably the result of increased flow secondary to the increase in cardiac index (as shear stress increases, the synthesis of vasodilators such as nitric oxide increases). The mean portosystemic pressure gradient (PPG) is significantly reduced compared with baseline up to 14 months after TIPS placement, although this effect appears to decrease progressively over time probably as a result of its progressive occlusion.[22]

Liver synthetic function deteriorates after TIPS, as evidenced by an increase in Child-Pugh score (CPS) from the first day to 1 month after TIPS,[19,20,22,23] however by 3 months post-TIPS, CPS has been shown to be similar to baseline,[22,24] and most studies show an improvement in CPS 7 to 14 months after TIPS placement,[22,24] probably as a result of resolution/improvement of ascites.

Despite an early deterioration in liver synthetic function and a worsening in the hyperdynamic circulatory state of cirrhosis (decreased systemic vascular resistance, increased cardiac index), urine sodium significantly increases as soon as 7 days[23] and definitely 1 month after TIPS,[20,21,25] persisting for up to 14 months.[22,24] The increase in urinary sodium correlates closely with a decrease in plasma renin activity.[19,20–25] Interestingly, one study shows that the increase in urinary sodium excretion occurs only in cirrhotic patients with ascites (particularly those with refractory ascites) but does not occur in those without ascites.[23] Of note, no significant differences in glomerular filtration rate, creatinine clearance, serum creatinine, or serum sodium are observed after TIPS placement in patients with refractory ascites.

TIPS FOR REFRACTORY ASCITES

Uncontrolled Trials

Ferral et al first reported in 1993 the efficacy of TIPS in the treatment of refractory ascites.[26] In this study, complete resolution of ascites was achieved in seven of 14 patients although two patients developed new encephalopathy, four patients developed shunt dysfunction, and eight patients died. Since then, four retrospective cohort studies and eight prospective cohort studies of TIPS in patients with refractory ascites in which patients have been followed for more than 6 months have been published.[27] Success in TIPS placement in these studies was essentially 100%. In one of the studies, technical failures occurred in 4/50 (8%) patients, three of whom had markedly shrunken liver positioned high in the abdomen.

In uncontrolled studies, TIPS has been shown to eliminate and/or make ascites easier to manage in the majority of patients (70%); however, diuretics are still required (at lower doses) in essentially all patients. Shunt dysfunction (with consequent recurrence of ascites) occurs in a third of the patients and new or worsened hepatic encephalopathy occurs in over 25% of the patients. In a median follow-up of around 11 months, the observed mortality in these studies was quite variable but averaged around 50%.[28]

Controlled Trials of TIPS versus LVP

Five prospective randomized trials comparing TIPS versus LVP have been published in full to date[21,29–32] and are summarized in Tables 1 and 2.

Not unexpectedly, all five trials demonstrate that TIPS is more effective than LVP in the control of ascites (Table 2), and except for one,[29] all studies demonstrate a higher incidence of encephalopathy[21,31] or of severe encephalopathy[30,32] in patients treated with TIPS. Regarding mortality, the most important end point, one study shows a higher mortality in patients randomized to TIPS due to a higher mortality in Child C patients[21]; two trials, which include the largest number of patients, show no differences in mortality between the TIPS and LVP groups[30,31]; one trial shows a significant survival benefit in favor of the TIPS group[32]; and in the remaining trial, treatment with TIPS was independently predictive of a better survival; however, differences in survival probability were not statistically different.[29]

Table 1 Baseline Characteristics of Patients Included in Controlled Studies of TIPS versus LVP for Refractory or Recidivant ascites

