

# ACR Appropriateness Criteria<sup>®</sup>

## Radiologic Management of Portal Hypertension

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### Abstract

Cirrhosis is a heterogeneous disease that cannot be studied as a single entity and is classified in two main prognostic stages: compensated and decompensated cirrhosis. Portal hypertension, characterized by a pathological increase of the portal pressure and by the formation of portal-systemic collaterals that bypass the liver, is the initial and main consequence of cirrhosis and is responsible for the majority of its complications. A myriad of treatment options exists for appropriately managing the most common complications of portal hypertension, including acute variceal bleeding and refractory ascites.

The American College of Radiology Appropriateness Criteria are evidence-based guidelines for specific clinical conditions that are reviewed annually by a multidisciplinary expert panel. The guideline development and revision include an extensive analysis of current medical literature from peer reviewed journals and the application of well-established methodologies (RAND/UCLA Appropriateness Method and Grading of Recommendations Assessment, Development, and Evaluation or GRADE) to rate the appropriateness of imaging and treatment procedures for specific clinical scenarios. In those instances where evidence is lacking or equivocal, expert opinion may supplement the available evidence to recommend imaging or treatment.

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**Key Words:** Appropriateness Criteria, Appropriate Use Criteria, AUC, Hepatorenal syndrome, Portal hypertension, Refractory ascites, Upper gastrointestinal bleeding, Variceal bleeding

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ACR Appropriateness Criteria® Radiologic Management of Portal Hypertension. [Variants 1 to 7](#) and [Table 1](#).

**Variant 1.** Acute variceal bleeding. Child-Pugh class A, cirrhotic with index bleed from acute esophageal variceal hemorrhage, MELD 10, no encephalopathy. Initial therapy.

Procedure	Appropriateness Category
Endoscopic management	Usually Appropriate
Medical therapy with vasoactive drugs	Usually Appropriate
Transjugular intrahepatic portosystemic shunt	Usually Not Appropriate
Surgical shunt	Usually Not Appropriate
Coated esophageal self-expandable metal stent	Usually Not Appropriate

**Variant 2.** Acute variceal bleeding. Child-Pugh class B, cirrhotic with active esophageal variceal hemorrhage, MELD 12, previously treated with octreotide and variceal ligation (EVL) on three prior occasions, no encephalopathy.

Procedure	Appropriateness Category
Endoscopic management	Usually Appropriate
Medical therapy with vasoactive drugs	Usually Appropriate
Transjugular intrahepatic portosystemic shunt	Usually Appropriate
Surgical shunt	May Be Appropriate
Coated esophageal self-expandable metal stent	Usually Not Appropriate

**Variant 3.** Acute variceal bleeding. Child-Pugh class C, cirrhotic with active esophageal and junctional variceal hemorrhage, previously treated with octreotide and endoscopic sclerotherapy, MELD 17, intermittent mild hepatic encephalopathy managed as an outpatient with nutritional support.

Procedure	Appropriateness Category
Endoscopic management	Usually Appropriate
Medical therapy with vasoactive drugs	Usually Appropriate
Transjugular intrahepatic portosystemic shunt	Usually Appropriate
Coated esophageal self-expandable metal stent	May Be Appropriate
Surgical shunt	May Be Appropriate

**Variant 4.** Acute variceal bleeding. Child-Pugh class C, cirrhotic with hepatocellular carcinoma, branch portal vein tumor thrombus, and active esophageal and gastroesophageal type 1 (GOV1) variceal hemorrhage, MELD 24.

Procedure	Appropriateness Category
Endoscopic management	Usually Appropriate
Medical therapy with vasoactive drugs	Usually Appropriate
Percutaneous transhepatic embolization	Usually Appropriate
Coated esophageal self-expandable metal stent	May Be Appropriate
Transjugular intrahepatic portosystemic shunt	May Be Appropriate
Surgical shunt	Usually Not Appropriate

**Variant 5.** Ascites. Initial therapy for Child-Pugh class B cirrhotic asymptomatic patient with small-volume ascites.

Procedure	Appropriateness Category
Medical therapy/dietary modification	Usually Appropriate
Large-volume paracentesis	Usually Not Appropriate
Volume expansion	Usually Not Appropriate
Peritoneovenous shunt	Usually Not Appropriate
Transjugular intrahepatic portosystemic shunt	Usually Not Appropriate

**Variant 6.** Ascites. Child-Pugh class B cirrhotic with chronic ascites despite daily diuretic therapy and low-sodium diet.

Procedure	Appropriateness Category
Medical therapy/dietary modification	Usually Appropriate
Large-volume paracentesis	Usually Appropriate
Transjugular intrahepatic portosystemic shunt	Usually Appropriate
Volume expansion	Usually Appropriate
Peritoneovenous shunt	Usually Not Appropriate

**Variant 7.** Ascites. Child-Pugh class B cirrhotic with chronic ascites undergoing weekly large-volume paracentesis; rapidly declining renal function unresponsive to diuretic withdrawal.

Procedure	Appropriateness Category
Transjugular intrahepatic portosystemic shunt	Usually Appropriate
Medical therapy/dietary modification	Usually Appropriate
Volume expansion	Usually Appropriate
Large-volume paracentesis	May Be Appropriate
Peritoneovenous shunt	Usually Not Appropriate

**Table 1.** Appropriateness category names and definitions

Appropriateness Category Name	Appropriateness Rating	Appropriateness Category Definition
Usually Appropriate	7, 8, or 9	The imaging procedure or treatment is indicated in the specified clinical scenarios at a favorable risk-benefit ratio for patients.
May Be Appropriate	4, 5, or 6	The imaging procedure or treatment may be indicated in the specified clinical scenarios as an alternative to imaging procedures or treatments with a more favorable risk-benefit ratio, or the risk-benefit ratio for patients is equivocal.
May Be Appropriate (Disagreement)	5	The individual ratings are too dispersed from the panel median. The different label provides transparency regarding the panel's recommendation. "May be appropriate" is the rating category and a rating of 5 is assigned.
Usually Not Appropriate	1, 2, or 3	The imaging procedure or treatment is unlikely to be indicated in the specified clinical scenarios, or the risk-benefit ratio for patients is likely to be unfavorable.

## SUMMARY OF LITERATURE REVIEW

### Introduction/Background

Portal hypertension is a common clinical syndrome, hemodynamically defined by a pathological increase of the portal pressure and by the formation of portal-systemic collaterals that bypass the liver by diverting part of the portal blood flow to the systemic circulation [1]. Portal hypertension can arise from any condition that increases resistance to portal blood flow, including both fixed structural changes (distortion of the liver microcirculation by fibrosis, angiogenesis, nodule formation, and vascular occlusion) and dynamic changes (increased vascular tone resulting from the net effect of vasodilators and vasoconstrictors on vascular smooth muscle cells of the hepatic vasculature and on activated hepatic stellate cells and myofibroblasts in the fibrous septa). Because portal hypertension can arise from any condition interfering with blood flow at any level within the portal system, it is critical to characterize portal hypertension according to the anatomic location of impaired portal blood flow. Accordingly, the causes of portal hypertension can be classified as prehepatic (involving the splenic, mesenteric, or extrahepatic portal vein), intrahepatic (parenchymal liver diseases), and posthepatic (diseases blocking the hepatic venous outflow) [1]. In Western countries, cirrhosis is by far the most common cause of portal hypertension and therefore has been the most widely investigated [2].

Portal hypertension may be asymptomatic until complications develop. Complications of portal hypertension include acute variceal hemorrhage, ascites, portal hypertensive gastropathy, spontaneous bacterial peritonitis, hepatorenal syndrome (HRS), hepatopulmonary syndrome, hepatic hydrothorax, and portopulmonary hypertension. Management of patients with portal hypertension is aimed at the prevention and treatment of its complications.

It is important to note that most randomized controlled trials discussing treatment of acute variceal bleeding tend to combine all variceal subtypes (esophageal, junctional gastroesophageal, and gastric), making interpretation of published results problematic at best. The radiologic management of gastroesophageal varices type 2 (GOV2) (cardiofundal) and isolated gastric varices (IGV1/2) is comprehensively discussed in the ACR Appropriateness Criteria® topic on “Radiologic Management of Gastric Varices” [3]. To this end, the scope of this document will instead focus on the management of esophageal varices and those gastroesophageal varices extending across the cardia into the lesser curve of the stomach, ie, gastroesophageal varices type 1 (GOV1).

Inpatient mortality among patients with cirrhosis in the United States has decreased steadily in the last 20 years

despite increases in patient age and medical complexity [4]. This is almost certainly due in part to the widespread dissemination and implementation of treatment guidelines for the management of acute variceal bleeding incorporating the use of vasoactive drugs, early endoscopic therapy and advanced endoscopic techniques, and prophylactic antibiotics.

