The Role of Transjugular Intrahepatic Portosystemic Shunt in the Management of Portal Hypertension

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Preamble

The recommendations in this article provide a data-supported approach. They are based on the following: (1) a formal review and analysis of recently published world literature on the topic (as listed in MEDLINE); (2) the American College of Physicians' *A Manual for Assessing Health Practices and Designing Practice Guidelines*[1]; (3) policy guidelines, including the American Association for the Study of Liver Diseases' Policy Statement on Development and Use of Practice Guidelines and the American Gastroenterological Association's Policy Statement on the Use of Medical Practice Guidelines[2]; and (4) the authors' years of experience in the care of patients with portal hypertension and use of transjugular intrahepatic portosystemic shunt in the management of these disorders. These recommendations are fully endorsed by the American Association for the Study of Liver Diseases and the Society for Interventional Radiology.

Intended for use by physicians, these recommendations suggest preferred approaches to the diagnostic, therapeutic, and preventative aspects of care. They are intended to be flexible, in contrast to standards of care, which are inflexible policies designed to be followed in every case. Specific recommendations are based on relevant published information. In an attempt to characterize the quality of evidence supporting recommendations, the Practice Guidelines Committee of the American Association for the Study of Liver Diseases requires a grade to be assigned and reported with each recommendation (Table 1).

Introduction

Transjugular intrahepatic portosystemic shunt (TIPS) has been in use for more than 20 years to treat the complications of portal hypertension, and TIPS have been created in thousands of patients with liver disease worldwide.[3-6] Despite the extensive use of TIPS to treat the complications of portal hypertension, there initially was a lack of consensus regarding which patients should receive TIPS instead of other forms of therapy. A 1995 conference sponsored by the National Institutes of Health concluded that TIPS was effective in the acute control and prevention of recurrent bleeding from varices, but it was unclear when TIPS should be used instead of medical and surgical therapy for these complications of portal hypertension. In addition, the efficacy of TIPS to control refractory ascites or treat Budd-Chiari syndrome was unclear but promising.[7] Since then, more than 1,000 patients have been enrolled in multiple controlled trials comparing TIPS with endoscopic and pharmacological therapy in the prevention of rebleeding from varices and with large-volume paracentesis in the treatment of refractory ascites associated with cirrhosis. Furthermore, approximately 1,000 papers have been published on TIPS in the English literature alone. This body of work allows for more definitive recommendations about in whom and when to use TIPS in the treatment of the complications of portal hypertension.

The guidelines are divided into two large categories. The first category is a review of the technical aspects of the procedure, its complications, and the data on which patients are most at risk for an adverse outcome following TIPS. The second category is a review of the indications for TIPS. The use of TIPS for primary prevention of variceal bleeding and the control of acute bleeding are discussed first. Next, the two indications for TIPS that have been subjected to controlled trials (prevention of recurrent bleeding from varices and refractory ascites) are discussed, and guidelines are developed. Lastly, all of the other indications for TIPS that have been described in the literature but have not been subjected to controlled trials are discussed, and guidelines are created.

Abbreviations: TIPS, transjugular intrahepatic portosystemic shunt; MELD, model for end-stage liver disease; HVPG, hepatic venous pressure gradient; PTFE, polytetrafluoroethylene; PHG, portal hypertensive gastropathy; GAVE, gastric antral vascular ectasia; LVP, large volume paracentesis; HRS, hepatorenal syndrome; BCS, Budd-Chiari syndrome.

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Received November 8, 2004; accepted November 18, 2004.

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Published online in Wiley InterScience (www.interscience.wiley.com).

DOI 10.1002/hep.20559

Conflict of interest: Drs. Boyer and Haskal are paid consultants for W. L. Gore and Associates, Inc., the manufacturer of a polytetrafluoroethylene-covered stent used for TIPS.

Table 1. Quality of Evidence on Which a Recommendation is Based

Grade	Definition
I	Randomized controlled trials
II-1	Controlled trials without randomization
II-2	Cohort or case–control analytical studies
II-3	Multiple time series, dramatic uncontrolled experiments
III	Opinions of respected authorities, descriptive epidemiology

To prepare these guidelines, a MEDLINE search was performed on papers published between 1966 and 2004. Nine hundred eight papers were found under the subject heading "transjugular intrahepatic portosystemic shunt." Controlled trials and large series were sought. Recently published papers were also used as a source of references missed by the MEDLINE search, as were the personal files of the two authors.

The Procedure

A TIPS is created by an interventional radiologist or, in Europe, by a specially trained physician. The technique is reviewed in several publications and will not be discussed here.[3,4,7] The procedure may be performed under conscious sedation (most common) or general anesthesia. If the procedure is going to be prolonged or the patient is hemodynamically unstable, then general anesthesia is preferred because it allows for careful monitoring by the anesthesiologist. The success rate with TIPS for the decompression of the portal vein is high—more than 90% of cases in most series.[8-14] The Society of Interventional Radiology developed guidelines for creation of a TIPS in 2001, and the consensus was that a technically successful outcome (including both creation of the shunt and a decrease in portal pressure to $<$12 mm Hg) should be achieved in 95% of patients, and clinical success (resolution of the complication of portal hypertension) should be achieved in 90% of cases. Failure to achieve this threshold should lead to a review of departmental policy and procedures.[15,16]

Early mortality following TIPS placement was originally reported to be quite high as a result of poor patient selection, but subsequent analysis demonstrated that preprocedure clinical features (such as high model for end-stage liver disease [MELD] or APACHE II scores, high total bilirubin levels, emergent versus elective setting, or presence of pneumonia; see Mortality) accounted for this high death rate. In most situations, death is due to progressive liver disease, perhaps as a result of portal diversion, and is not due to complications of the procedure itself, such as intraperitoneal bleeding (see Mortality).[14,17-19] In a retrospective series of 1,750 patients, the incidence of fatal complications (intra-abdominal hemorrhage, laceration of the hepatic artery or portal vein, and right heart failure) was 1.7% (range, 0.6%-4.3%). Interestingly, the risk of fatal complications was 3% in institutions that had performed fewer than 150 TIPS total compared with 1.4% in those that had performed a greater number.[14] These data suggest that there is a learning curve associated with the safe creation of a TIPS. Major procedural complications are expected in no more than 3% of cases; if rates exceed these levels, internal quality assessment should be considered.[16] Authors of manuscripts on TIPS have been asked by the Society of Interventional Radiology to report the approximate number of TIPS performed in their centers before instituting the reported study to obtain a better understanding of the amount of training required to perform TIPS with an acceptable morbidity and mortality, and it is hoped these data are forthcoming.[16]