First Author	Therapy	*n*	Age (y)	ETOH (%)	Refractory Ascites (%)	CPS (% Child C)	Bilirubin (mg/dL)	Creatinine (mg/dL)	Serum Na (mEq/L) (% < 130)	U_{Na} (mEq/L) (% < 10)	PPG (mm Hg)
Lebrec[21]	LVP	12	52	83	100	9.2 (33%)	1.6	1.0	130	< 5	22 → 20
	TIPS	13	50	77	100	9.3 (31%)	2.0	1.0	130	< 5	20 → 13
Rossle[29]	LVP	29	61	74	52	8.7 (23%)	1.8	1.4	131 (13%)	61 (10%)	—
	TIPS	31	58	83	59	9.1 (38%)	1.8	1.3	130 (17%)	45 (40%)	24 → 10
Gines[30]	LVP	35	56	60	100	9.2 (43%)	2.4	1.4	— (48%)	9	—
	TIPS	35	59	51	100	9.3 (37%)	2.0	1.4	— (54%)	7	19.1 → 8.7
Sanyal[31]	LVP	57	52	33	100	9.3 (NR)	1.9	0.98	NR	NR	—
	TIPS	52	56	32	100	9.2 (NR)	1.9	1.07	NR	NR	19.8 → 8.3
Salerno[32]	LVP	33	60	39	64	9.4 (38% B/C)	1.9	1.12	133	38	—
	TIPS	33	58	45	73	9.4 (27% B/C)	1.7	1.15	133	38	22.5 → 8.7

Abbreviations: LVP, large-volume paracentesis; TIPS, transjugular intrahepatic portosystemic shunt; CPS, Child-Pugh score; Na, sodium; U_{Na}, urinary sodium; PPG, portosystemic pressure gradient; NR, not reported.
Values given are mean values or percentages.

Table 2 Controlled Studies of TIPS versus Large-Volume Paracentesis for Refractory or Recidivant Ascites

First Author	Therapy	*n*	Follow-up (mo)	Favorable Response	New or Worse Encephalopathy	TIPS Dysfunction	Mortality	Predictors of Death
Lebrec[21]	LVP	12	NR	0 (4 months)	0	—	4 (33%)	Child C
	TIPS	13	NR	5 (38%)	3 (23%)	3 (23%)	9 (69%)	
Rossle[29]	LVP	29	44	7 (24%) (3 months)	3 (10%)	—	23 (79%)	Age > 60; bilirubin > 3; serum sodium < 125; treatment assigned
	TIPS	31	45	20 (64%)	6 (19%)	13 (42%)	15 (48%)	
Gines[30]	LVP	35	11	6 (17%)	12 (34%)*	—	18 (51%)	CPS
	TIPS	35	9	18 (51%)	21 (60%)*	13 (37%)	20 (57%)	BUN
Sanyal[31]	LVP	57	NR	9 (16%)	12 (21%)	—	19 (33%)	None found
	TIPS	52	NR	30 (58%)	20 (38%)	53% (6 months)	18 (35%)	
Salerno[32]	LVP	33	15	14 (42%)	0.36†	—	20 (61%)	MELD; treatment assigned
	TIPS	33	21	26 (79%)	0.97†	12 (36%)	13 (39%)	

Values given are mean values or percentages.
Abbreviations: LVP, large-volume paracentesis; TIPS, transjugular intrahepatic portosystemic shunt; CPS, Child-Pugh score; BUN, blood urea nitrogen; MELD, model of end-stage liver disease; NR, not reported.
*Severe encephalopathy.
†Episodes of severe encephalopathy per patient.

Of note, in these studies TIPS was technically unsuccessful in ~5% of cases.

As can be observed in Table 1, cirrhotic patients included in these trials are quite homogeneous, with a median age of 56 years, a CPS around 9.2, and a comparable decrease in PPG after TIPS insertion. However, the two trials that showed a survival benefit may have included patients with less severe liver disease as indicated by higher urinary sodium excretion levels and the inclusion of patients with recidivant ascites.[29,32] A higher sodium excretion is an indirect indicator of lesser activation of sodium-retaining neurohumoral systems and therefore of less vasodilatation and less advanced liver disease. Contrary to refractory ascites that is defined as a weight loss < 200 g/d despite maximal diuretic therapy, patients with recidivant ascites are those in whom tense ascites recurs at least three times in the course of 12 months but these patients still respond to diuretics and therefore have a less severe liver disease.[7] Furthermore, unlike all other trials, in the trial by Rossle et al,[29] LVP was not routinely associated to albumin administration, a factor that could have potentially increased mortality in the group randomized to LVP.

The highest mortality was observed in patients included in the study by Gines et al,[30] in whom hyponatremia was more frequent and who also had higher creatinine levels (Table 1). This is not surprising as hyponatremia and renal dysfunction have both been described as being predictors of poor survival in cirrhosis,[33,34] and, more recently, a serum sodium < 130 mmol/L and a serum creatinine > 1.7 mg/dL have been identified as the only independent predictors of survival in patients undergoing TIPS for variceal hemorrhage.[35]

Two recent meta-analysis, one that included four of the above-mentioned trials with a total of 264 patients[36] and a more recent one that included all five trials with a total of 330 patients,[37] come to the same conclusions. That is, that TIPS is more effective than LVP in the control of ascites (up to 12 months after randomization), that mortality does not differ between these two treatments and that hepatic encephalopathy occurs significantly more often in TIPS-treated patients.