Ascites is the most common complication in patients with cirrhosis. A decade after the initial diagnosis of compensated cirrhosis, nearly 60% of patients will have developed ascites [5]. Ascites heralds the onset of decompensation of liver disease and survival of these patients changes from 80% at 5 years [6] to 50% at 5 years [7] in the absence of liver transplantation. The characteristic hemodynamic changes and circulatory dysfunction accompanying the progression of cirrhosis predispose these patients to other complications, including dilutional hyponatremia, refractory ascites, HRS, and spontaneous bacterial peritonitis. When cirrhosis becomes refractory to conventional medical treatment, the prognosis worsens considerably with 1-year mortality rates ranging from 20% to 50% [5,8-10].

HRS is a frequent and grave complication of refractory ascites. Arterial vasodilation in the splanchnic circulation, which is triggered by portal hypertension, is thought to play a critical role in the hemodynamic changes and the decline in renal function in cirrhosis [11,12]. Based upon the rapidity of decline in renal function, there are two frequently distinguished HRS subtypes: a progressive, severe type 1 and a type 2 that shows a more constant renal dysfunction and is commonly associated with refractory ascites [13,14].

### Diagnosis of Cirrhosis and Portal Hypertension

Assessment of portal hypertension in patients with cirrhosis stratifies patients according to their risk of clinical decompensation and death, correlates with morbidity and mortality after hepatocellular carcinoma resection, and predicts the risk of treatment failure and death in patients with acute variceal bleeding [15,16]. Although liver biopsy remains the reference standard for the assessment and diagnosis of cirrhosis, hepatic vein catheterization with measurement of the hepatic venous pressure gradient (HVPG) is currently the benchmark technique for determining portal pressure. The HVPG quantifies the degree of portal hypertension due to sinusoidal resistance to blood flow. The HVPG is calculated as the difference between the wedged hepatic venous pressure and the free hepatic venous pressure. A normal HVPG is between 1 and 5 mmHg; portal hypertension is present if the HVPG is  $\geq 6$  mmHg.

Clinically significant portal hypertension occurs when the HVPG is  $\geq 10$  mmHg, at which point complications such as esophageal varices and ascites may develop. Other HVPG values have been shown to correlate with clinical outcome: an HVPG  $\geq 16$  mmHg is independently associated with higher mortality in patients with compensated and decompensated cirrhosis [17], and a reduction of HVPG by  $>20\%$  of baseline values or  $\leq 12$  mmHg is correlated with considerable reduction of risk of variceal bleeding during treatment with nonselective beta blockers [15,18].

Given that liver biopsy and hepatic vein catheterization are invasive, in recent years considerable investigation has been devoted to the development of noninvasive methods for the diagnosis of cirrhosis and portal hypertension, including ultrasonography (US) and transient elastography. The noninvasive radiologic diagnosis of liver fibrosis and cirrhosis is comprehensively discussed in the ACR Appropriateness Criteria® topic on “Chronic Liver Disease” [19].

## DISCUSSION OF PROCEDURES BY VARIANT

### **Variant 1: Acute variceal bleeding. Child-Pugh class A, cirrhotic with index bleed from acute esophageal variceal hemorrhage, MELD 10, no encephalopathy. Initial therapy**

**Medical Therapy With Vasoactive Drugs.** The first step in stopping acute variceal bleeding is the initiation of vasoactive pharmacologic agents [20] and performing endoscopic therapy after initial resuscitation when the patient is stable and bleeding has slowed or ceased. The rationale for this approach comes from several randomized controlled trials showing that early administration of a vasoactive agent facilitates endoscopy, improves early hemostasis, and lowers rate of rebleeding at 5 days [21-25]. A meta-analysis from Banares et al [26] of eight studies comparing endoscopic treatment alone with endoscopic plus vasoconstrictor treatment for acute esophageal variceal hemorrhage supports this, showing that 5-day hemostasis and 5-day mortality rates were significantly lower in patients receiving combination therapy than in those receiving endoscopic treatment alone. Five-day hemostasis was 58% in patients receiving endoscopic treatment alone compared with 77% in patients receiving combined therapy.

The aim of medical therapy for acute bleeding from esophageal varices is to reduce splanchnic blood flow and portal pressure. Two recent meta-analyses showed that the use of vasoactive agents was associated with a significantly lower risk of acute mortality and transfusion requirements,

improved hemostasis, and shorter hospital stay [20,27]. Importantly, no significant differences in efficacy were found between the different vasoactive drugs [20,27], and drug choice may be dictated by pre-existing medical comorbidities.

In addition to the use of vasoconstrictors, antibiotic prophylaxis in patients with cirrhosis and acute upper gastrointestinal bleeding who are hospitalized reduces the risk of mortality, bacterial infections, and rebleeding. In 2002, a systematic review conducted by Soares-Weiser et al [28] of eight trials evaluated the effects of antibiotic prophylaxis compared with placebo or no antibiotic prophylaxis in 864 patients with cirrhosis and acute gastrointestinal hemorrhage. A significant beneficial effect on decreasing mortality (relative risk [RR]: 0.73; 95% confidence interval [CI], 0.55-0.95) and the incidence of bacterial infections (RR: 0.40; 95% CI, 0.32-0.51) was observed. In an updated meta-analysis of 12 trials with over 1,200 patients by Chavez-Tapia et al [29], antibiotic prophylaxis was associated with reduced mortality (RR: 0.79; 95% CI, 0.63-0.98), mortality from bacterial infections (RR: 0.43; 95% CI, 0.19-0.97), bacterial infections (RR: 0.35; 95% CI, 0.26-0.47), rebleeding (RR: 0.53; 95% CI, 0.38-0.74), and days of hospitalization (mean difference:  $-1.91$ ; 95% CI,  $-3.80$  to  $0.02$ ).

**Endoscopic Management.** Therapeutic endoscopic options for esophageal varices and GOV1, including endoscopic variceal ligation (EVL) and endoscopic sclerotherapy (ES), are highly efficacious, achieving 85% to 90% rates of initial control of bleeding [30]. A trial by Lo et al [31] showed the combination of EVL and terlipressin infusion for 2 days was superior to infusion of terlipressin alone for 5 days in the reduction of very early rebleeding and treatment failure in patients with active variceal bleeding at endoscopy. As a result, combination therapy with vasoactive drugs and endoscopy has become the favored treatment algorithm in managing acute bleeding from esophageal varices. Although used with regularity outside of the United States, terlipressin is an investigational product and its safety and efficacy have not been established by the FDA.

EVL and ES are equally efficient regarding variceal eradication and recurrence during short interval follow-up, but numerous studies have shown that fewer sessions are necessary with EVL [32-34]. In a prospective randomized study by Ferrari et al [35], variceal eradication was achieved in 73.9% and 78.3% of patients treated with EVL and ES, respectively. However, mean number of effective sessions was  $2.91 \pm 2.04$  in the EVL group compared with  $4.73 \pm 3.04$  in the ES group ( $P = .02$ ).



Santos et al [36] prospectively compared EVL with *N*-butylcyanoacrylate ES in 38 patients, showing no significant differences in rates of variceal eradication (90% versus 72%,  $P = .39$ ), mortality (55% versus 56%,  $P = .52$ ), or major complications (5% versus 17%,  $P = .32$ ). Two additional randomized controlled trials specifically comparing EVL and ES in acute bleeding esophageal varices [32,37] showed that both modalities effectively arrested active bleeding. However, EVL was more effective than ES in decreasing the risk of rebleeding from esophageal varices with fewer complications. Ligation can also achieve obliteration of esophageal varices more rapidly than sclerotherapy. A meta-analysis of seven randomized trials involving 547 patients with acute bleeding from esophageal varices comparing EVL to ES confirmed that ligation reduced the rebleeding rate (odds ratio, 0.52 [95% CI, 0.37-0.74]), the mortality rate (odds ratio, 0.67 [95% CI, 0.46-0.98]), and the rate of death due to bleeding (odds ratio, 0.49 [95% CI, 0.24-0.99]) [38]. These data resulted in the Baveno VI Consensus Workshop [30] endorsing EVL as the recommended endoscopic therapy for acute bleeding esophageal varices, although ES may be used in the acute setting if EVL is technically difficult or unavailable.

Early data investigating a special subset of these patients with coexistent large esophageal varices, hypersplenism, and thrombocytopenia have showed a role for combined EVL plus partial splenic embolization (PSE) in prolonging variceal eradication and reducing mortality [39-41].

