American College of Radiology
ACR Appropriateness Criteria®
Radiologic Management of Portal Hypertension

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

RADIOLOGIC MANAGEMENT OF PORTAL HYPERTENSION

Expert Panels on Interventional Radiology and Vascular Imaging: Jason W. Pinchot, MD[a]; Sanjeeva P. Kalva, MD[b]; Bill S. Majdalany, MD[c]; Charles Y. Kim, MD[d]; Osmanuddin Ahmed, MD[e]; Sumeet K. Asrani, MD, MSc[f]; Brooks D. Cash, MD[g]; Jens Eldrup-Jorgensen, MD[h]; A. Tuba Kendi, MD[i]; Matthew J. Scheidt, MD[j]; David M. Sella, MD[k]; Karin E. Dill, MD[l]; Eric J. Hohenwalter, MD.[m]

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

[a]Panel Chair, University of Wisconsin, Madison, Wisconsin. [b]Panel Chair, Massachusetts General Hospital, Boston, Massachusetts. [c]Panel Vice-Chair, Emory Healthcare, Atlanta, Georgia. [d]Panel Vice-Chair, Duke University Medical Center, Durham, North Carolina. [e]University of Chicago, Chicago, Illinois. [f]Baylor University Medical Center, Dallas, Texas; American Association for the Study of Liver Diseases. [g]University of Texas Health Science Center at Houston and McGovern Medical School, Houston, Texas; American Gastroenterological Association. [h]Tufts University School of Medicine, Boston, Massachusetts; Society for Vascular Surgery. [i]Mayo Clinic, Rochester, Minnesota. [j]Froedtert & The Medical College of Wisconsin, Milwaukee, Wisconsin. [k]Mayo Clinic, Jacksonville, Florida. [l]Specialty Chair, Emory University Hospital, Atlanta, Georgia. [m]Specialty Chair, Froedtert & The Medical College of Wisconsin, Milwaukee, Wisconsin.

Reprint requests to: publications@acr.org

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 ≥6 mmHg. Clinically significant portal hypertension occurs when the HVPG is ≥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 ≥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 ≤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 ± 2.04 in the EVL group compared with 4.73 ± 3.04 in the ES group (P = .02). Santos et al [36] prospectively compared EVL with *N*-butyl-cyanoacrylate 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, 0.24–0.996]) [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 Monescillo et al [59] involving patients at high risk for treatment failure, as defined by HVPG ≥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.

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 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 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 of Child-Pugh class C), 2) MELD 19 criteria (patients with MELD scores of ≥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 ≥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 ≥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 ≥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 at [73] reported early mortality in 46% of early TIPS-eligible patients with a MELD score of ≥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 ≤10, 11 to 18, 19 to 25, and ≥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 (≥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 ≥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 at [73] reported early mortality in 46% of early TIPS-eligible patients with a MELD score of ≥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 ≤10, 11 to 18, 19 to 25, and ≥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 ≥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 V2-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_2 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 (≤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 at 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 α-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 Lebrec 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 prostacyclines) 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 at 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 α-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 ± 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 ± 2 days compared with 4.1 ± 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, 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.

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.

References

1. Bosch J, Berzigotti A, Garcia-Pagan JC, Abraldes JG. The management of portal hypertension: rational basis, available treatments and future options. J Hepatol 2008;48 Suppl 1:S68-92.
2. Bari K, Garcia-Tsao G. Treatment of portal hypertension. World J Gastroenterol 2012;18:1166-75.
3. Kim CY, Pinchot JW, Ahmed O, et al. ACR Appropriateness Criteria® Radiologic Management of Gastric Varices. J Am Coll Radiol 2020;17:S239-S54.
4. Schmidt ML, Barritt AS, Orman ES, Hayashi PH. Decreasing mortality among patients hospitalized with cirrhosis in the United States from 2002 through 2010. Gastroenterology 2015;148:967-77 e2.