The purpose of a TIPS is to decompress the portal venous system and therefore prevent rebleeding from varices or stop or reduce the formation of ascites. Regarding varices, it is well established that if the hepatic venous pressure gradient (HVPG) can be reduced to less than 12 mm Hg, the risk of bleeding will fall significantly. More recent data suggest that achieving a HVPG of less than 12 mm Hg may not be required to prevent rebleeding. In one series, the risk of rebleeding following TIPS revision was 18%, 7%, and 1% in patients whose HVPG had been reduced by 0%, 25% to 50%, and more than 50%, respectively.[20] In a second series, a 50% reduction in the initial HVPG was associated with a rebleeding rate at 1 year of 11%, whereas patients with a lesser reduction had a 31% probability of rebleeding during the first year.[21] In the latter study, the only absolute value for prevention of rebleeding was an HVPG of less than 12 mm Hg, but at the cost of an increased incidence of encephalopathy. Although the gold standard for prevention of rebleeding remains an HVPG of less than 12 mm Hg, further studies are needed to determine if lesser reductions have acceptable efficacy with a lower incidence of encephalopathy.

The optimal HVPG that needs to be obtained for the control of refractory ascites associated with cirrhosis is even less clear. In one series, the degree of portal decompression did not correlate with successful treatment of refractory ascites associated with cirrhosis, and the authors suggested that a HVPG of less than 8 mm Hg should be the hemodynamic goal.[22] The selection of a value of 8 mm Hg is based on limited data, and because the development of ascites associated with cirrhosis reflects changes in both hepatic and renal function, it may be difficult to establish an absolute value of decompression that needs to be achieved in most patients with re-

fractory ascites. In patients with significant pre-existing encephalopathy in whom a TIPS may still be necessary for ascites control, a higher gradient may be appropriate (to limit worsening encephalopathy); this affords the opportunity to further enlarge the TIPS at a later date if diuresis is inadequate and encephalopathy is satisfactorily controlled. Further study in this area is warranted.

Finally, in the authors' experience the effective gradient needed to prevent rebleeding from gastric varices may be lower than 12 mm Hg and, even with apparent decompression embolization of the gastric varices, may be required to minimize the risk of early rebleeding. Also, rebleeding from gastric varices may occur with small increases in portal pressure, suggesting that surveillance of this group of patients following TIPS is of particular importance.[21]

Further complicating the issue is the problem of how the pressures are obtained. The classic way is to measure the free and wedged hepatic vein pressure and then subtract the two values yielding the HVPG.[23] The use of the free hepatic vein or inferior vena cava pressure is necessary to correct for the intra-abdominal pressure and allows for measurement of the true pressure gradient across the liver. However, most radiologists use the right atrial pressure as the reference point because the hepatic vein is now part of the shunt; thus a free hepatic vein pressure cannot be obtained after shunt creation, because the diverted portal flow artifactually raises the pressure within the outflow hepatic vein that drains the TIPS. The right atrium is of course in the chest, and the basal pressure in the chest is lower than the intra-abdominal pressure; therefore, the true HVPG is not measured using this reference point. In addition, once the TIPS has been created, the right atrial pressure tends to rise, thus complicating the measurement. One solution to this problem is to use the inferior vena cava pressure as the reference value, but this has not been adopted by the interventional radiological community. No standardization of where in the inferior vena cava the pressure should be obtained has limited this approach, and currently the right atrial pressure is used by most interventional radiologists despite the above limitations. Some of these uncertainties could be resolved with standardization of how the HVPG is measured during creation of a TIPS so that the measurements are uniform and can be used to judge hemodynamic success more accurately.

Pre-TIPS Evaluation and Contraindications

Most patients who are referred for a TIPS should be under the care of a gastroenterologist or hepatologist, who in consultation with an interventional radiologist must reach the decision that TIPS is the appropriate form of treatment for a complication of portal hypertension. As discussed in the following section, it is clear that there are predictors of a poor outcome following TIPS. However, the risk of the procedure must always be balanced with the severity of the complication from which the patient is suffering and the likelihood of the patient surviving long enough to receive a liver transplant following creation of a TIPS. Thus, the decision to perform or not perform TIPS in a high-risk patient should be reached by the gastroenterologist/hepatologist and the interventional radiologist together. Ideally, in a high-risk patient, a transplant center should also be consulted preceding the final decision. In the emergent setting of acute, uncontrolled variceal hemorrhage, contacts with transplantation centers may be secondary to the need for shunt creation.

Table 2. Contraindications to Placement of a TIPS

Absolute	Relative
Primary prevention of variceal bleeding	Hepatoma, especially if central
Congestive heart failure	Obstruction of all hepatic veins
Multiple hepatic cysts	Portal vein thrombosis
Uncontrolled systemic infection or sepsis	Severe coagulopathy (INR >5)
Unrelieved biliary obstruction	Thrombocytopenia of less than 20,000/cm^3
Severe pulmonary hypertension	Moderate pulmonary hypertension

Abbreviation: INR, international normalized ratio.

Table 2 lists contraindications to the creation of a TIPS. These include both absolute contraindications to any form of portosystemic diversion, be it surgical or percutaneous. Absolute contraindications include congestive heart failure, severe tricuspid regurgitation, and severe pulmonary hypertension (mean pulmonary pressures > 45 mm Hg, as these patients are not candidates for a liver transplant).[24] Whether patients with more mild pulmonary hypertension can receive a TIPS safely is unclear. Relative contraindications include anatomical ones that can complicate the creation of the shunt and reduce the technical success, including portal venous obstruction, large hepatic tumors, extensive polycystic liver disease, and hepatic vein obstruction. It is well established that shunts can be created in all of these cases with the right experience and under appropriate clinical circumstances, but the difficulty of creating the TIPS needs to be balanced with the need of the patient. Situations in which these relative contraindications might be outweighed by clinical necessity include palliative TIPS in patients with hepatoma and refractory variceal bleeding, recanalization of occluded portal veins in patients with recurrent variceal bleeding or refractory ascites, and a patient with Budd-Chiari syndrome and progressive liver failure in whom there are no patent hepatic veins.