Aside from these end points, a preventive effect of TIPS on the development of hepatorenal syndrome was observed in the trial by Gines et al,[30] effect that is likely related to suppression of the renin-angiotensin-aldosterone system; however, this beneficial effect was not confirmed in a meta-analysis.[36] Another potential benefit of TIPS is an improvement in quality of life demonstrated in an uncontrolled study particularly in patients with a complete response (elimination of ascites).[38] However, these results could not be confirmed in the only randomized controlled study that evaluated quality of life using the SF-36 questionnaire.[31]

Furthermore, in the study by Gines et al, costs were greater in the TIPS group compared with the LVP group,[30] partly due to an occlusion rate of 37% requiring shunt revision. It should be noted that all these studies used uncovered stents. Polytetrafluoroethylene-covered stents improve TIPS patency and decrease the number of clinical relapses and reinterventions while actually decreasing the risk of encephalopathy.[39] A retrospective study suggests that patients undergoing TIPS with covered stents (50% for refractory ascites) have higher 2-year survival rates when compared with patients undergoing TIPS placement with bare stents.[40] The benefits of covered-stents in the setting of refractory ascites require evaluation in prospective studies.

Although studies report a decrease in diuretic requirement in patients treated with TIPS, it appears

Table 3 Uncontrolled Prospective Cohort Studies of TIPS for Refractory Ascites That Report on Predictors of Response and/or Mortality

First Author	*n*	Favorable Response	Responders Requiring Diuretics	Predictors of an Unfavorable Response	Mortality	Predictors of Survival
Quiroga[22]	17	15 (88%)	NR	NR	5 (29%)	Plasma norepinephrine
Ochs[51]	50	46 (92%)	46 (100%)	None found	31 (62%)	Age < 60; bilirubin < 1.3; complete response
Somberg[25]	24	19 (79%)	2/5 (40%)	Serum creatinine > 2	NR	NR
Crenshaw[48]	54	40 (74%)	40 (100%)	Serum creatinine > 1.5	27 (50%)	Complete response
Martinet[45]	30	26 (87%)	26 (100%)	Post-TIPS PCG > 16 mm Hg	17 (57%)	Child-Pugh score
Nazarian[49]	50	23 (46%)	NR	Creatinine > 1.9 and bilirubin > 3.0	30 (60%)	Creatinine < 1.9 and bilirubin < 3.0
Deschenes[50]	53	25 (47%)	NR	Creatinine clearance < 36 mL/min	23 (43%) (6 months)	NR

Abbreviations: NR, not reported; PCG, portocaval gradient.

that all patients continue to require diuretics (Table 3), probably because TIPS improves but does not normalize sodium excretion. In fact, the use of diuretics immediately after the procedure is theoretically advantageous as it will reduce central pressure and increase flow through the shunt.

Controlled Trial of TIPS versus Peritoneovenous Shunt

The peritoneovenous shunt (PVS) leads to expansion of blood volume, suppression of sodium-retaining neurohumoral systems, and increased responsiveness to diuretics. In controlled trials comparing PVS versus LVP, PVS has shown to be better than LVP in the long-term control of ascites without differences in survival.[12,13] However, the frequent occlusion and complication rates have led to considering that PVS has only a small role in the treatment of refractory ascites.[9] In fact, a recent randomized trial comparing TIPS versus PVS in 32 patients with refractory ascites shows that although ascites control was achieved sooner with PVS (73% versus 46% after 1 month), TIPS provided significantly longer long-term efficacy (86% versus 40% after 3 years), without differences in survival.[41] There was a high rate of shunt occlusion in both groups with median shunt patencies of 4.4 months and 4 months for TIPS and PVS, respectively; however, the assisted shunt patency after PVS was lower than after TIPS (13 versus 31 months). Therefore, PVS should be restricted to non-TIPS candidates.