5. Gines P, Quintero E, Arroyo V, et al. Compensated cirrhosis: natural history and prognostic factors. Hepatology 1987;7:122-8.
6. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hepatol 2006;44:217-31.
7. Planas R, Montoliu S, Balleste B, et al. Natural history of patients hospitalized for management of cirrhotic ascites. Clin Gastroenterol Hepatol 2006;4:1385-94.
8. D'Amico G, Luca A. Natural history. Clinical-haemodynamic correlations. Prediction of the risk of bleeding. Baillieres Clin Gastroenterol 1997;11:243-56.
9. Runyon BA. Refractory ascites. Semin Liver Dis 1993;13:343-51.
10. Russo MW, Sood A, Jacobson IM, Brown RS, Jr. Transjugular intrahepatic portosystemic shunt for refractory ascites: an analysis of the literature on efficacy, morbidity, and mortality. Am J Gastroenterol 2003;98:2521-7.
11. Gines P, Guevara M, Arroyo V, Rodes J. Hepatorenal syndrome. Lancet 2003;362:1819-27.
12. Gines P, Schrier RW. Renal failure in cirrhosis. N Engl J Med 2009;361:1279-90.
13. Salerno F, Gerbes A, Gines P, Wong F, Arroyo V. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. Gut 2007;56:1310-8.
14. Salerno F, Gerbes A, Gines P, Wong F, Arroyo V. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. Postgrad Med J 2008;84:662-70.
15. Abraldes JG, Villanueva C, Banares R, et al. Hepatic venous pressure gradient and prognosis in patients with acute variceal bleeding treated with pharmacologic and endoscopic therapy. J Hepatol 2008;48:229-36.
16. Bosch J, Groszmann RJ, Shah VH. Evolution in the understanding of the pathophysiological basis of portal hypertension: How changes in paradigm are leading to successful new treatments. J Hepatol 2015;62:S121-30.
17. Silva-Junior G, Baiges A, Turon F, et al. The prognostic value of hepatic venous pressure gradient in patients with cirrhosis is highly dependent on the accuracy of the technique. Hepatology 2015;62:1584-92.
18. D'Amico G, Garcia-Pagan JC, Luca A, Bosch J. Hepatic vein pressure gradient reduction and prevention of variceal bleeding in cirrhosis: a systematic review. Gastroenterology 2006;131:1611-24.
19. Horowitz JM, Kamel IR, Arif-Tiwari H, et al. ACR Appropriateness Criteria(R) Chronic Liver Disease. J Am Coll Radiol 2017;14:S391-S405.
20. Wells M, Chande N, Adams P, et al. Meta-analysis: vasoactive medications for the management of acute variceal bleeds. Aliment Pharmacol Ther 2012;35:1267-78.
21. Avgerinos A, Nevens F, Raptis S, Fevery J. Early administration of somatostatin and efficacy of sclerotherapy in acute oesophageal variceal bleeds: the European Acute Bleeding Oesophageal Variceal Episodes (ABOVE) randomised trial. Lancet 1997;350:1495-9.
22. Cales P, Masliah C, Bernard B, et al. Early administration of vapreotide for variceal bleeding in patients with cirrhosis. N Engl J Med 2001;344:23-8.
23. Garcia-Pagan JC, Reverter E, Abraldes JG, Bosch J. Acute variceal bleeding. Semin Respir Crit Care Med 2012;33:46-54.
24. Levacher S, Letoumelin P, Pateron D, Blaise M, Lapandry C, Pourriat JL. Early administration of terlipressin plus glyceryl trinitrate to control active upper gastrointestinal bleeding in cirrhotic patients. Lancet 1995;346:865-8.
25. Villanueva C, Ortiz J, Sabat M, et al. Somatostatin alone or combined with emergency sclerotherapy in the treatment of acute esophageal variceal bleeding: a prospective randomized trial. Hepatology 1999;30:384-9.
26. Banares R, Albillos A, Rincon D, et al. Endoscopic treatment versus endoscopic plus pharmacologic treatment for acute variceal bleeding: a meta-analysis. Hepatology 2002;35:609-15.
27. Wang C, Han J, Xiao L, Jin CE, Li DJ, Yang Z. Efficacy of vasopressin/terlipressin and somatostatin/octreotide for the prevention of early variceal rebleeding after the initial control of bleeding: a systematic review and meta-analysis. Hepatol Int 2015;9:120-9.
28. Soares-Weiser K, Brezis M, Tur-Kaspa R, Leibovici L. Antibiotic prophylaxis for cirrhotic patients with gastrointestinal bleeding. Cochrane Database Syst Rev 2002:CD002907.
29. Chavez-Tapia NC, Barrientos-Gutierrez T, Tellez-Avila F, et al. Meta-analysis: antibiotic prophylaxis for cirrhotic patients with upper gastrointestinal bleeding - an updated Cochrane review. Aliment Pharmacol Ther 2011;34:509-18.