Preprocedure laboratory studies include serum electrolytes, blood count, coagulation parameters, and tests of liver and kidney function. Cross-sectional liver imaging via Duplex ultrasound, computed tomography, or magnetic resonance imaging is appropriate in all but the most life-threatening situations to assess portal vein patency or the presence of liver masses. When a history of congestive heart failure, tricuspid regurgitation, cardiomyopathy, or pulmonary hypertension is present, cardiac evaluation is appropriate before a TIPS procedure. This evaluation may include an echocardiogram, cardiology consultation, and, possibly, atrial fluid challenge. In the absence of a cardiac history, the routine performance of an echocardiogram preceding a TIPS is unnecessary in the opinion of the authors; however, others feel that because up to 16% of patients referred for liver transplantation may have pulmonary hypertension, an echocardiogram should be performed on all patients before a TIPS is created.[24] Elevated right atrial pressures (typically measured at the start of the TIPS procedure) may warrant abandonment or delay of the procedure pending diuresis or further medical evaluation. Lastly, patients with a significant coagulopathy may be able to undergo a TIPS following the use of clotting factors or platelets. The finding of a small liver during the evaluation is not a contraindication to creation of a TIPS, but it does indicate that the procedure may be difficult and prolonged.

Mortality

The 1-year mortality rates for TIPS are dependent somewhat on the indication for the procedure. When a TIPS has been placed for bleeding varices, 1-year survival varies from 48% to 90%. Survival rates are similar when the indication is ascites (48%-76%).[25-30] In one series but not another, survival rates were significantly worse when the indication was refractory ascites compared with variceal bleeding.[26,29] These differences likely reflect variations in the severity of liver disease between the different studies.

As the use of TIPS has increased, there has been interest in models that predict outcome. MELD and a number of other models have been developed to predict survival following TIPS.[25-29] The modified MELD model utilizes serum bilirubin level, international normalized ratio for prothrombin time, and serum creatinine level (cause of cirrhosis was also used previously but has since been abandoned). These three variables are used to create the following equation: [3.8 $\log_e$ (bilirubin [g/dL]) + 11.2 $\log_e$ (international normalized ratio) + 9.6 $\log_e$ (creatinine [mg/dL]. A second model used a bilirubin level of greater than 3.0 mg/dL (1 point), an alanine aminotransferase level of greater than 100 IU/L (1 point), pre-TIPS encephalopathy (1 point), and urgency of TIPS (2 points) and divided patients into three groups (low risk, 0 points; medium risk, 1-3 points; high risk, 4-5 points).[26] These two models and Child-Turcotte-Pugh scores were used prospectively in a subsequent study to predict survival.[30] All three accurately predicted 3-month survival to a similar degree, whereas 1-year survival was predicted best by the MELD model. Short-term mortality has also been predicted by using bilirubin alone or a combination of serum bilirubin, APACHE-II score, and TIPS urgency.[31,32] Irrespective of which model is chosen, the short-term and 1-year survival can be predicted with some accuracy. These survival estimates can be used to advise patients about expected outcomes and can also be used to decide which patients will require referral to a liver transplant center.

Recommendations

1. TIPS should only be performed by experienced interventional radiologists (or specially trained physicians). Success and complication rates should be monitored; if they fail to meet expected rates, review of the program should be considered (evidence: grade III).

2. The decision to perform a TIPS, especially in a high-risk patient, should be reached by a team consisting of a gastroenterologist/hepatologist, interventional radiologist, and, where appropriate, a transplant physician (evidence: grade III).

3. Preceding creation of a TIPS, tests of liver and kidney function should be performed in addition to cross-sectional imaging of the liver to assess portal system patency and exclude liver masses (evidence: grade III).

4. Reduction in HVPG to less than 12 mm Hg should be achieved when the indication is bleeding esophageal varices. Embolization of gastric varices may be required despite adequate decompression of the portal venous system (evidence: grade II-2).

5. The degree of reduction in HVPG to control ascites is unclear, but at present a gradient of 8 mm Hg or less has been suggested to be a reasonable goal (evidence: grade II-2).

6. Patients with high predicted 30-day mortalities should be informed of their prognosis, and TIPS should be performed only in the absence of other options (evidence: grade II-2).

7. In high-risk patients, the need for liver transplantation should be discussed before the performance of an elective TIPS (evidence: grade III).

Table 3. Complications of TIPS

Complications	Frequency (%)
TIPS dysfunction	
Thrombosis	10–15
Occlusion/stenosis	18–78
Transcapsular puncture	33
Intraperitoneal bleed	1–2
Hepatic infarction	~1
Fistulae	Rare
Hemobilia	<5
Sepsis	2–10
Infection of TIPS	Rare
Hemolysis	10–15
Encephalopathy	
New/worse	10–44
Chronic	5–20
Stent migration or placement into inferior vena cava or too far into portal vein	10–20

NOTE. Data are from Boyer and Vargus[116] and Rössle et al.[117]

Complications

The most common complications and their reported frequencies are listed in Table 3.

TIPS dysfunction is defined as a loss of decompression of the portal venous system due to occlusion or stenosis of the TIPS. Although there is no consistency between investigators as to the exact criteria that should be used to define TIPS dysfunction in reference to degree of stenosis, a value of 50% is frequently used. In addition, a rise in the HVPG to greater than 12 mm Hg or a recurrence of the complication of portal hypertension for which the TIPS was performed indicates TIPS dysfunction.[33] Occlusion of the TIPS can either be due to thrombosis or hyperplasia of the intima. Thrombosis of the TIPS usually occurs early and can happen within 24 hours of TIPS creation. The frequency of this complication is on the order of 10% to 15%.[34,35] The cause of the thrombosis may be leakage of bile into the shunt, hypercoagulable syndromes, or inadequate coverage of the TIPS tract with sufficient stents.[36,37] Thrombosis of the TIPS is identified using Doppler ultrasound, and patency is re-established through repeat catheterization. In one controlled trial, use of the anticoagulant phenprocoumon was associated with a lower rate of complete occlusion within the first 3 months following TIPS placement.[38] However, in the absence of more studies, the routine use of anticoagulation is not recommended.