**Surgical Shunt.** Although portal decompressive surgery and esophageal transection are efficacious in achieving hemostasis, the postoperative course is often fraught with chronic or recurrent portal-systemic encephalopathy, and the mortality in these patients has been shown to be quite high (45%-79%) [42,43]. For this reason, surgical procedures in patients experiencing a first episode of acute variceal bleeding are generally limited to the small number of patients in whom medical and/or endoscopic variceal control has failed and in situations when a transjugular intrahepatic portosystemic shunt (TIPS) is not an option because of anatomical or technical problems or lack of local expertise.

**Transjugular Intrahepatic Portosystemic Shunt.** Early TIPS with expanded polytetrafluoroethylene (ePTFE)-covered stents within 72 hours (ideally <24 hours) should be considered in patients bleeding from esophageal varices or GOV1 and GOV2 at high risk of treatment failure (Child-Pugh class B with active bleeding or Child-Pugh class C with Model for End-Stage Liver Disease [MELD] <14 points) after initial pharmacologic and/or endoscopic therapy [30]. This specific variant deals with a Child-Pugh class

A patient with a MELD of 10; therefore, TIPS does not reflect initial therapy and should only be considered if medical and/or endoscopic variceal control fails to control bleeding.

**Coated Esophageal Self-Expandable Metal Stent.** There is no relevant literature supporting the use of coated esophageal self-expandable metal stent (SEMS) in this clinical setting.

**Variant 2: Acute variceal bleeding. Child-Pugh class B, cirrhotic with active esophageal variceal hemorrhage, MELD 12, previously treated with octreotide and variceal ligation (EVL) on three prior occasions, no encephalopathy**

**Medical Therapy With Vasoactive Drugs.** The first step in stopping acute variceal bleeding is the initiation of vasoactive pharmacologic agents [20] and performing endoscopic therapy after initial resuscitation when the patient is stable and bleeding has slowed or ceased. The rationale for this approach comes from several randomized controlled trials showing that early administration of a vasoactive agent facilitates endoscopy, improves early hemostasis, and lowers rate of rebleeding at 5 days [21-25]. A meta-analysis from Banares et al [26] of eight studies comparing endoscopic treatment alone with endoscopic plus vasoconstrictor treatment for acute esophageal variceal hemorrhage supports this, showing that 5-day hemostasis and 5-day mortality rates were significantly lower in patients receiving combination therapy than in those receiving endoscopic treatment alone. Five-day hemostasis was 58% in patients receiving endoscopic treatment alone compared with 77% in patients receiving combined therapy.

The aim of medical therapy for acute bleeding from esophageal varices is to reduce splanchnic blood flow and portal pressure. The most common vasoactive agents used to control bleeding and to prevent variceal rebleeding include terlipressin, somatostatin, or octreotide [27].

**Endoscopic Management.** Therapeutic endoscopic options for esophageal varices and GOV1, including EVL and ES, are highly efficacious, achieving 85% to 90% rates of initial control of bleeding. A trial by Lo et al [31] showed the combination of EVL and terlipressin infusion for 2 days was superior to infusion of terlipressin alone for 5 days in the reduction of very early rebleeding and treatment failure in patients with active variceal bleeding at endoscopy. As a result, combination therapy with vasoactive drugs and endoscopy has become the favored

treatment algorithm in managing acute bleeding from esophageal varices.

Early data investigating a special subset of these patients with coexistent large esophageal varices, hypersplenism, and thrombocytopenia have showed that there is a role for combined EVL plus PSE in prolonging variceal eradication and reducing mortality [39-41].

**Surgical Shunt.** Numerous randomized controlled trials comparing a variety of surgical shunts were published and results showed that all types of surgical shunts were effective at preventing rebleeding, but no one technique showed a survival advantage relative to others [42,44,45]. A number of randomized trials have compared surgical shunts and TIPS, but there is considerable heterogeneity in study design and surgical techniques. Rosemurgy et al [46] in an 18-year follow-up of a prospective randomized trial comparing TIPS, with a small-diameter (8 mm) prosthetic H-graft portocaval shunt for portal decompression was presented. The study showed a survival benefit of H-graft portocaval shunt compared with TIPS for patients with Child-Pugh class A (91 months versus 19 months;  $P = .009$ ) or class B (63 months versus 21 months;  $P = .02$ ) liver disease. Shunt failure occurred later after H-graft portocaval shunt than TIPS (45 months versus 22 months;  $P = .04$ ). A primary critique of this study was that patients were not truly randomized but, rather, sequentially entered into the study.

In another prospective trial by Henderson et al [47], 140 patients with Child-Pugh class A or B cirrhosis and refractory variceal bleeding were randomized to receive distal splenorenal shunt or TIPS for portal decompression. There was no significant difference in rebleeding, hepatic encephalopathy, or survival between distal splenorenal shunt and TIPS, however, shunt dysfunction (stenosis and thrombosis) and reintervention were significantly higher in the TIPS group. Three prospective randomized trials and one retrospective case-controlled study were identified in a meta-analysis of comparative trials of TIPS and surgical shunting that was undertaken by Clark et al [48]. Significantly, better 2-year survival and less frequent shunt failure were seen in patients undergoing surgical shunting compared with TIPS. However, newer commercially available ePTFE-covered stent grafts were not available when these studies were published. Comparative trials of surgical shunts and covered stent grafts have not been undertaken to evaluate shunt dysfunction and the need for reintervention in this setting. Nonetheless, despite these data, the evolution of medical and surgical care over the last several decades has been toward minimally invasive therapeutics, and the surgical management of portal hypertension has

disappeared from the armamentarium of well-trained general surgeons [48].

**Transjugular Intrahepatic Portosystemic Shunt.** A number of studies have specifically addressed the efficacy of TIPS versus endoscopic therapy to manage portal hypertension complicated by recurrent esophageal variceal hemorrhage [49-55]. Despite considerable heterogeneity of control groups, early studies clearly showed that TIPS reduced the risk of rebleeding but did so at the cost of increased hepatic encephalopathy without improved survival [56,57]. As a result, TIPS was largely relegated to the role of “rescue therapy” when all other pharmacologic and endoscopic options had failed. In the last decade, two seminal studies have challenged this salvage role and shown that early pre-emptive TIPS for acute variceal bleeding improves clinical outcomes [58,59].

In a prospective study by Monesillo et al [59] involving patients at high risk for treatment failure, as defined by HVPG  $\geq 20$  mmHg, early treatment with TIPS improved the prognosis in comparison with medical treatment alone. High-risk patients were randomly allocated either to receive TIPS within the first 24 hours after admission or to receive pharmacologic and/or endoscopic therapy alone. The medical treatment group had more treatment failures, transfusion requirements, need for intensive care, and worse actuarial probability of survival. A cogent critique of this study, however, was that the interventions administered in the medical treatment group were not the current standard of care, which may have resulted in worse outcomes than expected in this group. In addition, in the high-risk TIPS group, all TIPS were created with bare stents—this was true of all TIPS prior to 2000—and not stent grafts. The use of stent grafts would have almost certainly magnified the benefits seen in the TIPS cohort, as the use of commercially available ePTFE-covered stent grafts is associated with reduced TIPS dysfunction and superior TIPS patency when compared with bare stents [60-65].

In a more recent prospective study from García-Pagán et al [58], 63 high-risk patients (Child-Pugh class C with MELD  $< 14$  or Child-Pugh class B with active bleeding at endoscopy), who had been treated with vasoactive drugs plus endoscopic therapy, were randomized to receive TIPS within 72 hours after randomization (with ePTFE-covered stent grafts) or continue vasoactive drug therapy followed after 3 to 5 days by treatment with propranolol or nadolol and long-term endoscopic band ligation. In this study, early TIPS significantly improved 1-year actuarial rebleeding and survival with no increased risk of hepatic encephalopathy, further supporting the potential of this therapy to improve outcomes in patients with acute variceal bleeding at high

risk of failure. A postrandomized controlled observational study in a nearly similar patient cohort using similar interventions was able to replicate these results [66], as was a second observational study with identical inclusion criteria [67]. In the latter study by Rudler et al [67], the 1-year actuarial rate of those remaining free of variceal rebleeding was 97% in the early TIPS group versus 51% in the standard treatment group.