30. de Franchis R. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. J Hepatol 2015;63:743-52.
31. Lo GH, Chen WC, Wang HM, et al. Low-dose terlipressin plus banding ligation versus low-dose terlipressin alone in the prevention of very early rebleeding of oesophageal varices. Gut 2009;58:1275-80.
32. Lo GH, Lai KH, Cheng JS, et al. A prospective, randomized trial of sclerotherapy versus ligation in the management of bleeding esophageal varices. Hepatology 1995;22:466-71.
33. Masci E, Stigliano R, Mariani A, et al. Prospective multicenter randomized trial comparing banding ligation with sclerotherapy of esophageal varices. Hepatogastroenterology 1999;46:1769-73.
34. Van Stiegmann G, Isshi K. Elastic band ligation for bleeding esophagogastric varices. Hepatogastroenterology 1997;44:620-4.
35. Ferrari AP, de Paulo GA, de Macedo CM, Araujo I, Della Libera E, Jr. Efficacy of absolute alcohol injection compared with band ligation in the eradication of esophageal varices. Arq Gastroenterol 2005;42:72-6.
36. Santos MM, Tolentino LH, Rodrigues RA, et al. Endoscopic treatment of esophageal varices in advanced liver disease patients: band ligation versus cyanoacrylate injection. Eur J Gastroenterol Hepatol 2011;23:60-5.
37. Villanueva C, Piqueras M, Aracil C, et al. A randomized controlled trial comparing ligation and sclerotherapy as emergency endoscopic treatment added to somatostatin in acute variceal bleeding. J Hepatol 2006;45:560-7.
38. Laine L, Cook D. Endoscopic ligation compared with sclerotherapy for treatment of esophageal variceal bleeding. A meta-analysis. Ann Intern Med 1995;123:280-7.
39. Ohmoto K, Yoshioka N, Tomiyama Y, et al. Improved prognosis of cirrhosis patients with esophageal varices and thrombocytopenia treated by endoscopic variceal ligation plus partial splenic embolization. Dig Dis Sci 2006;51:352-8.
40. Taniai N, Onda M, Tajiri T, Toba M, Yoshida H. Endoscopic variceal ligation (EVL) combined with partial splenic embolization (PSE). Hepatogastroenterology 1999;46:2849-53.
41. Taniai N, Onda M, Tajiri T, Yoshida H, Mamada Y. Combined endoscopic and radiologic intervention to treat esophageal varices. Hepatogastroenterology 2002;49:984-8.
42. D'Amico G, Pagliaro L, Bosch J. The treatment of portal hypertension: a meta-analytic review. Hepatology 1995;22:332-54.
43. Jalan R, John TG, Redhead DN, et al. A comparative study of emergency transjugular intrahepatic portosystemic stent-shunt and esophageal transection in the management of uncontrolled variceal hemorrhage. Am J Gastroenterol 1995;90:1932-7.
44. Henderson JM. Variceal bleeding: which shunt? Gastroenterology 1986;91:1021-3.
45. Zakim D, Boyer TD. *Hepatology : a textbook of liver disease.* 4th ed. Philadelphia: Saunders; 2003.
46. Rosemurgy AS, Frohman HA, Teta AF, Luberice K, Ross SB. Prosthetic H-graft portacaval shunts vs transjugular intrahepatic portasystemic stent shunts: 18-year follow-up of a randomized trial. J Am Coll Surg 2012;214:445-53; discussion 53-5.
47. Henderson JM, Boyer TD, Kutner MH, et al. Distal splenorenal shunt versus transjugular intrahepatic portal systematic shunt for variceal bleeding: a randomized trial. Gastroenterology 2006;130:1643-51.
48. Clark W, Hernandez J, McKeon B, et al. Surgical shunting versus transjugular intrahepatic portasystemic shunting for bleeding varices resulting from portal hypertension and cirrhosis: a meta-analysis. Am Surg 2010;76:857-64.
49. Cabrera J, Maynar M, Granados R, et al. Transjugular intrahepatic portosystemic shunt versus sclerotherapy in the elective treatment of variceal hemorrhage. Gastroenterology 1996;110:832-9.
50. Cello JP, Ring EJ, Olcott EW, et al. Endoscopic sclerotherapy compared with percutaneous transjugular intrahepatic portosystemic shunt after initial sclerotherapy in patients with acute variceal hemorrhage. A randomized, controlled trial. Ann Intern Med 1997;126:858-65.
51. Jalan R, Forrest EH, Stanley AJ, et al. A randomized trial comparing transjugular intrahepatic portosystemic stent-shunt with variceal band ligation in the prevention of rebleeding from esophageal varices. Hepatology 1997;26:1115-22.
52. Merli M, Salerno F, Riggio O, et al. Transjugular intrahepatic portosystemic shunt versus endoscopic sclerotherapy for the prevention of variceal bleeding in cirrhosis: a randomized multicenter trial. Gruppo Italiano Studio TIPS (G.I.S.T.). Hepatology 1998;27:48-53.
53. Rossle M, Deibert P, Haag K, et al. Randomised trial of transjugular-intrahepatic-portosystemic shunt versus endoscopy plus propranolol for prevention of variceal rebleeding. Lancet 1997;349:1043-9.