COMPLICATIONS OF TIPS FOR REFRACTORY ASCITES

In uncontrolled studies of TIPS placement in patients with refractory ascites, the procedure-related complication rate is around 9%, distributed as follows: intraperitoneal hemorrhage (3%), acute renal failure (3%) most described as being secondary to contrast media, sepsis (1.5%), and hemolysis (1.2%). A unique complication that has been described in these patients is the development of strangulated umbilical hernia following resolution after TIPS.[42] In controlled studies, the procedure-related complications were only specified in the study by Gines et al[30] and consisted of heart failure in 4 (11%) and severe hemolysis in 3 (9%) patients.

The most frequent complication related to TIPS placement is the development of hepatic encephalopathy, especially during the first months. As mentioned previously, this complication appears to develop less frequently with the use of covered stents.[39] A recent controlled trial performed in 75 patients evaluated whether prophylactic therapies for encephalopathy (lactitol or rifaximin) were useful in preventing post-TIPS encephalopathy.[43] The incidence of encephalopathy in this study was 33% and the 1-month cumulative probability of developing encephalopathy (or severe encephalopathy) was not significantly different among the three groups (lactitol, rifaximin, and no treatment). Results were the same when the 25 patients in which TIPS was performed for refractory ascites were analyzed. Therefore, prophylactic therapy for encephalopathy cannot be recommended in this setting. Previous hepatic encephalopathy was the most important independent predictor of post-TIPS encephalopathy.

Another recently described complication of TIPS appears to be a higher incidence of hepatocellular carcinoma (HCC) in cirrhotic patients treated with bare-stent TIPS. In a case-control study, the cumulative probability of developing HCC at 1, 3, and 5 years was 3, 24, and 34% for the TIPS cohort (138 patients) and 1, 6, and 25%, for the non-TIPS cohort, respectively.[44] This observation suggests the need for a strict HCC surveillance program for these patients.

PORTOSYSTEMIC PRESSURE GOALS AND POST-TIPS MONITORING

As mentioned above, a hepatic venous pressure gradient of 12 mm Hg has been identified as a threshold PPG necessary for ascites development. Therefore, achieving a PPG of less than 12 mm Hg should be the goal of therapy. In fact, a post-TIPS PPG >16 mm Hg was found to be a predictor of nonresponse in one study,[45] and another study of TIPS for portal hypertension demonstrates that the portosystemic pressure gradient increased to 12 mm Hg in all patients who developed ascites post-TIPS placement.[46]

On the other hand, two studies have shown that a low PPG is an independent predictor of the development of post-TIPS encephalopathy. In one of them, performed in 47 patients, the portocaval gradient cutoff was < 10 mm Hg.[47] Interestingly, in a more recent study from the same group of investigators, performed in 75 patients, a post-TIPS portosystemic gradient of < 5 mm Hg was the cutoff pressure related to the occurrence of encephalopathy.[43] Therefore, although the post-TIPS PPG goal should be less than 12 mm Hg, it should also be greater than 5 mm Hg.

As opposed to the performance of TIPS for variceal hemorrhage, where serial assessments of TIPS patency and pressure monitoring may be warranted, when TIPS is performed for refractory ascites, TIPS functional assessment is not necessary unless there is recurrence of ascites, a clinically obvious event indicative of TIPS dysfunction.

PREDICTORS OF RESPONSE AND MORTALITY

In prospective cohort studies of TIPS for refractory ascites (Table 3), the most common predictive factor of an unfavorable response is serum creatinine[25,48,49] or creatinine clearance.[50] On the other hand, patients with a complete response after TIPS have been shown to have a better survival.[48,51] Creatinine, bilirubin, and CPS have also been identified as predictors of survival in these studies.

The MELD (model of end-stage liver disease) model was designed to predict 3-month post-TIPS survival and uses a continuous function of serum bilirubin levels, international normalized ratio for prothrombin time, and serum creatinine.[52] Only 25% of patients in this study had TIPS placed for management of refractory ascites. Several recent studies have compared MELD with the CPS in predicting post-TIPS survival with divergent results. One study shows that the MELD score is better than CPS score in predicting 3-month survival but not in predicting long-term survival,[53] although another study finds no differences in short-term survival and only a marginal advantage of MELD in long-term survival.[54] Another study shows that both scores are equally predictive of 1-month, 3-month, and 1-year post-TIPS survival,[55] with a cutoff for the CPS of 11. In these studies refractory ascites is the reason for TIPS placement in only a minority of patients, and it has been shown that patients undergoing TIPS for refractory ascites have a significantly poorer survival than patients with variceal bleeding.[55,56] In prospective randomized trials of TIPS for refractory ascites (Table 2), CPS is identified as a predictor of survival in two studies[21,30] and MELD is the strongest predictor of survival in the most recent study[32]; however, the CPS is still more useful in clinical practice.