Interestingly, a meta-analysis by Halabi et al [68] reviewed nine randomized controlled trials comparing TIPS to endoscopic intervention. This meta-analysis included many of the aforementioned studies that had led to the adoption of TIPS as rescue therapy [50-52,54,55,69] as well as the García-Pagán et al seminal work. When subgroup analysis was conducted, thus restricting analysis of these randomized controlled trials to only high-risk patients (Child-Pugh class B or C) and to those receiving early TIPS (within 5 days of randomization), TIPS yielded results superior to endoscopic therapy with risk reduction in 1-year mortality (RR, 0.68; 95% CI, 0.49-0.96,  $P = .03$ ) and 1-year incidence of variceal rebleeding (RR, 0.28; 95% CI, 0.20-0.40,  $P < .001$ ). No significant difference in the 1-year incidence of hepatic encephalopathy was observed (RR, 1.36; 95% CI, 0.72-2.56,  $P = .34$ ) although more considerable heterogeneity was noted among studies in this outcome. As a result, the updated Baveno VI Consensus Workshop [30] emphasizes the critical importance of early TIPS placement (within 72 hours, ideally in  $<24$  hours) with ePTFE-covered stent grafts in patients bleeding from esophageal varices or GOV1 and GOV2 at high risk of treatment failure (Child-Pugh class B with active bleeding or Child-Pugh class C with MELD  $<14$  points) after initial pharmacologic and endoscopic therapy.

**Coated Esophageal Self-Expandable Metal Stent.** There is no relevant literature supporting the use of SEMS in this clinical setting.

**Variant 3: Acute variceal bleeding. Child-Pugh class C, cirrhotic with active esophageal and junctional variceal hemorrhage, previously treated with octreotide and endoscopic sclerotherapy, MELD 17, intermittent mild hepatic encephalopathy managed as an outpatient with nutritional support**

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**Endoscopic Management.** Therapeutic endoscopic options for esophageal varices and GOV1, including EVL and ES, are highly efficacious, achieving 85% to 90% rates of initial control of bleeding. A trial by Lo et al [31] showed the combination of EVL and terlipressin infusion for 2 days was superior to infusion of terlipressin alone for 5 days in the reduction of very early rebleeding and treatment failure in patients with active variceal bleeding at endoscopy. As a result, combination therapy with vasoactive drugs and endoscopy has become the favored treatment algorithm in managing acute bleeding from esophageal varices.

Early data investigating a special subset of these patients with coexistent large esophageal varices, hypersplenism, and thrombocytopenia have showed a role for combined EVL plus PSE in prolonging variceal eradication and reducing mortality [39-41].

**Surgical Shunt.** By survival curve analysis, Rosemurgy et al [70] demonstrated that actual survival after H-graft shunts was superior to that after TIPS. However, those results only applied to patients of Child-Pugh class A and/or B or with MELD scores  $<13$ , which differs from the patient in this variant. The 18-year follow-up of this prospective randomized controlled trial comparing TIPS with small-diameter prosthetic H-graft portocaval shunt for portal decompression demonstrated patients of Child-Pugh class C disease who underwent TIPS survived longer than patients of Child-Pugh class C who underwent H-graft portocaval shunt (45 months versus 22 months;  $P = .04$ ) [41]. Importantly, this work preceded the advent of commercially available ePTFE-covered stent grafts, which



have become the standard of care for TIPS placement due to a dramatic reduction in late TIPS stenosis and dysfunction [48].

**Transjugular Intrahepatic Portosystemic Shunt.** The results of the Barcelona group randomized controlled trial [57] and the subsequent postsurveillance study from the same group [61] were instrumental in the Baveno V and later Baveno VI Consensus Workshop [30] emphasizing the critical importance of early TIPS placement (within 72 hours, ideally <24 hours) with ePTFE-covered stent grafts in patients bleeding from esophageal varices or GOV1 and GOV2 at high risk of treatment failure (Child-Pugh class B with active bleeding or Child-Pugh class C with MELD <14 points) after initial pharmacologic and endoscopic therapy. However, the clinical criteria used to define high-risk patients eligible for early TIPS have several shortcomings: the prognostic value of their high-risk criteria had not until recently been confirmed in observational studies, and several of the studies were hampered by considerable subjectivity (for instance, what constitutes “active bleeding at endoscopy” and some components of the Child-Pugh score). As such, the most recent Baveno recommendations [26] include the need to refine the criteria to identify candidates for early TIPS.

Several alternatives seeking to refine the early TIPS criteria have been proposed [71,72]. In an observational multicenter study undertaken to validate pre-existing systems of risk stratification, Conejo et al [73] observed 915 patients with cirrhosis and acute variceal bleeding who received standard treatment (drugs, antibiotics, and endoscopic ligation, with TIPS as the rescue treatment) over an 8-year period in Canada and Europe. The high-risk criteria studied included three rules thought to discriminate patients at high risk of death from those with low risk: 1) early TIPS criteria (Child-Pugh class B with active bleeding at endoscopy or Child-Pugh class C), 2) MELD 19 criteria (patients with MELD scores of  $\geq 19$ ), and 3) Child-Pugh class C-C1 criteria (Child-Pugh class C with plasma level of creatinine of 1 mg/dL or more and a MELD of  $\geq 19$ ). Results of this observational study revealed patients with Child-Pugh class B cirrhosis and active variceal bleeding who receive standard therapy, regardless of the presence of active bleeding, have a 3-fold lower mortality than patients with Child-Pugh class C cirrhosis. Patients with Child-Pugh class C cirrhosis and/or MELD  $\geq 19$ , were considered to be of high risk of death (28.3% of patients classified as high risk by the early TIPS criteria died, whereas only 7.0% of patients classified as low risk died; 46.0% of patients classified as high risk by the MELD 19 criteria died, whereas only 8.1% of patients classified as low risk died; 51.9% of patients classified as high risk by the Child-Pugh

class C-C1 criteria died, whereas only 10.9% of patients classified as low risk died). Certainly, further research is necessary to define the optimum risk stratification for comparative effectiveness research and real-world practice, but such efforts at external validation prove invaluable to understanding and optimizing early TIPS in the high-risk cirrhotic patient with acute variceal bleeding.

Although the Child-Pugh score is decisive for selection of patients at high risk, some argue that it fails in predicting outcomes in early or emergent TIPS-treated patients. Objective variables at admission such as MELD score have been shown to be a more valid metric for risk stratification and predictor of early death in patients undergoing elective and emergent TIPS procedures [74-78]. In one prospective observational study, Reverter et al [72] showed that a MELD score of  $\geq 19$  resulted in a high risk (20% or greater) of death within 6 weeks in patients with acute variceal bleeding. Similarly, a MELD score of  $>20$  was predictive of mortality in a study of Asian patients treated for acute variceal hemorrhage with TIPS [79]. The aforementioned observational study of 915 patients by Conejo et al [73] reported early mortality in 46% of early TIPS-eligible patients with a MELD score of  $\geq 19$ . Casadaban et al [75] confirmed the MELD score to be an excellent predictor of 90-day mortality in the emergent TIPS population (area under receiver operator characteristic [AUROC] = 0.842; 95% CI, 0.755-0.928). Using AUROC analysis, a MELD cutoff at 18 had a sensitivity and specificity of 80.9% and 69.4%, respectively, for predicting 90-day post-TIPS mortality, and the 90-day post-TIPS mortality rates for MELD scores  $\leq 10$ , 11 to 18, 19 to 25, and  $\geq 26$  measured 9%, 13%, 36%, and 83%, respectively [75].

### **Coated Esophageal Self-Expandable Metal Stent.**

When applied as salvage therapy in patients with advanced liver disease (high HVPG, Child-Pugh class C), TIPS placement can result in deterioration of liver function as portal blood flow is diverted away from the liver parenchyma. With this in mind, emerging technologies that attempt to provide usefulness in the management of patients with acute esophageal variceal hemorrhage that are not suitable candidates for TIPS are being investigated. Esophageal-coated self-expanding metal stents provide rapid control of bleeding by tamponade of varices in the distal esophagus, however, there is no risk of treatment-related liver dysfunction as can be seen in patients with advanced liver disease post-TIPS. Following successful preclinical animal studies, five small case series [80-84] reported excellent control of bleeding (85% to 100%) with low risk of stent migration in patients with uncontrolled esophageal variceal hemorrhage and contraindication to TIPS placement

(advanced liver disease, hepatocellular carcinoma, multisystem organ failure). However, mortality was quite high across studies with rates of 26.5% to 56% at 30 days and 50% to 77% at 42 to 60 days. Undoubtedly, self-expanding metal stents are an interesting alternative to balloon tamponade or emergent salvage TIPS as a bridging intervention to definitive management, and further investigation is warranted.