The major difficulty with TIPS is the unpredictable patency of the shunts as a result of pseudointimal hyperplasia within the parenchymal tract or within the outflow hepatic vein. The occluded stents are coated by a collagenous matrix that is covered by endothelial cells.[36,37,39–41] The incidence of stenosis varies from 18% to 78% depending upon the surveillance techniques used, frequency of assessment, and definitions of failure, (*e.g.*, elevated portasystemic gradient, ultrasound velocity criteria, or percent diameter stenosis).[9,11,12,42-46] Most physicians rely on Doppler ultrasound to identify TIPS stenosis. Unfortunately, the earlier studies claiming greater than 90% accuracy for sonographic prediction of shunt dysfunction have failed to stand under the light of larger prospective or retrospective studies. In one series, several ultrasonographic features were used to identify TIPS stenosis, including flow reversal, jet lesion, and decreased flow in the TIPS or portal vein. The sensitivity of each of these tests varied from 10% to 26% with a specificity of 88% to 100%. Thus the negative predictive value was poor and the positive predictive value was acceptable.[47] In a second series of 31 occluded or stenotic stents, ultrasound predicted shunt malfunction in only 11 and incorrectly predicted patency in 20; thus the sensitivity was only 35%.[48] Many of the sonographic studies are methodologically flawed, because sonographic criteria of shunt dysfunction were used to trigger TIPS venography; however, when sonography suggested no shunt dysfunction, proof of shunt patency via venography was not performed. Part of the difficulty of using sonography is that it is an imaging technique that measures velocity, from which diameter within a conduit can be estimated. However, with TIPS it is portal decompression—not percent shunt stenosis—that is important in assessing TIPS function. One prospective study compared 151 Doppler sonograms with TIPS venograms and assessment of portal pressure. Using a success or failure definition of a portosystemic gradient of less than 15 mm Hg or 15 mm Hg or more, respectively, sonography provided a sensitivity and specificity of only 86% and 48%, respectively.[49] Thus an abnormal Doppler ultrasound is predictive of occlusion or stenosis, whereas a normal ultrasound does not exclude TIPS dysfunction. The best indicator of TIPS dysfunction is a recurrence of the problem for which the TIPS was originally inserted: either variceal bleeding, hepatic hydrothorax, or ascites. If recurrent varices are identified by upper endoscopy, then the TIPS most likely is insufficient.[47] Documentation of patency can only be achieved with certainty through recatheterization of the shunt.

The development of covered stents should reduce the frequency of TIPS dysfunction.[50] Two large series have recently been published that have examined the use of polytetrafluoroethylene (PTFE)-covered stent grafts for TIPS. One of the reports is of a series of 71 patients, all of whom received the covered stents, whereas the second report is a randomized controlled trial comparing the covered stents with the standard bare stents.[33,51] In the nonrandomized series, a total of 8 shunt revisions were performed for an incidence of 11.3%, and primary pa-

tency rates at 6 and 12 months were calculated to be 87% and 81%, respectively.[51] Although these results are better than what would be expected with bare stents, all patients did not undergo venography and therefore the true incidence of shunt stenosis is unknown. In the randomized study, 80 patients with cirrhosis and either uncontrolled or recurrent bleeding from varices or refractory ascites were enrolled in the study. Patients were followed with Doppler ultrasound, and venography was performed at 6, 12, and 24 months post-TIPS. Five (13%) of the 39 patients receiving the PTFE-covered stent grafts had shunt dysfunction, whereas 18 (44%) of those receiving the bare stent had shunt dysfunction ($P < .001$). In addition, early thrombosis of the TIPS was observed in three patients who received the bare stents. The actuarial rates of primary patency in the covered and bare stent groups were 86% and 47%, respectively, at year 1 and 80% and 19%, respectively, at year 2. Recurrence of the complication of portal hypertension for which the TIPS was placed was also significantly more common in the bare stent group compared with the PTFE-covered stent group. The incidence of hepatic encephalopathy was less in the PTFE-covered stent group (difference not significant), and survival was the same.[33] The PTFE-covered stents have recently been approved for use in the United States by the Food and Drug Administration.[52] The use of the PTFE-coated stent grafts should decrease significantly the incidence of shunt dysfunction and recurrence of the complications of portal hypertension. It is unclear, however, whether this development will improve the cost-effectiveness of TIPS compared with other forms of therapy.

Puncture of the liver capsule is common, but serious intraperitoneal bleeding is infrequent (1% to 2% of cases). Similarly, creation of a biliary venous or hepatic artery–portal vein fistula is rare. The development of jaundice or sepsis following TIPS suggests the former, whereas pulsatile flow in the portal vein suggests the latter.[53,54] Hemolysis may occur following TIPS placement and appears to be due to damage to the red cells by the stent.[55-57] Recognition that the rise in bilirubin levels is due to hemolysis is an important diagnosis, because an alternative diagnosis is liver failure following TIPS, which caries a poor prognosis.[58] Hepatic infarction is a rare complication of TIPS and is generally related to injury and/or thrombosis of the hepatic artery that supplies the affected segment.[59]

Hepatic encephalopathy and TIPS dysfunction are the two complications that have limited the effectiveness of TIPS most significantly. The incidence of new or worsening encephalopathy following TIPS is 20% to 31%.[25,60,61] In controlled trials comparing TIPS with alternative forms of therapy, the incidence of encephalopathy is always greater in those who received a TIPS (see sections Esophageal Variceal Bleeding and Ascites Associated with Cirrhosis). Pre-TIPS factors associated with an increased risk of post-TIPS encephalopathy in one study included etiology of liver disease other than alcohol, female sex, and hypoalbuminemia.[61] In a second series, increasing age, past history of encephalopathy, and evidence of encephalopathy at the time of TIPS were predictive of post-TIPS encephalopathy.[60] It is important to note that if encephalopathy is precipitated by variceal bleeding, prevention of rebleeding should make it less likely that the patient will have recurrent encephalopathy. Only if the hepatic encephalopathy is uncontrollable is a TIPS contraindicated.[15] In most patients, the encephalopathy responds to standard therapy, and only rarely ($\approx$5%) must the TIPS be occluded to control the encephalopathy.[62,63] A TIPS also can be reduced in caliber should excessive encephalopathy prove difficult to control and yet allow for continued portal decompression.[64] There is no data supporting the use of lactulose in all patients following a TIPS to reduce the incidence of encephalopathy.