CANDIDATES FOR TIPS

The evidence-based consensus recommendation put forward recently is that first-line treatment of refractory ascites is repeated LVP + albumin and that TIPS should be considered when the frequency of paracentesis is greater than two to three times per month.[9] A good predictor of post-TIPS survival is the CPS, and a score higher than 11 should be considered a contraindication for TIPS placement. TIPS should also be avoided in elderly patients and in those with heart dysfunction.[9] Patients with alcoholic cirrhosis who are drinking alcohol may improve with abstinence and therefore TIPS should be delayed in these patients. The efficacy of the newly available covered stents needs to be prospectively evaluated in patients with refractory ascites.

REFERENCES

1. Loureiro-Silva MR, Cadelina GW, Groszmann RJ. Deficit in nitric oxide production in cirrhotic rat livers is located in the sinusoidal and postsinusoidal areas. Am J Physiol Gastrointest Liver Physiol 2003;284:G567–G574
2. Rector WG. Portal hypertension: a permissive factor only in the development of ascites and variceal bleeding. Liver 1986;6:221–226
3. Morali GA, Sniderman KW, Deitel KM, et al. Is sinusoidal portal hypertension a necessary factor for the development of hepatic ascites? J Hepatol 1992;16:249–250
4. Villanueva C, Minana J, Ortiz J, et al. Endoscopic ligation compared with combined treatment with nadolol and isosorbide mononitrate to prevent recurrent variceal bleeding. N Engl J Med 2001;345:647–655
5. Abraldes JG, Tarantino I, Turnes J, et al. Hemodynamic response to pharmacological treatment of portal hypertension and long-term prognosis of cirrhosis. Hepatology 2003;37: 902–908
6. Schrier RW, Arroyo V, Bernardi M, et al. Peripheral arterial vasodilation hypothesis: a proposal for the initiation of renal sodium and water retention in cirrhosis. Hepatology 1988;8: 1151–1157
7. Arroyo V, Gines P, Gerbes AL, et al. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. Hepatology 1996;23:164–176