**Variant 4: Acute variceal bleeding. Child-Pugh class C, cirrhotic with hepatocellular carcinoma, branch portal vein tumor thrombus, and active esophageal and gastroesophageal type 1 (GOV1) variceal hemorrhage, MELD 24**

**Medical Therapy With Vasoactive Drugs.** The first step in stopping acute variceal bleeding is the initiation of vasoactive pharmacologic agents [20] and performance of endoscopic therapy after initial resuscitation when the patient is stable and bleeding has slowed or ceased. The rationale for this approach comes from several randomized controlled trials showing that early administration of a vasoactive agent facilitates endoscopy, improves early hemostasis, and lowers rate of rebleeding at 5 days [21-25]. A meta-analysis from Banares et al [26] of eight studies comparing endoscopic treatment alone with endoscopic plus vasoconstrictor treatment for acute esophageal variceal hemorrhage supports this, showing that 5-day hemostasis and 5-day mortality rates were significantly lower in patients receiving combination therapy than in those receiving endoscopic treatment alone. Five-day hemostasis was 58% in patients receiving endoscopic treatment alone compared with 77% in patients receiving combined therapy.

The aim of medical therapy for acute bleeding from esophageal varices is to reduce splanchnic blood flow and portal pressure. The most common vasoactive agents used to control bleeding and to prevent variceal rebleeding include terlipressin, somatostatin, or octreotide [27].

**Endoscopic Management.** Therapeutic endoscopic options for esophageal varices and GOV1, including EVL and ES, are highly efficacious, achieving 85% to 90% rates of initial control of bleeding. A trial by Lo et al [31] showed that the combination of EVL and terlipressin infusion for 2 days was superior to infusion of terlipressin alone for 5 days in the reduction of very early rebleeding and treatment failure in patients with active variceal bleeding at endoscopy. As a result, combination therapy with vasoactive drugs and endoscopy has become the favored treatment algorithm in managing acute bleeding from esophageal varices.

Early data investigating a special subset of these patients with coexistent large esophageal varices, hypersplenism, and thrombocytopenia have showed a role for combined EVL plus PSE in prolonging variceal eradication and reducing mortality [39-41].

**Surgical Shunt.** There is no relevant literature supporting the use of decompressive surgical shunt placement in this clinical setting.

**Transjugular Intrahepatic Portosystemic Shunt.** The patient in this variant is a Child-Pugh class C cirrhotic patient with branch portal vein thrombosis and a very high MELD score. Poor survival has been demonstrated in patients with high MELD scores ( $\geq 19$ ), particularly if hemodynamically unstable at the time of admission [85]. In the Reverter et al prospective observational study [72], these findings were confirmed, showing that a MELD score of  $\geq 19$  has a high risk (20% or greater) of death within 6 weeks in patients with acute variceal bleeding. Similarly, a MELD score of  $>20$  was predictive of mortality in a study of Asian patients treated for acute variceal hemorrhage with TIPS [79]. The aforementioned observational study of 915 patients by Conejo et al [73] reported early mortality in 46% of early TIPS-eligible patients with a MELD score of  $\geq 19$ . Casadaban et al [75] confirmed the MELD score to be an excellent predictor of 90-day mortality in the emergent TIPS population (AUROC = 0.842; 95% CI, 0.755-0.928). Using AUROC analysis, a MELD cutoff at 18 had a sensitivity and specificity of 80.9% and 69.4%, respectively, for predicting 90-day post-TIPS mortality, and the 90-day post-TIPS mortality rates for MELD scores  $\leq 10$ , 11 to 18, 19 to 25, and  $\geq 26$  measured 9%, 13%, 36%, and 83%, respectively [75].

Portal vein thrombosis is common in patients with advanced cirrhosis—although incompletely understood, reduced portal blood flow is thought to play a critical role—and has been shown to negatively impact survival [86,87]. Historically, there has been considerable debate about portal thrombosis and TIPS placement. For some researchers, portal vein thrombosis reflects an absolute contraindication to TIPS [88], whereas for others it is a relative contraindication because of technical difficulties [89,90]. More recently, however, many investigators now consider portal vein thrombosis an indication for TIPS [91-93]. A systematic review and meta-analysis by Valentin et al [94] of 18 observational, prospective, and randomized controlled trials evaluating patients with a diagnosis of portal vein thrombosis who underwent TIPS revealed a pooled technical success rate of 86.7% (95% CI, 78.6%-92.1%). The pooled rate of portal vein

recanalization after TIPS was 84.4% (95% CI, 78.4%-89.0%), whereas the pooled mean change in the portosystemic gradient was 14.5 mmHg (95% CI, 1.3-17.7 mmHg). In the 10 trials that reported data on the rate of hepatic encephalopathy, the pooled rate of hepatic encephalopathy was 41% (95% CI, 19.2%-32.6%). These data, in concert with advancements in the use of adjunctive tools, such as intracardiac echocardiography, to facilitate TIPS in the patient with complex anatomy or portal vein thrombosis, have led many to endorse TIPS as a viable treatment option in patients with cirrhosis and portal vein thrombosis.

**Coated Esophageal Self-Expandable Metal Stent.** When applied as salvage therapy in patients with advanced liver disease (high HVPg, Child-Pugh class C), TIPS placement can result in deterioration of liver function as portal blood flow is diverted away from the liver parenchyma. With this in mind, emerging technologies that attempt to provide usefulness in the management of patients with acute esophageal variceal hemorrhage that are not suitable candidates for TIPS are being investigated. Esophageal-coated SEMSs provide rapid control of bleeding by tamponade of varices in the distal esophagus; however, there is no risk of treatment-related liver dysfunction as can be seen in patients with advanced liver disease post-TIPS. Following successful preclinical animal studies, five small case series [80-84] reported excellent control of bleeding (85% to 100%) with low risk of stent migration in patients with uncontrolled esophageal variceal hemorrhage and contraindication to TIPS placement (advanced liver disease, hepatocellular carcinoma, multisystem organ failure). However, mortality was quite high across studies with rates of 26.5% to 56% at 30 days and 50% to 77% at 42 to 60 days. Undoubtedly, SEMSs are an interesting alternative to balloon tamponade or emergent salvage TIPS as a bridging intervention to definitive management, and further investigation is warranted.

**Percutaneous Transhepatic Embolization.** Conventional percutaneous transhepatic variceal embolization (PTVE) was introduced over 30 years ago for the treatment of esophageal and gastric varices [95], but this approach has not become widely adopted because of high rebleeding rates. The present role of PTVE remains limited to those patients in whom TIPS placement presents an unnecessarily high risk of hepatic encephalopathy or impaired liver function. A retrospective study by Tian et al [96] comparing long-term results of PTVE with cyanoacrylate and TIPS for treatment of esophageal variceal bleeding in 139 cirrhotic patients demonstrated rebleeding rates of 20.8% and 30.2% in the PTVE and TIPS groups, respectively ( $P = .229$ ). For

patients with MELD scores  $\geq 18$  at 1, 3, and 5 years, the survival rates were 96.7%, 72.0%, and 36.0%, respectively, in the PTVE group. This compares with 1-, 3-, and 5-year survival rates of 84.2%, 39.9%, and 16.0%, respectively, in the TIPS group ( $P = .037$ ). Patients in the PTVE group also have less postprocedural encephalopathy (16.7% following PTVE versus 58.1% following TIPS,  $P = .000$ ) and demonstrated a trend toward improvement in mean MELD scores following treatment. A retrospective study of 65 patients with acute massive variceal hemorrhage treated with combined PTVE with PSE (PTVE/PSE) or PTVE alone demonstrated a clinically significant benefit on cumulative recurrent bleeding rates and survival at 6-, 12-, and 24-months in those who underwent the combined approach. These data suggest improved long-term efficacy of combined PTVE/PSE versus PTVE alone for decreasing rebleeding and maintaining hepatic reserve in patients with cirrhosis and esophagogastric variceal massive hemorrhage unable to undergo other procedures [96].

A transsplenic approach to recanalize portal occlusion, restore portal flow, and embolize varices can be suitable for use in patients unfit for surgery in whom medical and endoscopic management have failed and options for conventional TIPS procedure are compromised. In select patients, in whom transhepatic access is not feasible (chronic intrahepatic portal vein stenosis or occlusion, cavernous transformation) or desirable (liver transplant recipients, for instance), percutaneous transsplenic access provides a straightforward way to access the portal venous system as well as gastric or esophageal varices [97]. There is a paucity of data reporting outcomes of transsplenic variceal embolization, however, a small subset of case studies and limited single-institution series have described local experience with the procedure. Gong et al [98] successfully performed percutaneous transsplenic variceal embolization in 16 of 18 patients (89%) with hepatocellular carcinoma complicated by portal vein tumor thrombus and concurrent gastro-fundal variceal bleeding. Fifteen of 16 patients whose varices were successfully embolized had no recurrent esophageal or gastro-fundal variceal bleeding during follow-up to 12 months. In one case series by Tuite et al [99], 3 patients with life-threatening variceal hemorrhage secondary to portal vein thrombosis underwent endovascular variceal embolization via the transsplenic route. Each patient underwent successful portal or splenic vein recanalization with or without TIPS creation and variceal embolization with conventional catheter and guidewire techniques. Nevertheless, a transsplenic access route must be respected as an approach of last resort as complications in the form of intra-abdominal or intrasplenic bleeding might require transarterial embolization or open surgical conversion.