TIPS in the Transplant Candidate

Patients awaiting liver transplantation frequently bleed from varices or have refractory ascites associated with cirrhosis and therefore are candidates for a TIPS. Because these patients will subsequently undergo a hepatectomy, there are complications involved with TIPS that are unique to this population. A TIPS is created within the substance of the liver, and most interventional radiologists attempt to place the stent as close as possible to the hepatic vein/inferior vena cava ostium to reduce the risk of developing stenosis within the hepatic vein. With the exception of cases of benign or malignant portal vein thrombosis, the stent should extend the shortest possible distance into the main portal vein, both to allow creation of a durable shunt and yet not complicate the portal-to-portal vein anastomosis performed during transplantation. When the stent extends into the inferior vena cava (or atrium) or deep into the main portal vein, transplantation difficulties can arise. In one series of 12 patients who had a TIPS preceding liver transplantation, 4 patients had portal vein stents near the coronary vein or extending into the superior mesenteric vein, and venous reconstruction was required in 1 patient.[65] In a second series of 24 patients who had a TIPS created before transplantation, 8 patients had more complicated surgeries that were attributable to the presence of a TIPS. Four of the stents were in the inferior vena cava, one was in the superior mesenteric vein, and in three the portal vein was thrombosed. Despite being able to complete the trans-

plant in all 8 patients, patient and graft survival were somewhat worse in those with complications related to the presence of the TIPS.[66] However, in other series, despite the technical issues that arose during the transplant because of the presence of the shunt, operative time and patient and graft survival were the same in patients who were transplanted in the presence and absence of a TIPS.[67,68] All patients who have a TIPS created should be considered possible liver transplant candidates; thus care should be taken to not extend the stents beyond the minimum necessary portions of the portal and hepatic vein/inferior vena cava junction required to insure a functioning shunt. If the patient is being considered for living related transplantation, then lining the entire hepatic vein to the inferior vena cava may complicate transplantation, because a cuff of hepatic vein is required to complete the transplant in these patients.

Recommendations

8. Physicians who perform TIPS need to be aware of both the procedural complications and the complications due to portal diversion and must be experienced in their management (evidence: grade II-3).

9. Each center performing TIPS should have an established program of TIPS surveillance, and although there are no established guidelines, Doppler ultrasound should be performed before the patient is discharged from the hospital and at specified intervals following the procedure and the yearly anniversary of the TIPS thereafter (evidence: grade II-1).

10. Ultrasonographic findings suggesting TIPS dysfunction or recurrence of the complication of portal hypertension that lead to the initial TIPS should lead to repeat shunt venography and intervention, as indicated. The recurrence of symptoms in the face of a "normal" ultrasound does not eliminate the need for TIPS venography (evidence: grade II-2).

11. TIPS stenosis is common, especially in the first year, and Doppler ultrasound lacks the sensitivity and specificity needed to identify many of these patients. Therefore, repeat catheterization of the TIPS or upper endoscopy should be performed at the 1-year anniversary of placement, especially in those patients who bled from varices (evidence: grade II-3).

Indications

Table 4 lists the variety of conditions for which TIPS has been used. It is recognized that a number of listed indications, such as hepatorenal syndrome or Budd-Chiari syndrome, may never be assessed in larger prospective randomized controlled trials because of their low incidence. Accordingly, for these conditions recommendations will be based on review of uncontrolled series and expert opinion.

Table 4. Indications for TIPS

Efficacy Determined by Controlled Trials	Efficacy Assessed in Uncontrolled Series
Secondary prevention variceal bleeding	Refractory acutely bleeding varices
Refractory cirrhotic ascites	Portal hypertensive gastropathy
	Bleeding gastric varices
	Gastric antral vascular ectasia
	Refractory hepatic hydrothorax
	Hepatorenal syndrome (type 1 or type 2)
	Budd-Chiari syndrome
	Veno-occlusive disease
	Hepatopulmonary syndrome

Primary Prevention of Variceal Bleeding

The development of varices is a common sequela of portal hypertension. The frequency of esophageal varices varies from 30% to 70% in patients with cirrhosis, and 9% to 36% will have so-called "high-risk" varices. Esophageal varices will develop in patients with cirrhosis at a yearly rate of 5% to 8%, but in only 1% to 2% will the varices be large enough to pose a risk of bleeding. In patients with small varices, approximately 4% to 30% of the patients will develop large varices each year and will therefore be at risk of bleeding.[69-72] Use of treatments to prevent bleeding from these varices that have never bled is termed "primary prophylaxis," and beta-blockers are currently considered the best approach to prevent bleeding in this group of patients.[70] Previously, when surgical shunts were used as primary prophylaxis bleeding from varices was prevented, but this occurred at the unacceptable cost of increased mortality in the shunted patients compared with the control patients.[73] No trials comparing TIPS with other forms of therapy in the prevention of the first bleed from varices have been performed. Because TIPS, like a surgical shunt, brings with it the risks of hepatic encephalopathy, liver failure, and procedural complications, it cannot be recommended for primary prophylaxis, and its use should be limited to unique situations.

Acutely Bleeding Esophageal Varices Refractory to Medical Treatment

Most patients who present with actively bleeding varices can be controlled with pharmacological and endoscopic therapy. However, an occasional patient will rebleed or continue to bleed despite aggressive management, and these patients become candidates for portal decompression. Previous experience with surgical shunts

Table 5. Surgical Shunts and TIPS vs Endoscopic Therapy in the Prevention of Rebleeding

	Rebleeding Rate			Encephalopathy			Mortality		
Number of Patients	Endo	PCS	TIPS	Endo	PCS	TIPS	Endo	PCS	TIPS
376	49.8%	12.4%*		8.6%	17.2%†		28.8%	28.8%	
811	46.6%		18.9%*	18.7%		34.0%†	26.5%		27.3%

NOTE. Data are from D'Amico et al.[70] and Papatheodoridis et al.[77]
Abbreviations: Endo, endoscopic therapy; PCS, portacaval shunt.
*Meta-analysis revealed that rebleeding was significantly less with PCS or TIPS compared with endoscopic therapy.
†Meta-analysis revealed that incidence of encephalopathy was greater with PCS or TIPS compared with endoscopic therapy.

was poor because of the high mortality (31%-77%) associated with urgent or emergent shunting.[69,70] Although TIPS has now been used in this situation successfully, it is important to note that its urgency is an independent predictor of early mortality.[26,28] One report analyzed 15 studies in which TIPS was used to control bleeding in patients who had failed medical therapy. TIPS controlled bleeding in 93.6% ± 6.7% of patients, and early rebleeding was seen in only 12.4% ± 6.1% of the patients; however, hospital mortality at 6 weeks was high (35.8% ± 16%).[74] It is clear that the preprocedural condition of the patients (MELD score, APACHE II score, urgent indication) predict the 30-day survival after TIPS in this group of patients. Although TIPS has not been compared with alternative treatments in the acutely bleeding patient, nonselective portacaval shunts have been compared with endoscopic therapy. Shunts were more effective than endoscopic therapy in the control of bleeding, but mortality rates of 31% to 77% were observed.[70] Similar results would be expected if TIPS were compared with endoscopic therapy in the acute control of bleeding, but these studies are unlikely to occur given the desperate state of many of these patients. Pending the development of alternative therapies, TIPS will remain the only alternative to control acute variceal bleeding that is refractory to medical therapy.