8. Salerno F, Borroni G, Moser P, et al. Survival and prognostic factors of cirrhotic patients with ascites: a study of 134 outpatients. Am J Gastroenterol 1993;88:514–519
9. Moore KP, Wong F, Gines P, et al. The management of ascites in cirrhosis: consensus conference of the International Ascites Club. Hepatology 2003;38:258–266
10. Gines A, Fernandez-Esparrach G, Monescillo A, et al. Randomized trial comparing albumin, dextran-70 and polygeline in cirrhotic patients with ascites treated by paracentesis. Gastroenterology 1996;111:1002–1010
11. Ruiz del Arbol L, Monescillo A, Jimenez W, et al. Paracentesis-induced circulatory dysfunction: mechanism and effect on hepatic hemodynamics in cirrhosis. Gastroenterology 1997;113:579–586
12. Gines P, Arroyo V, Vargas V, et al. Paracentesis with intravenous infusion of albumin as compared with peritoneovenous shunting in cirrhosis with refractory ascites. N Engl J Med 1991;325:829–835
13. Gines A, Planas R, Angeli P, et al. Treatment of patients with cirrhosis and refractory ascites by LeVeen shunt with titanium tip. Comparison with therapeutic paracentesis. Hepatology 1995;22:124–131
14. Castells A, Salo J, Planas R, et al. Impact of shunt surgery for variceal bleeding in the natural history of ascites in cirrhosis: a retrospective study. Hepatology 1994;20:584–591
15. Voorhees ABJ, Price JBJ, Britton RC. Portasystemic shunting procedures for portal hypertension: twenty-six year experience in adults with cirrhosis of the liver. Am J Surg 1970;119:501–505
16. Orloff MJ, Orloff MS, Orloff SL, et al. Experimental, clinical, and metabolic results of side-to-side portacaval shunt for intractable cirrhotic ascites. J Am Coll Surg 1997;184:557–570
17. Franco D, Vons C, Traynor O, et al. Should portosystemic shunt be reconsidered in the treatment of intractable ascites in cirrhosis? Arch Surg 1988;123:987–991
18. Luca A, D'Amico G, LaGalla R, et al. TIPS for prevention of recurrent bleeding in patients with cirrhosis: meta-analysis of randomized clinical trials. Radiology 1999;212:411–421
19. Wong F, Sniderman K, Liu P, et al. Transjugular intrahepatic portosystemic stent shunt: effects on hemodynamics and sodium homeostasis in cirrhosis and refractory ascites. Ann Intern Med 1995;122:816–822
20. Wong F, Sniderman K, Liu P, et al. The mechanism of the initial natriuresis after transjugular intrahepatic portosystemic shunt. Gastroenterology 1997;112:899–907
21. Lebrec D, Giuily N, Hadengue A, et al. Transjugular intrahepatic portosystemic shunts—comparison with paracentesis in patients with cirrhosis and refractory ascites: a randomized trial. J Hepatol 1996;25:135–144
22. Quiroga J, Sangro B, Nunez M, et al. Transjugular intrahepatic portal-systemic shunt in the treatment of refractory ascites: effect on clinical, renal, humoral, and hemodynamic parameters. Hepatology 1995;21:986–994
23. Gerbes AL, Gulberg V, Waggershauser T, et al. Renal effects of transjugular intrahepatic portosystemic shunt in cirrhosis: comparison of patients with ascites, with refractory ascites or without ascites. Hepatology 1998;28:683–688
24. Wong W, Liu P, Blendis L, et al. Long-term renal sodium handling in patients with cirrhosis treated with transjugular intrahepatic portosystemic shunts for refractory ascites. Am J Med 1999;106:315–322
25. Somberg KA, Lake JR, Tomlanovich SJ, et al. Transjugular intrahepatic portosystemic shunts for refractory ascites: assessment of clinical and hormonal response and renal function. Hepatology 1995;21:709–716
26. Ferral H, Bjarnason H, Wegryn SA, et al. Refractory ascites: early experience with transjugular intrahepatic portosystemic shunt. Radiology 1993;189:795–801
27. Russo MW, Sood A, Jacobson IM, et al. Transjugular intrahepatic portosystemic shunt for refractory ascites: an analysis of the literature on efficacy, morbidity, and mortality. Am J Gastroenterol 2003;98:2521–2527
28. Garcia-Tsao G.Transjugular intrahepatic portosystemic shunt for the management of refractory ascites in cirrhosis. In: Gines P, Arroyo V, Rodes J, Schrier RW, eds. Ascites and Renal Dysfunction in Liver Disease. 2nd edition. Oxford: Blackwell Publishing; 2005:251–259
29. Rossle M, Ochs A, Gulberg V, et al. A comparison of paracentesis and transjugular intrahepatic portosystemic shunting in patients with ascites. N Engl J Med 2000;342:1701–1707
30. Gines P, Uriz J, Calahorra B, et al. Transjugular intrahepatic portosystemic shunting versus repeated paracentesis plus intravenous albumin for refractory ascites in cirrhosis: a multicenter randomized comparative study. Gastroenterology 2002;123:1839–1847
31. Sanyal AJ, Genning C, Reddy KR, et al. The North American Study for the treatment of refractory ascites. Gastroenterology 2003;124:634–641
32. Salerno F, Merli M, Riggio O, et al. Randomized controlled study of TIPS versus paracentesis plus albumin in cirrhosis with severe ascites. Hepatology 2004;40:629–635
33. Arroyo V, Rodes J, Gutierrez Lizarraga MA, et al. Prognostic value of spontaneous hyponatremia in cirrhosis with ascites. Am J Dig Dis 1976;21:249–256
34. Llach J, Gines P, Arroyo V, et al. Prognostic value of arterial pressure, endogenous vasoactive systems, and renal function in cirrhotic patients admitted to the hospital for the treatment of ascites. Gastroenterology 1988;94:482–487
35. Schepke M, Roth F, Koch L, et al. Prognostic impact of renal impairment and sodium imbalance in patients undergoing transjugular intrahepatic portosystemic shunting for the prevention of variceal rebleeding. Digestion 2003;67:146–153
36. Saab S, Nieto J, Ly D, et al. TIPS versus paracentesis for cirrhotic patients with refractory ascites. Cochrane Database Syst Rev 2004;3:CD004889
37. Deltenre P, Mathurin P, Dharancy S, et al. Transjugular intrahepatic portosystemic shunt in refractory ascites: a meta-analysis. Liver Int 2005;25:349–356
38. Gulberg V, Liss I, Bilzer M, et al. Improved quality of life in patients with refractory or recidivant ascites after insertion of transjugular intrahepatic portosystemic shunts. Digestion 2002;66:127–130
39. Bureau C, Garcia-Pagan JC, Otal P, et al. Improved clinical outcome using polytetrafluoroethylene-coated stents for TIPS: results of a randomized study. Gastroenterology 2004;126:469–475
40. Angermayr B, Cejna M, Koenig F, et al. Survival in patients undergoing transjugular intrahepatic portosystemic shunt: ePTFE-covered stentgrafts versus bare stents. Hepatology 2003;38:1043–1050
41. Rosemurgy AS, Zervos EE, Clark WC, et al. TIPS versus peritoneovenous shunt in the treatment of medically