54. Sanyal AJ, Freedman AM, Luketic VA, et al. Transjugular intrahepatic portosystemic shunts compared with endoscopic sclerotherapy for the prevention of recurrent variceal hemorrhage. A randomized, controlled trial. Ann Intern Med 1997;126:849-57.
55. Sauer P, Theilmann L, Stremmel W, Benz C, Richter GM, Stiehl A. Transjugular intrahepatic portosystemic stent shunt versus sclerotherapy plus propranolol for variceal rebleeding. Gastroenterology 1997;113:1623-31.
56. Luca A, D'Amico G, La Galla R, Midiri M, Morabito A, Pagliaro L. TIPS for prevention of recurrent bleeding in patients with cirrhosis: meta-analysis of randomized clinical trials. Radiology 1999;212:411-21.
57. Papatheodoridis GV, Goulis J, Leandro G, Patch D, Burroughs AK. Transjugular intrahepatic portosystemic shunt compared with endoscopic treatment for prevention of variceal rebleeding: A meta-analysis. Hepatology 1999;30:612-22.
58. Garcia-Pagan JC, Caca K, Bureau C, et al. Early use of TIPS in patients with cirrhosis and variceal bleeding. N Engl J Med 2010;362:2370-9.
59. Monescillo A, Martinez-Lagares F, Ruiz-del-Arbol L, et al. Influence of portal hypertension and its early decompression by TIPS placement on the outcome of variceal bleeding. Hepatology 2004;40:793-801.
60. Angeloni S, Merli M, Salvatori FM, et al. Polytetrafluoroethylene-covered stent grafts for TIPS procedure: 1-year patency and clinical results. Am J Gastroenterol 2004;99:280-5.
61. Angermayr B, Cejna M, Koenig F, et al. Survival in patients undergoing transjugular intrahepatic portosystemic shunt: ePTFE-covered stentgrafts versus bare stents. Hepatology 2003;38:1043-50.
62. Bureau C, Garcia Pagan JC, Layrargues GP, et al. Patency of stents covered with polytetrafluoroethylene in patients treated by transjugular intrahepatic portosystemic shunts: long-term results of a randomized multicentre study. Liver Int 2007;27:742-7.
63. Jung HS, Kalva SP, Greenfield AJ, et al. TIPS: comparison of shunt patency and clinical outcomes between bare stents and expanded polytetrafluoroethylene stent-grafts. J Vasc Interv Radiol 2009;20:180-5.
64. Rossi P, Salvatori FM, Fanelli F, et al. Polytetrafluoroethylene-covered nitinol stent-graft for transjugular intrahepatic portosystemic shunt creation: 3-year experience. Radiology 2004;231:820-30.