Esophageal Variceal Rebleeding

Once varices have bled, the risk of rebleeding is at least 50% and many of these patients will die.[75,76] Hence, a number of therapies have been used to prevent rebleeding in these patients, most of which have been subjected to controlled trials.[70] When surgical shunts were compared with endoscopic therapy, rebleeding rates were reduced, whereas the incidence of hepatic encephalopathy was increased in the surgical groups and mortality was unaffected (Table 5).[69,70] When TIPS was first developed, it was hoped that the effect on rebleeding would mirror that of surgical shunts but with lower rates of encephalopathy because of the ability to tailor shunt size to the minimum necessary diameter required to decompress the portal system. This has not proven to be the case for a variety of reasons, including the unpredictable patencies of uncovered stents and the lack of controlled trials using stents of different diameters to prevent rebleeding. In 1999, a meta-analysis of the 11 published controlled trials comparing TIPS with endoscopic therapy was reported.[77] The results with TIPS mirror the results with surgical shunts—that is, there is less rebleeding compared with endoscopic therapy, but at the price of more encephalopathy without an improvement in survival (Table 5). As has been seen in the trials comparing surgical shunts with endoscopic therapy, the rate of crossover between treatment groups was greater for endoscopic therapy (17%) than with TIPS (2%). The cost of treating the patients with TIPS was greater than the cost of endoscopic therapy because of the need for frequent reintervention to maintain TIPS patency.[78] TIPS has also been compared with pharmacological therapy in a small number of patients. In one series of approximately 90 patients, the risk of rebleeding during 2 years of follow-up was 39% in those who received pharmacological therapy and 13% in those receiving TIPS. The frequency of encephalopathy was approximately twice in the patients treated with TIPS. Child-Turcotte-Pugh class improved in 72% of the drug group but in only 45% of the TIPS group. The 2-year probability of survival was the same in both groups (72%). Endoscopic reintervention was required in 12 of the drug-treated patients, and in 5 patients portal decompression, either via TIPS or surgery, was required for variceal rebleeding. The cost of therapy for patients receiving TIPS was twice that of the pharmacological group, in part because 70% of the TIPS patients required reintervention.[79] It is important to note the variation in the cohorts among the different trials, because in some studies patients were medical failures with several bleeds, whereas in others they had a single bleed before being randomized.

It is clear from the above studies that both TIPS and surgical shunts are the most effective method for the prevention of rebleeding. There has been one published trial in which TIPS was compared with a surgically placed

H-graft shunt.[80] The patients were not randomized but were done as pairs (*i.e.*, one receiving a surgical shunt and the second receiving a TIPS). A total of 132 patients were in the study. The frequency of rebleeding was 16% in the TIPS group and 3% in the surgical group. The patients undergoing TIPS required frequent interventions to maintain TIPS patency. Thirty-day and total mortality were 15% versus 20% and 43% versus 30% in the TIPS and surgery groups, respectively. Another randomized controlled trial comparing TIPS with distal splenorenal shunt has been completed. Rebleeding was seen in 5.5% of the distal splenorenal shunt patients and 9% of the TIPS patients (difference not significant). However, only 11% of the distal splenorenal shunt patients required reintervention to maintain patency, whereas 82% of the TIPS patients required reintervention. Survival was the same in both groups (J. M. Henderson, personal communication). Thus, both TIPS and distal splenorenal shunt are effective in preventing rebleeding in patients who have failed pharmacological or endoscopic therapy, but TIPS patients require more frequent reintervention to prevent rebleeding.

Bleeding From Gastric Varices

The efficacy of TIPS in the control of rebleeding from gastric varices has been reported in a number of small series. In most of the series, the outcome of patients with bleeding gastric varices was compared with those who had bled from esophageal varices. In none of the trials were the patients randomized to alternative therapies, and in most the TIPS was performed because of refractory bleeding. In some series, the initial HVPG in patients with gastric varices was lower than that of patients with esophageal varices, whereas in other series no differences were observed.[81-83] In these small series, TIPS was equally effective at controlling bleeding from gastric as well as esophageal varices.[81-84] Controlled trials comparing surgical shunts or glue in the treatment of these patients would help to better define the role of TIPS in the management of patients with bleeding from gastric varices. In the authors' opinion, TIPS is an important tool in the control of gastric variceal bleeding, though the final portosystemic gradient required to achieve variceal decompression may be lower than what is required for esophageal variceal bleeding, and embolization of the varices also may be required.

Prevention of Bleeding From Portal Hypertensive Gastropathy and Gastric Antral Vascular Ectasia

The diagnosis of portal hypertensive gastropathy (PHG) and gastric antral vascular ectasia (GAVE) are made endoscopically. The mucosa in PHG may show a mosaic-like pattern ("snake skin"), or, in more severe cases, cherry red and black-brown spots. The changes are usually seen in the fundus or body of the stomach. GAVE is localized to the antrum and is characterized by red patches or spots that may be diffuse or linear in appearance. PHG is limited to patients with portal hypertension, whereas GAVE can be seen in a variety of different disorders, including cirrhosis.[85] The effect of TIPS on PHG and GAVE has been examined in several small series. In one report, 75% of patients with severe PHG showed both endoscopic improvement and a decrease in the need for transfusions.[86] In another series, 9 of 10 patients showed endoscopic improvement in PHG following TIPS.[87] In contrast, bleeding from GAVE in patients with cirrhosis was unaffected by TIPS.[86]

Recommendations

12. The use of TIPS to prevent bleeding from varices that have never bled is contraindicated because of the risk of increasing morbidity and mortality (evidence; grade III).

13. TIPS is effective in controlling acute bleeding from varices that is refractory to medical therapy and is preferred to surgery in this situation (evidence: grade II-3).

14. TIPS should not be used for the prevention of rebleeding in patients who have bled only once from esophageal varices, and its use should be limited to those who fail pharmacological and endoscopic therapy (evidence: grade I).

15. TIPS is effective in the prevention of rebleeding from gastric and ectopic varices (including intestinal, stomal, and anorectal varices) and is the preferred approach for the prevention of rebleeding in this group of patients (evidence: grade II-3).