### Variant 5: Ascites. Initial therapy for Child-Pugh class B cirrhotic asymptomatic patient with small-volume ascites

**Medical Therapy/Dietary Modification.** A detailed discussion of the medical management of patients with uncomplicated ascites is beyond the scope of this literature review. Nonetheless, it is critical to recognize that the standard treatment protocol for ascites caused by end-stage liver disease is a stepwise approach, beginning with management of underlying liver disease (including abstinence from alcohol), dietary sodium restriction, diuretic therapy, and paracentesis [100,101].

**Large-Volume Paracentesis.** Although diagnostic paracentesis with concomitant analysis of the ascitic fluid is fundamental to caring for patients with new uncomplicated ascites prior to any therapy to exclude causes of ascites other than cirrhosis and rule out spontaneous bacterial peritonitis, large-volume paracentesis is generally only reserved for patients with large or gross ascites marked by abdominal distension (grade 3 ascites or anticipated fluid volume in excess of 5 L).

**Volume Expansion.** As the basic pathophysiological process that leads to ascites is a reduction of the effective arterial blood volume, albumin has been advocated as a treatment for many of the complications of cirrhosis and ascites [102-104]. In one retrospective study of 19 cirrhotic patients with contraindications to TIPS (portal vein thrombosis, advanced age, encephalopathy, hyperbilirubinemia), chronic intravenous infusion of albumin (50 g/wk) resulted in a significant loss of body weight in 89% of patients and no significant change in serum biochemistries 8 weeks after initiation of therapy [100]. In one randomized controlled trial of cirrhotic patients with ascites, weekly infusions of intravenous albumin (25 g/wk) in addition to standard diuretics was shown to produce improved diuretic responsiveness, shorter hospitalization, lower likelihood of hospital readmission, and lower probability of ascites reaccumulation, however, there was no effect on survival [105]. A subsequent randomized controlled trial by the same investigators showed that the long-term albumin administration beyond 1 year (25 g/wk up to 1 year, 25 g every 2 weeks thereafter) after first-onset ascites significantly improved patients' survival and decreased the risk of ascites recurrence [106]. To date, the requirement for intravenous infusion limits standardized recommendation of albumin use.

**Transjugular Intrahepatic Portosystemic Shunt.** There is no relevant literature regarding the use of TIPS in this clinical setting.

**Peritoneovenous Shunt.** There is no relevant literature regarding the use of peritoneovenous shunts in this clinical setting.

### Variant 6: Ascites. Child-Pugh class B cirrhotic with chronic ascites despite daily diuretic therapy and low-sodium diet

**Medical Therapy/Dietary Modification.** A detailed discussion of the medical management of patients in this setting is beyond the scope of this review. Circulatory dysfunction and activation of neuro-humoral systems with sodium and water retention play a fundamental role in the pathogenesis of refractory ascites. There has been an increasing interest in research on drugs that may improve circulatory and renal function, particularly vasoconstrictors and selective antagonists of the V<sub>2</sub>-receptors of vasopressin, known as vaptans. It has been hypothesized that vaptans may reduce the recurrence of ascites by increasing free-water clearance. In the largest trial to date [107], 1,200 patients with difficult-to-treat ascites with and without concomitant diuretic treatments were included in three randomized double-blind studies comparing Satavaptan, a selective V<sub>2</sub> receptor antagonist, with placebo (spironolactone). Satavaptan was no more effective than placebo in the control of ascites. In addition, in one of the three studies, mortality was actually higher in patients treated with Satavaptan compared with placebo (hazard ratio: 1.47; 95% CI, 1.01-2.15); no significant differences in mortality between the two groups were observed in the other two studies. On the contrary, three multicenter randomized controlled trials [108-110] comparing Satavaptan to low-dose diuretic therapy in cirrhotic patients with ascites demonstrated beneficial clinical effects on ascites, including more rapid mobilization of ascitic fluid, decreased frequency of paracenteses, and improvements in serum sodium levels. Additional well-designed randomized trials are requisite to fully understanding the role of vasopressin receptor antagonists in the management of recidivant ascites.

However, literature supports stopping beta-blockers [111] and consideration of stopping other medications that may decrease renal perfusion.

**Large-Volume Paracentesis.** Serial large-volume paracentesis has become the mainstay in the management of diuretic-resistant and diuretic-intractable ascites [112-115]. Although therapeutic paracentesis relieves symptoms rapidly with few technical complications, it does not correct the underlying mechanisms of ascites formation and has negative effects of systemic hemodynamics and renal function [116].



Two randomized controlled trials of 158 cirrhotic patients with tense ascites comparing serial large-volume paracentesis and intravenous albumin infusion with standard diuretic therapy (spironolactone and furosemide) showed that large-volume paracentesis (4-8 L/d) was safer and more effective for the treatment of tense ascites than the use of high-dose diuretics [117,118]. The incidence of hepatic encephalopathy, renal impairment, electrolyte abnormalities, and hemodynamic disturbances was significantly higher in those patients treated with diuretics, resulting in prolonged hospitalization in this cohort.

Large-volume paracentesis does not alter the pathogenesis of ascites formation, and ascites will recur following paracentesis. The interval between consecutive paracenteses can be widely variable and must be weighed against the compliance with dietary sodium restriction, patient body habitus, rate of ascites reaccumulation, and overall capacity to tolerate tense ascites and abdominal distension. The frequency and the volume of large-volume paracentesis can be determined from a patient's sodium intake.

Adherence to a sodium-restricted diet ( $\leq 88$  mmol/d) should result in ascites accumulation of  $<4$  L/wk [101]. Those patients requiring removal of  $>8$  L every 2 weeks **are almost certainly noncompliant with dietary sodium restriction, and counseling with a dietician is recommended to reduce the burden of frequent paracenteses for both the patient and the physician.**

The most frequent complication of serial large-volume paracentesis is asymptomatic hypovolemia and renal impairment, an event called (post-) paracentesis-induced circulatory dysfunction (PICD). This is discussed in the Volume Expansion section below.

**Volume Expansion.** The most frequent complication of serial large-volume paracentesis is asymptomatic hypovolemia and renal impairment, an event called (post-) PICD. Although the pathophysiology and factors predicting the development of PICD have not been fully elucidated, the phenomenon is thought to be secondary to the rapid drop in intra-abdominal pressure following paracentesis, thereby improving venous return to the right heart and transiently increasing cardiac output [119-121]. This hyperkinetic circulatory state increases shear stress within peripheral vessels, consequently decreasing the effective arterial blood volume. This is documented by significantly increased activation of the renin-angiotensin-aldosterone system and sympathetic nervous system as well as stimulation of vasopressin secretion with subsequent free-water retention. PICD, strictly defined as an increase in plasma renin activity of  $>50\%$  of the pretreatment value on days 4 to 6 after paracentesis, develops in up to 80% of patients in the absence of volume expansion at the time of paracentesis [119,121,122].

Because PICD does not occur after every session of large-volume paracentesis, there is considerable debate regarding the use and choice of volume expanders following paracentesis. In a prospective study by Ginés et al [123], 289 cirrhotic patients were randomized to treatment by total paracentesis plus intravenous albumin, dextran-70, or polygeline. PICD occurred more frequently in patients treated with dextran-70 (34.4%;  $P = .018$ ) or polygeline (37.8%;  $P = .004$ ) than in those receiving albumin (18.5%). Planas et al [124] confirmed these findings in a randomized trial of 88 patients randomized to receive dextran-70 versus albumin as plasma expanders following total paracentesis. There was a significant increase in plasma renin activity and aldosterone concentration (30% over baseline values) observed in 51% of patients treated with dextran-70 and in only 15% of those treated with albumin ( $P = .0012$ ). Other volume expanders, such as saline infusion, have been shown to be less effective than albumin in the prevention of PICD [125], although differences between cohorts were not shown to be significant when the total volume of ascites evacuated was  $<6$  L per session. Another randomized, double-blind study by Moreau et al [126] supports the use of albumin compared with polygeline infusion, showing that patients in the polygeline group had a 1.6-fold higher risk for developing a liver-related complication than those in the albumin group. Present recommendations by the International Ascites Club advocate for the infusion of albumin of 6 to 8 g/L of ascetic fluid removed for large-volume paracentesis of  $>6$  L [127].