65. Saad WE, Darwish WM, Davies MG, Waldman DL. Stent-grafts for transjugular intrahepatic portosystemic shunt creation: specialized TIPS stent-graft versus generic stent-graft/bare stent combination. J Vasc Interv Radiol 2010;21:1512-20.
66. Garcia-Pagan JC, Di Pascoli M, Caca K, et al. Use of early-TIPS for high-risk variceal bleeding: results of a post-RCT surveillance study. J Hepatol 2013;58:45-50.
67. Rudler M, Rousseau G, Thabut D. Salvage transjugular intrahepatic portosystemic shunt followed by early transplantation in patients with Child C14-15 cirrhosis and refractory variceal bleeding: a strategy improving survival. Transpl Int 2013;26:E50-1.
68. Halabi SA, Sawas T, Sadat B, et al. Early TIPS versus endoscopic therapy for secondary prophylaxis after management of acute esophageal variceal bleeding in cirrhotic patients: a meta-analysis of randomized controlled trials. J Gastroenterol Hepatol 2016;31:1519-26.
69. Pomier-Layrargues G, Villeneuve JP, Deschenes M, et al. Transjugular intrahepatic portosystemic shunt (TIPS) versus endoscopic variceal ligation in the prevention of variceal rebleeding in patients with cirrhosis: a randomised trial. Gut 2001;48:390-6.
70. Rosemurgy AS, Bloomston M, Clark WC, Thometz DP, Zervos EE. H-graft portacaval shunts versus TIPS: ten-year follow-up of a randomized trial with comparison to predicted survivals. Ann Surg 2005;241:238-46.
71. Augustin S, Altamirano J, Gonzalez A, et al. Effectiveness of combined pharmacologic and ligation therapy in high-risk patients with acute esophageal variceal bleeding. Am J Gastroenterol 2011;106:1787-95.
72. Reverter E, Tandon P, Augustin S, et al. A MELD-based model to determine risk of mortality among patients with acute variceal bleeding. Gastroenterology 2014;146:412-19 e3.
73. Conejo I, Guardascione MA, Tandon P, et al. Multicenter External Validation of Risk Stratification Criteria for Patients With Variceal Bleeding. Clin Gastroenterol Hepatol 2018;16:132-39 e8.
74. Al Sibae MR, Cappell MS. Accuracy of MELD scores in predicting mortality in decompensated cirrhosis from variceal bleeding, hepatorenal syndrome, alcoholic hepatitis, or acute liver failure as well as mortality after non-transplant surgery or TIPS. Dig Dis Sci 2011;56:977-87.