16. Pending further studies, in patients with good liver function, either a TIPS or a surgical shunt are appropriate choices for the prevention of rebleeding in patients who have failed medical therapy (evidence: grade II-2).

17. In patients with poor liver function, TIPS is preferred to surgical therapy in the prevention of rebleeding in patients who have failed medical therapy (evidence: grade III).

18. The use of TIPS in the management of PHG should be limited to those who have recurrent bleeding despite the use of beta-blockers (evidence: grade II-3).

19. TIPS is ineffective in controlling bleeding from GAVE in patients with cirrhosis and should not be used in this situation (evidence: grade II-3).

Table 6. TIPS Versus Large-Volume Paracentesis in Treatment Refractory Ascites Associated with Cirrhosis

	Number of Patients		Ascites Improved		Survival*		New or Severe Encephalopathy	
Reference	TIPS	LVP	TIPS	LVP	TIPS	LVP	TIPS	LVP
Lebrec et al.[90]	13	12	38%	0%	29%	60%	15%	6%
Rossle et al.[91]	29	31	84%†	43%	58%	32%	23%	13%
Gines et al.[92]	35	35	51%†	17%	26%	30%	60%†	34%
Sanyal et al.[22]	52	57	58%†	16%	35%	33%	38%	21%
Salerno et al.[93]	33	33	79%†‡	42%	59%†	29%	61%	39%

*Transplant-free survival after 2 years for first three studies.
†Significant difference between two groups.
‡End point was failure, which was defined as the need for at least four LVPs for recurrent ascites.

Ascites Associated With Cirrhosis

Ascites develops in patients with cirrhosis because of the development of portal hypertension in concert with splanchnic vasodilation, renal sodium retention, and active renal vasoconstriction.[88] As the liver disease progresses, the ascites becomes more resistant to diuretic therapy, and refractory ascites develops. Ascites is said to be refractory to medical treatment when it is unresponsive to sodium restriction and the use of high doses of diuretics (400 mg/d spironolactone and 160 mg/d furosemide) or the patient is intolerant of diuretic therapy.[89] Once refractory ascites develops, prognosis is poor; approximately 50% of patients die within 12 months.[88] A number of approaches have been taken in the management of patients with refractory ascites, including peritoneo-venous shunts, repeated large volume paracentesis (LVP), and TIPS. Peritoneo-venous shunts have been abandoned because of a lack of efficacy and high rate of complication except in unusual circumstances.[88] TIPS has been compared with LVP in the treatment of patients with refractory ascites associated with cirrhosis. The data from five published controlled trials are shown in Table 6. There were a total of 330 patients enrolled in these five trials.[22,90-93] In the TIPS groups, the percentage (mean ± SD) of patients who showed improvement in their ascites (lack of need for paracentesis) was 62.0% ± 19.2%, while in the LVP groups improvement was seen in 23.6% ± 18.5% of patients. The transplant-free 2-year survival in three of the studies[90-92] was similar (37% ± 17.7% for the TIPS patients and 40.1% ± 16.8% for the LVP patients), and in the fourth study[22] survival was also similar in the two groups. Only in the most recently published report was survival significantly better in the TIPS group.[93] Encephalopathy occurred somewhat more frequently in the TIPS groups compared with the LVP groups (39.4% ± 20.9% and 22.6% ± 13.9%, respectively). Somewhat surprisingly, there was no difference in the quality of life between the two groups in one of the studies.[23] Cost-effectiveness was not examined in any of the studies.

Refractory Hepatic Hydrothorax

Hepatic hydrothorax develops in patients who have ascites associated with cirrhosis when there is direct communication between the abdominal and thoracic cavities. It may develop in patients with or without clinically apparent ascites. In most patients, the defect is in the diaphragm that overlies the dome of the liver.[94] In a series of small studies, the effect of TIPS on patients with recurrent hepatic hydrothorax has been relatively uniform, with either resolution of the hepatic hydrothorax or a decrease in the need for thoracentesis.[95-97] The impact of TIPS on the survival of these patients cannot be determined, because there was no control group; however, overall survival was poor. Because the therapeutic alternatives in these patients are limited, TIPS is an important tool for the management of this complication of ascites.

Hepatorenal Syndrome

Hepatorenal syndrome (HRS) is a dreaded complication of cirrhosis, because its development is associated with a poor prognosis. HRS exists in two forms. Type 1 HRS is defined as the rapid (over a 2-week period) development of renal failure, whereas in type 2 HRS the renal failure develops more slowly.[88,89] The prognosis for patients with type 1 HRS is significantly worse than for those with type 2 HRS.[88] TIPS has been used in a number of patients with HRS. In these small series, the use of TIPS has been associated with improvements in glomerular filtration rates and renal plasma flow, as well as falls in serum creatinine and plasma aldosterone levels.[98-100] However, because none of the trials was controlled, no comparative survival benefit has been shown. In one series, only 20% of the patients with type 1 HRS were alive 1 year after TIPS creation, whereas with type 2 HRS approximately 45% were alive after 1 year.[98] These results are somewhat better than expected based on the experience of others; however, care must be exercised in comparing uncontrolled studies, because severity of disease may not be the same across studies.[88] In one of the controlled trials in which

TIPS was compared with LVP in the control of refractory ascites associated with cirrhosis as discussed above, a reduced incidence of HRS in those receiving a TIPS was observed.[22] Similar to the findings when TIPS has been used for other complications of portal hypertension, pre-TIPS bilirubin levels were predictive of survival in these patients as well.[98] Finally, creation of a TIPS in HRS patients can be difficult because of concerns about fluid overload and the need to limit the volume of contrast used. TIPS needs to be compared with other therapies such as terlipressin and other vasoactive compounds before its role in the treatment of HRS is determined, and currently its use should be considered investigatory.[88,101]

Recommendations

20. Although TIPS will decrease the need for repeated large-volume paracentesis in patients with refractory ascites associated with cirrhosis, it should be used only in those patients who are intolerant of repeated large-volume paracentesis (evidence: grade I).

21. TIPS is effective in the control of hepatic hydrothorax, but it should be used only in patients whose effusion cannot be controlled by diuretics and sodium restriction (evidence: grade II-3).

22. TIPS is not recommended for the treatment of HRS, especially type 1 HRS, pending the publication of controlled trials (evidence: grade II-3).