It has been suggested that the administration of vasoconstrictors, such as terlipressin [128-130] or midodrine [122,131], instead of intravenous albumin may show benefit in PICD prevention, as vasodilatation plays a fundamental role in the development of PICD. In a prospective trial by Singh et al [131], 40 patients undergoing paracentesis were randomized to receive midodrine, an oral  $\alpha$ -adrenergic agonist, or intravenous albumin. Plasma renin activity at baseline and at 6 days after paracentesis did not differ between the two groups, leading the investigators to suggest that midodrine may be as effective as albumin in preventing PICD in cirrhotic patients. Compared with albumin, additional benefits of midodrine include its ability to orally dose the medication. A conflicting opinion regarding the efficacy of midodrine was made following a smaller single-center pilot study by Appenrodt et al [122]. In this study, 24 patients were randomized to receive oral midodrine or intravenous albumin after large-volume paracentesis. PICD, defined in this study as a rise in plasma renin concentration on day 6 by  $>50\%$  of the baseline value, developed in 60% of the midodrine group and only in 31% of the albumin group. The results undoubtedly question the efficacy of midodrine in preventing the development of PICD, but the study was



severely limited by its small sample size and fixed dosing regimen that did not consider dynamic hemodynamic parameters. Further investigation is warranted to elucidate the role of concurrent midodrine with large-volume paracentesis.

**Transjugular Intrahepatic Portosystemic Shunt.** The first randomized study of TIPS for the treatment of refractory ascites by Lebrech et al [132] reported high mortality in patients receiving TIPS, despite improved control of ascites in Child-Pugh class B cirrhotic patients. A second study by Rössle et al [133] of 60 patients randomized to receive TIPS or large-volume paracentesis for refractory ascites showed improved control of ascites and a trend toward improved survival following TIPS. In this study, the probability of survival without liver transplantation was 69% and 58% at 1 and 2 years, respectively, in the shunt group, as compared with 52% and 32%, respectively, in the paracentesis group ( $P = .11$  for the overall comparison). One of the largest international, multicenter, prospective, randomized controlled trials to date from The North American Study for the Treatment of Refractory Ascites sought to clarify this problem by comparing the clinical use of repeated total paracentesis, sodium restriction, and diuretic therapy (medical therapy arm), with uncovered TIPS plus medical therapy (TIPS arm) in patients with cirrhosis and refractory ascites [134]. TIPS plus medical therapy was significantly superior to medical therapy alone in preventing recurrence of ascites ( $P < .001$ ), but there was no significant difference between groups in transplant-free survival, overall survival, or quality of life. Incidence of moderate to severe encephalopathy in the TIPS groups was higher than in those receiving medical therapy alone (20 of 52 patients receiving TIPS developed encephalopathy versus 12 of 57 patients in the medical arm,  $P = .058$ ). The increased rate of encephalopathy in the TIPS group was felt to offset any improvement due to better control of ascites in this group. One criticism of this study was the means by which quality of life was measured—a general quality of life questionnaire was used in this trial—whereas data from a disease-specific questionnaire may have yielded somewhat different results. Several additional randomized controlled trials have compared uncovered TIPS with paracentesis in the management of refractory ascites in cirrhotic patients [135-137]. Despite the demonstration that TIPS was efficacious in controlling ascites, its use came at the cost of increased hepatic encephalopathy and no significant survival benefits.

Importantly, Salerno et al [13] conducted a meta-analysis of four of the abovementioned randomized control trials [133-135,137], wherein individual patient data from each study were pooled, taking into account the

effect of time to death (and not just the number of deaths) to arrive at a more appropriate survival analysis. This survival analysis demonstrated conclusively that TIPS significantly improved the actuarial probability of transplant-free survival. This fact was supported by an updated meta-analysis by Bai et al [116] that pooled data from all six of the prior randomized control trials comparing serial paracentesis to TIPS [132-137]. This study confirmed the effect of TIPS on transplant-free survival with appropriate survival analysis taking into account time-to-event outcomes. The consistency of survival improvement in these two meta-analysis performed with varying methods has increased confidence that TIPS performs better than serial paracentesis in the management of refractory ascites.

**Peritoneovenous Shunt.** Originally introduced by Leveen et al [138] in the 1970s, peritoneovenous shunting was a method devised whereby continuous abdominal paracentesis was facilitated by recirculating protein-rich ascitic fluid back into the central circulation by means of a surgically placed subcutaneous cannula with a one-way pressure valve. Although some still consider peritoneovenous shunting as a treatment of last resort in diuretic-resistant patients with contraindication to TIPS or pediatric serial paracentesis [139], the procedure has been virtually abandoned because of well-documented serious adverse events including shunt occlusion, peritoneal infection, ascitic leak, bleeding, disseminated intravascular coagulation, pneumothorax, and pneumoperitoneum [113,140-144]. Despite an insignificant trend toward earlier relief of ascites compared with TIPS for patients [143], the host of complications and risk of early shunt dysfunction have made peritoneovenous shunts nearly obsolete.

**Variant 7: Ascites. Child-Pugh class B cirrhotic with chronic ascites undergoing weekly large-volume paracentesis; rapidly declining renal function unresponsive to diuretic withdrawal**

**Medical Therapy/Dietary Modification.** Boyer et al [145] prospectively compared 97 patients treated with terlipressin and albumin with 99 patients treated with placebo and albumin in the setting of HRS-1, and found the group also treated with terlipressin had a greater improvement in renal function (serum creatinine decrease of 1.1 mg/dL versus 0.6 mg/dL), but similar rates of HRS reversal (serum creatinine  $<1.5$  mg/dL) in both groups. Transplant-free survival, overall survival, and adverse events were similar between the two groups.

A meta-analysis by Gifford et al involving 12 randomized control trials including 700 patients with HRS-1 found

that treatment with terlipressin in addition to albumin resulted in more frequent reversal of HRS-1, but found a benefit in mortality to be less clear [146].

**Volume Expansion.** In advanced cirrhosis, portal hypertension results in profound hemodynamic derangement, which in turn leads to marked splanchnic vasodilation [147]. This results in the activation of both the sympathetic nervous system and the renin-angiotensin-aldosterone system, leading to robust renal vasoconstriction, which plays a role in the pathogenesis of acute kidney injury in HRS (HRS-AKI). Potent splanchnic vasodilators (nitric oxide and prostacyclins) result in a decrease in the effective circulating blood volume. Intravascular volume assessment is a fundamental step to ensure that hypovolemia is adequately managed [147] and is in keeping with American Association for the Study of Liver Diseases and European Association for the Study of the Liver best practice guidelines [148,149]. Clinical guidelines recommend using vasoconstrictors in combination with albumin as the first-line treatment for HRS-AKI to counteract splanchnic arterial vasodilation [150]. Albumin effectively antagonizes the decreased effective circulating volume and increases mean arterial pressure, thereby combating the hemodynamic dysfunction of HRS. A number of studies and meta-analyses have been conducted to investigate the use of different vasopressors and albumin in managing HRS-AKI [145,151-158]. A network meta-analysis including 16 randomized controlled trials of patients with HRS by Sridharan et al [159] reported that the combinations of terlipressin and albumin, and noradrenalin and albumin, were more effective than albumin monotherapy to achieve complete reversal of HRS as defined by a reduction of serum creatinine concentration to  $<1.5$  mg/d.

Albumin has a dose-dependent effect on both survival and complications in patients with cirrhosis with acute renal failure (HRS and otherwise). The optimal dose of albumin used for HRS-AKI treatment is not established, and dosing varies considerably between studies. Salerno et al, in a recent meta-analysis including 19 clinical studies, showed the most important factor in predicting a successful clinical response to albumin therapy appears to be the cumulative dose [160]. This meta-analysis suggests a dose-response relationship between infused albumin and survival in patients with type 1 HRS. Increments of 100 g in cumulative albumin dose were accompanied by significantly increased survival (hazard ratio: 1.15; 95% CI, 1.02-1.31;  $P = .023$ ). Expected survival rates at 30 days among patients receiving cumulative albumin doses of 200, 400, and 600 g were 43.2% (95% CI, 36.4-51.3%), 51.4% (95% CI, 46.3-57.1%), and 59.0% (95% CI, 51.9-67.2), respectively [160].

**Large-Volume Paracentesis.** The most frequent complication of serial large-volume paracentesis is effective, asymptomatic hypovolemia and renal impairment, an event called (post-) PICD. Although the pathophysiology and factors predicting the development of PICD have not been fully elucidated, the phenomenon is thought to be secondary to the rapid drop in intra-abdominal pressure following paracentesis, thereby improving venous return to the right heart and transiently increasing cardiac output [119-121]. This hyperkinetic circulatory state increases shear stress within peripheral vessels, consequently decreasing the effective arterial blood volume. This is documented by significantly increased activation of the renin-angiotensin-aldosterone system and sympathetic nervous system as well as stimulation of vasopressin secretion with subsequent free-water retention. PICD, strictly defined as an increase in plasma renin activity of  $>50\%$  of the pretreatment value on days 4 to 6 after paracentesis, develops in up to 80% of patients in the absence of volume expansion at the time of paracentesis [119,121,122].