75. Casadaban LC, Parvinian A, Zivin SP, et al. MELD score for prediction of survival after emergent TIPS for acute variceal hemorrhage: derivation and validation in a 101-patient cohort. Ann Hepatol 2015;14:380-8.
76. Gaba RC, Couture PM, Bui JT, et al. Prognostic capability of different liver disease scoring systems for prediction of early mortality after transjugular intrahepatic portosystemic shunt creation. J Vasc Interv Radiol 2013;24:411-20, 20 e1-4; quiz 21.
77. Heinzow HS, Lenz P, Kohler M, et al. Clinical outcome and predictors of survival after TIPS insertion in patients with liver cirrhosis. World J Gastroenterol 2012;18:5211-8.
78. Montgomery A, Ferral H, Vasan R, Postoak DW. MELD score as a predictor of early death in patients undergoing elective transjugular intrahepatic portosystemic shunt (TIPS) procedures. Cardiovasc Intervent Radiol 2005;28:307-12.
79. Tzeng WS, Wu RH, Lin CY, et al. Prediction of mortality after emergent transjugular intrahepatic portosystemic shunt placement: use of APACHE II, Child-Pugh and MELD scores in Asian patients with refractory variceal hemorrhage. Korean J Radiol 2009;10:481-9.
80. Dechene A, El Fouly AH, Bechmann LP, et al. Acute management of refractory variceal bleeding in liver cirrhosis by self-expanding metal stents. Digestion 2012;85:185-91.
81. Fierz FC, Kistler W, Stenz V, Gubler C. Treatment of esophageal variceal hemorrhage with self-expanding metal stents as a rescue maneuver in a swiss multicentric cohort. Case Rep Gastroenterol 2013;7:97-105.
82. Wright G, Lewis H, Hogan B, Burroughs A, Patch D, O'Beirne J. A self-expanding metal stent for complicated variceal hemorrhage: experience at a single center. Gastrointest Endosc 2010;71:71-8.
83. Zakaria MS, Hamza IM, Mohey MA, Hubamnn RG. The first Egyptian experience using new self-expandable metal stents in acute esophageal variceal bleeding: pilot study. Saudi J Gastroenterol 2013;19:177-81.
84. Zehetner J, Shamiyeh A, Wayand W, Hubmann R. Results of a new method to stop acute bleeding from esophageal varices: implantation of a self-expanding stent. Surg Endosc 2008;22:2149-52.
85. Hermie L, Dhondt E, Vanlangenhove P, Hoste E, Geerts A, Defreyne L. Model for end-stage liver disease score and hemodynamic instability as a predictor of poor outcome in early transjugular intrahepatic portosystemic shunt treatment for acute variceal hemorrhage. Eur J Gastroenterol Hepatol 2018;30:1441-46.
86. D'Amico G, De Franchis R, Cooperative Study G. Upper digestive bleeding in cirrhosis. Post-therapeutic outcome and prognostic indicators. Hepatology 2003;38:599-612.
87. Englesbe MJ, Kubus J, Muhammad W, et al. Portal vein thrombosis and survival in patients with cirrhosis. Liver Transpl 2010;16:83-90.
88. Wong F, Blendis L. Transjugular intrahepatic portosystemic shunt for refractory ascites: tipping the sodium balance. Hepatology 1995;22:358-64.
89. Bilbao JI, Quiroga J, Herrero JI, Benito A. Transjugular intrahepatic portosystemic shunt (TIPS): current status and future possibilities. Cardiovasc Intervent Radiol 2002;25:251-69.
90. Nunes EL, dos Santos KR, Mondino PJ, Bastos Mdo C, Giambiagi-deMarval M. Detection of ileS-2 gene encoding mupirocin resistance in methicillin-resistant Staphylococcus aureus by multiplex PCR. Diagn Microbiol Infect Dis 1999;34:77-81.
91. Ochs A. Transjugular intrahepatic portosystemic shunt. Dig Dis 2005;23:56-64.
92. Senzolo M, Cholongitas E, Davies N, et al. Transjugular Intrahepatic Portosystemic Shunt (TIPS), the preferred therapeutic option for Budd Chiari syndrome associated with portal vein thrombosis. Am J Gastroenterol 2006;101:2163-4; author reply 64-5.
93. Senzolo M, Tibbals J, Cholongitas E, Triantos CK, Burroughs AK, Patch D. Transjugular intrahepatic portosystemic shunt for portal vein thrombosis with and without cavernous transformation. Aliment Pharmacol Ther 2006;23:767-75.
94. Valentin N, Korrapati P, Constantino J, Young A, Weisberg I. The role of transjugular intrahepatic portosystemic shunt in the management of portal vein thrombosis: a systematic review and meta-analysis. Eur J Gastroenterol Hepatol 2018;30:1187-93.
95. Lunderquist A, Vang J. Sclerosing injection of esophageal varices through transhepatic selective catheterization of the gastric coronary vein. A preliminary report. Acta Radiol Diagn (Stockh) 1974;15:546-50.