Budd-Chiari Syndrome

Budd-Chiari syndrome (BCS) results from blockage of exit of the blood from the liver as a result of hepatic vein thrombosis or obstruction of the inferior vena cava.[102,103] Liver injury results from hepatic congestion, and side-to-side portocaval shunts were used previously for the management of this disorder. More recently, the prognosis for these patients has been examined based on a number of variables, and although it is clear some of the patients require no intervention, for others the only solution appears to be a liver transplant. A model has been created using the following equation that allows for the prediction of survival of patients with BCS: 1.27 × encephalopathy + 1.04 × ascites + 0.72 × prothrombin time + 0.004 × bilirubin.[104] Based on this model, patients can be separated into three groups with good, intermediate, and poor 5-year survivals. Only in patients with an intermediate prognosis was a side-to-side portacaval shunt shown to have a positive impact on survival.[104] Although side-to-side portocaval shunts have been used effectively in this group of patients, operations within the portal space are to be avoided, if possible, because many of these patients may eventually require a liver transplant. There have been a number of case reports and two small series on the outcome of patients with BCS who have received a TIPS.[105,106] In one series, patients with good prognostic indices were treated symptomatically and with anticoagulation and did well.[105] In both series it was the patients with progressive disease who underwent a TIPS. Patients with acute hepatic failure due to BCS did poorly; half of the patients died in the immediate postprocedure period. Patients with more chronic disease did much better and had relief of symptoms, improvement in liver function, and a good intermediate (mean follow-up: 2-4 years) survival. Most of the patients had an underlying prothrombotic disorder and required long-term anticoagulation.[106] The frequency of TIPS insufficiency and thrombosis in the BCS patients did not differ from the frequency of these events in patients with cirrhosis. Despite these results, it remains unclear whether or not TIPS improves survival; but if TIPS is going to have an impact, it most likely will be in the patients with an intermediate prognosis.[102] Performing a TIPS in a patient with BCS can be difficult if the hepatic vein is completely occluded. In this situation, a transmesenteric TIPS may be performed, but this approach is limited to a few centers with extensive experience in creating a TIPS.[107,108]

Veno-occlusive Disease or Sinusoidal Obstruction Syndrome

Sinusoidal obstruction syndrome is seen most commonly following hematopoietic stem cell transplantation, but it can also occur following exposure to toxins in plants such as bushtea.[109] Symptoms vary from mild sodium retention to progressive liver failure leading to death. In patients with the severe form of the disease, ascites is common as a result of the development of portal hypertension. TIPS has been used in a small number of these patients.[109-113] In these series, TIPS improved ascites and lowered levels of aspartate aminotransferase and alanine aminotransferase but did not affect serum bilirubin levels. Most of the patients died despite the creation of the TIPS.

Hepatopulmonary Syndrome

Hepatopulmonary syndrome is a complication of cirrhosis in which shunts develop in the lung, leading to the development of hypoxia.[114] Six patients have been reported who had hepatopulmonary syndrome and received a TIPS; 5 of the 6 showed improvement in oxygenation, and some but not all showed a decrease in intrapulmonary shunts.[115] The mechanism through which TIPS may improve intrapulmonary shunting in patients with portal hypertension is unclear.

Recommendations

23. The decision to create a TIPS in a patient with Budd-Chiari syndrome should be based on the severity of disease, and only patients with moderate disease appear to be reasonable candidates for a TIPS (evidence: grade II-3).

24. Patients with BCS and mild disease can be managed medically, whereas those with more severe disease or acute hepatic failure are best managed by liver transplantation. (evidence: grade II-3).

25. The use of TIPS to treat sinusoidal obstruction syndrome cannot be recommended (evidence: grade II-3).

26. The use of TIPS to treat hepatopulmonary syndrome cannot be recommended (evidence: grade II-3).

Conclusions

TIPS is an important part of the current armamentarium used to treat the complications of portal hypertension. Most fellowship-trained interventional radiologists are capable of creating a TIPS in a patient with patent hepatic and portal veins. Creation of a TIPS ranks among the more complex procedures performed by interventional radiologists, and it is important that each physician monitor their success and complication rates. As with any complex intervention, the decision to create a TIPS should be reached by a gastroenterologist or hepatologist who is experienced in the management of these patients in concert with an interventional radiologist. Pre-TIPS evaluation includes routine tests of liver and kidney function as well as Doppler ultrasound, contrast-enhanced abdominal computed tomography, or magnetic resonance imaging of the liver. Once a TIPS is created, it cannot be forgotten—the patient requires frequent monitoring by Doppler ultrasound and clinic visits to look for the development of TIPS dysfunction. The use of PTFE-covered stents may reduce the risk of TIPS dysfunction, but this will not eliminate the need for continued surveillance.

TIPS will effectively prevent rebleeding from varices and decrease the need for repeat thoracentesis in patients with hepatic hydrothorax or for large-volume paracentesis in patients with refractory ascites. However, TIPS will increase the incidence of hepatic encephalopathy and will not improve survival in any of these patients. Hence, TIPS should not be considered as primary therapy for any complication of portal hypertension with the exception of bleeding gastric or ectopic varices. In all other situations, TIPS should only be created when the patient has failed other forms of medical therapy (*i.e.*, pharmacological or endoscopic therapy, diuretics, or repeated large-volume paracentesis or thoracentesis). In patients with good liver function and recurrent bleeding from varices despite medical treatment, it is unclear whether a surgical shunt or TIPS is the better form of therapy pending the publication of additional controlled trials. Which patients with BCS are best managed by TIPS remains undefined, although creation of a TIPS in select patients may be of benefit. Creation of a TIPS for the treatment of HRS or hepatopulmonary syndrome is of unproven benefit and should be considered investigatory.

Acknowledgment: The authors thank Mr. L.T. Tucker for his skilled secretarial assistance and the Practice Guidelines Committee of the AASLD for all of their help in the preparation of this manuscript. The members of the Practice Guidelines Committee include K. Rajender Reddy, M.D., Chair, Robert L. Carithers Jr., M.D., Stanley M. Cohen, M.D., Thomas W. Faust, M.D., Steven L. Flamm, M.D., Gregory J. Gores, M.D., Elizabeth Hespenheide, R.N., B.S.N., Michael R. Lucey, M.D., David R. Nelson, M.D., F. Fred Poordad, M.D., Margaret C. Shuhart, M.D., M.S., Brent A. Tetri, M.D., Zobair M. Younossi, M.D., M.P.H., and Nizar N. Zein, M.D.

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