Because PICD does not occur after every session of large-volume paracentesis, there is considerable debate regarding the use and choice of volume expanders following paracentesis. In a large, prospective study by Ginés et al [123], 289 cirrhotic patients were randomized to treatment by total paracentesis plus intravenous albumin, dextran-70, or polygeline. PICD occurred more frequently in patients treated with dextran-70 (34.4%;  $P = .018$ ) or polygeline (37.8%;  $P = .004$ ) than in those receiving albumin (18.5%). Planas et al [124] confirmed these findings in a randomized trial of 88 patients randomized to receive dextran-70 versus albumin as plasma expanders following total paracentesis. There was a significant increase in plasma renin activity and aldosterone concentration (30% over baseline values) observed in 51% of patients treated with dextran-70 and in only 15% of those treated with albumin ( $P = .0012$ ). Other volume expanders, such as saline infusion, have been shown to be less effective than albumin in the prevention of PICD [125], although differences between cohorts were not shown to be significant when the total volume of ascites evacuated was  $<6$  L per session. Another randomized, double-blind study by Moreau et al [126] supports the use of albumin compared with polygeline infusion, showing that patients in the polygeline group had a 1.6-fold higher risk for developing a liver-related complication than those in the albumin group. Present recommendations by the International Ascites Club advocate for the infusion of albumin of 6 to 8 g/L of ascetic fluid removed for large-volume paracentesis of  $>6$  L [127].

It has been suggested that the administration of vasoconstrictors, such as terlipressin [128-130] or midodrine

[122,131], instead of intravenous albumin may show benefit in PICD prevention, as vasodilatation plays a fundamental role in the development of PICD. In a prospective trial by Singh et al [131], 40 patients undergoing paracentesis were randomized to receive midodrine, an oral  $\alpha$ -adrenergic agonist, or intravenous albumin. Plasma renin activity at baseline and at 6 days after paracentesis did not differ between the two groups, leading the investigators to suggest that midodrine may be as effective as albumin in preventing PICD in cirrhotic patients. Compared with albumin, additional benefits of midodrine include its ability to orally dose the medication. A conflicting opinion regarding the efficacy of midodrine was made following a smaller single-center pilot study by Appenrodt et al [122]. In this study, 24 patients were randomized to receive oral midodrine or intravenous albumin after large-volume paracentesis. PICD, defined in this study as a rise in plasma renin concentration on day 6 by  $>50\%$  of the baseline value, developed in 60% of the midodrine group but only 31% of the albumin group. The results undoubtedly question the efficacy of midodrine in preventing the development of PICD, but the study was severely limited by its small sample size and fixed dosing regimen that did not consider dynamic hemodynamic parameters. Further investigation is warranted to elucidate the role of concurrent midodrine with large-volume paracentesis.

**Transjugular Intrahepatic Portosystemic Shunt.** Only five prospective studies that include a total of 91 patients have evaluated the role of TIPS in HRS [161-165]. Guevara et al [162] showed significant improvement in serum creatinine, blood urea nitrogen, renal plasma flow, and glomerular filtration rate after TIPS in 7 cirrhotic patients with type I HRS. Brensing et al [161] found that renal function improved following TIPS in nontransplantable cirrhotics with type 1 and 2 HRS. After TIPS, overall 6-month and 1-year survival rates were 71% and 48%, respectively, which was significantly better than the non-TIPS cohort. Testino et al [164] reported on 18 consecutive patients affected by advanced cirrhosis (Child-Pugh score of 10-12) and type 2 HRS awaiting liver transplant. Significant improvement in control of ascites and renal functional parameters was demonstrated in all patients 12 weeks following TIPS placement. Wong et al [165] demonstrated that TIPS may have a role in cirrhotic patients with type 1 HRS who initially respond to vasoconstrictor treatment. Medical therapy with midodrine, octreotide, and albumin for 14 days improved renal function and renal sodium excretion in 10 of 14 cirrhotic patients. Further improvements in renal functional parameters and sodium excretion were noted following TIPS placement in 5

patients, the medical treatment responders (mean glomerular filtration rate:  $96 \pm 20$  mL/min at 12 months,  $P < .01$  versus pre-TIPS). Regardless of the mechanism by which it occurs, it seems plausible in these data that TIPS placement, via significant suppression of the endogenous vasoactive systems and increased expansion in central blood volume, improves renal perfusion, glomerular filtration rate, urine sodium and water excretion, and hyponatremia in type 1 and 2 HRS [14].

**Peritovenous Shunt.** A study by Linas et al [166] prospectively compared peritovenous shunting in 10 patients to medical therapy in 10 patients in the setting of HRS, showing a significant increase in capillary wedge pressure and cardiac wedge pressure and, after 48 to 72 hours, a decrease in weight and creatinine in the peritovenous shunt group. Despite the improvement in renal function, only 1 patient in the peritovenous shunt group had prolonged survival (210 days), whereas in the remainder survival was  $13.8 \pm 2$  days compared with  $4.1 \pm 0.6$  days in the medical therapy group. The procedure has been virtually abandoned because of well-documented serious adverse events including shunt occlusion, peritoneal infection, ascitic leak, bleeding, disseminated intravascular coagulation, pneumothorax, and pneumoperitoneum [113,140-144]. Despite an insignificant trend toward earlier relief of ascites compared with TIPS for patients [143], the host of complications and risk of early shunt dysfunction have made peritoneovenous shunts nearly obsolete.

## SUMMARY OF RECOMMENDATIONS

- **Variant 1:** Endoscopic management or medical therapy with vasoactive drugs is usually appropriate for the initial therapy of a Child-Pugh class A patient with acute variceal bleeding, who is cirrhotic with index bleed from acute esophageal variceal hemorrhage, MELD 10, and no encephalopathy. These procedures are complementary (ie, more than one should be performed to effectively manage the patient's care).
- **Variant 2:** Endoscopic management or medical therapy with vasoactive drugs or TIPS is usually appropriate for a Child-Pugh class B patient with acute variceal bleeding, who is cirrhotic with active esophageal variceal hemorrhage, MELD 12, and was previously treated with octreotide and EVL on three prior occasions with no encephalopathy. These procedures are equivalent alternatives (ie, only one procedure will be ordered to provide the clinical information to effectively manage the patient's care).

- **Variant 3:** Endoscopic management or medical therapy with vasoactive drugs or TIPS is usually appropriate for a Child-Pugh class C patient with acute variceal bleeding, who is cirrhotic with active esophageal and junctional variceal hemorrhage and was previously treated with octreotide and ES, MELD 17, intermittent mild hepatic encephalopathy and managed as an outpatient with nutritional support. These procedures are equivalent alternatives (ie, only one procedure will be ordered to provide the clinical information to effectively manage the patient's care).
- **Variant 4:** Endoscopic management or medical therapy with vasoactive drugs or percutaneous transhepatic embolization is usually appropriate for a Child-Pugh class C patient with acute variceal bleeding, who is cirrhotic with hepatocellular carcinoma, branch portal vein tumor thrombus, and active esophageal and GOV1 variceal hemorrhage, MELD 24. These procedures are equivalent alternatives (ie, only one procedure will be ordered to provide the clinical information to effectively manage the patient's care).
- **Variant 5:** Medical therapy with dietary modification is usually appropriate for the initial therapy of a Child-Pugh class B cirrhotic asymptomatic patient with small-volume ascites.
- **Variant 6:** Medical therapy with dietary modification or large-volume paracentesis or TIPS or volume expansion is usually appropriate for a Child-Pugh class B cirrhotic patient, who is cirrhotic with chronic ascites despite daily diuretic therapy and a low-sodium diet. These procedures are equivalent alternatives (ie, only one procedure will be ordered to provide the clinical information to effectively manage the patient's care).
- **Variant 7:** TIPS or medical therapy with dietary modification or volume expansion is usually appropriate for a Child-Pugh class B patient who is cirrhotic with chronic ascites and undergoing weekly large-volume paracentesis and rapidly declining renal function unresponsive to diuretic withdrawal. These procedures are equivalent alternatives (ie, only one procedure will be ordered to provide the clinical information to effectively manage the patient's care).

## SUPPORTING DOCUMENTS

The evidence table, literature search, and appendix for this topic are available at <https://acsearch.acr.org/list>. The appendix includes the strength of evidence assessment and the final rating round tabulations for each recommendation.

For additional information on the Appropriateness Criteria methodology and other supporting documents go to [www.acr.org/ac](http://www.acr.org/ac).

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