intractable ascites: a prospective randomized trial. Ann Surg 2004;239:883–889
42. Trotter JF, Suhocki PV. Incarceration of umbilical hernia following transjugular intrahepatic portosystemic shunt for the treatment of ascites. Liver Transpl Surg 1999;5:209–210
43. Riggio O, Masini A, Efrati C, et al. Pharmacological prophylaxis of hepatic encephalopathy after transjugular intrahepatic portosystemic shunt: a randomized controlled study. J Hepatol 2005;42:674–679
44. Banares R, Nunez O, Escudero M, et al. Patients with cirrhosis and bare-stent TIPS may have increased risk of hepatocellular carcinoma. Hepatology 2005;41:566–571
45. Martinet JP, Fenyves D, Legault L, et al. Treatment of refractory ascites using TIPS: a caution. Dig Dis Sci 1997;42: 161–166
46. Casado M, Bosch J, Garcia-Pagan JC, et al. Clinical events following transjugular intrahepatic portosystemic shunt: correlation with hemodynamic findings. Gastroenterology 1998;114:1296–1303
47. Riggio O, Merli M, Pedretti G, et al. Hepatic encephalopathy after transjugular intrahepatic portosystemic shunt: incidence and risk factors. Dig Dis Sci 1996;41:578–584
48. Crenshaw WB, Gordon FD, McEniff NJ, et al. Severe ascites: efficacy of the transjugular intrahepatic portosystemic shunt in treatment. Radiology 1996;200:185–192
49. Nazarian GK, Bjarnason H, Dietz CAJ, et al. Refractory ascites: results of treatment with a transjugular intrahepatic portosystemic shunt. Radiology 1997;205:173–180
50. Deschenes M, Dufresne MP, Bui B, et al. Predictors of clinical response to transjugular intrahepatic portosystemic shunt (TIPS) in cirrhotic patients with refractory ascites. Am J Gastroenterol 1999;94:1361–1365
51. Ochs A, Rossle M, Haag K, et al. The transjugular intrahepatic portosystemic stent-shunt procedure for refractory ascites. N Engl J Med 1995;332:1192–1197
52. Malinchoc M, Kamath PS, Gordon FD, et al. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. Hepatology 2000;31:864–871
53. Salerno F, Merli M, Cazzaniga M, et al. MELD score is better than Child-Pugh score in predicting 3-month survival of patients undergoing transjugular intrahepatic portosystemic shunt. J Hepatol 2002;36:494–500
54. Schepke M, Roth F, Fimmers R, et al. Comparison of MELD, Child-Pugh, and Emory model for the prediction of survival in patients undergoing transjugular intrahepatic portosystemic shunting. Am J Gastroenterol 2003;98:1167–1174
55. Angermayr B, Cejna M, Karnel F, et al. Child-Pugh versus MELD score in predicting survival in patients undergoing transjugular intrahepatic portosystemic shunt. Gut 2003;52: 879–885
56. Membreno F, Baez AL, Pandula R, et al. Differences in long-term survival after transjugular intrahepatic portosystemic shunt for refractory ascites and variceal bleed. J Gastroenterol Hepatol 2005;20:474–481