96. Tian X, Shi Y, Hu J, Wang G, Zhang C. Percutaneous transhepatic variceal embolization with cyanoacrylate vs. transjugular intrahepatic portal systematic shunt for esophageal variceal bleeding. Hepatol Int 2013;7:636-44.
97. Chu HH, Kim HC, Jae HJ, et al. Percutaneous transsplenic access to the portal vein for management of vascular complication in patients with chronic liver disease. Cardiovasc Intervent Radiol 2012;35:1388-95.
98. Gong GQ, Wang XL, Wang JH, et al. Percutaneous transsplenic embolization of esophageal and gastrio-fundal varices in 18 patients. World J Gastroenterol 2001;7:880-3.
99. Tuite DJ, Rehman J, Davies MH, Patel JV, Nicholson AA, Kessel DO. Percutaneous transsplenic access in the management of bleeding varices from chronic portal vein thrombosis. J Vasc Interv Radiol 2007;18:1571-5.
100. Trotter J, Pieramici E, Everson GT. Chronic albumin infusions to achieve diuresis in patients with ascites who are not candidates for transjugular intrahepatic portosystemic shunt (TIPS). Dig Dis Sci 2005;50:1356-60.
101. Wong F. Management of ascites in cirrhosis. J Gastroenterol Hepatol 2012;27:11-20.
102. Barbano B, Sardo L, Gigante A, et al. Pathophysiology, diagnosis and clinical management of hepatorenal syndrome: from classic to new drugs. Curr Vasc Pharmacol 2014;12:125-35.
103. Fernandez J, Monteagudo J, Bargallo X, et al. A randomized unblinded pilot study comparing albumin versus hydroxyethyl starch in spontaneous bacterial peritonitis. Hepatology 2005;42:627-34.
104. Guevara M, Arroyo V. Hepatorenal syndrome. Expert Opin Pharmacother 2011;12:1405-17.
105. Gentilini P, Casini-Raggi V, Di Fiore G, et al. Albumin improves the response to diuretics in patients with cirrhosis and ascites: results of a randomized, controlled trial. J Hepatol 1999;30:639-45.
106. Romanelli RG, La Villa G, Barletta G, et al. Long-term albumin infusion improves survival in patients with cirrhosis and ascites: an unblinded randomized trial. World J Gastroenterol 2006;12:1403-7.
107. Wong F, Watson H, Gerbes A, et al. Satavaptan for the management of ascites in cirrhosis: efficacy and safety across the spectrum of ascites severity. Gut 2012;61:108-16.
108. Gines P, Wong F, Watson H, Milutinovic S, del Arbol LR, Olteanu D. Effects of satavaptan, a selective vasopressin V(2) receptor antagonist, on ascites and serum sodium in cirrhosis with hyponatremia: a randomized trial. Hepatology 2008;48:204-13.
109. Gines P, Wong F, Watson H, et al. Clinical trial: short-term effects of combination of satavaptan, a selective vasopressin V2 receptor antagonist, and diuretics on ascites in patients with cirrhosis without hyponatraemia--a randomized, double-blind, placebo-controlled study. Aliment Pharmacol Ther 2010;31:834-45.
110. Wong F, Gines P, Watson H, et al. Effects of a selective vasopressin V2 receptor antagonist, satavaptan, on ascites recurrence after paracentesis in patients with cirrhosis. J Hepatol 2010;53:283-90.
111. Serste T, Melot C, Francoz C, et al. Deleterious effects of beta-blockers on survival in patients with cirrhosis and refractory ascites. Hepatology 2010;52:1017-22.
112. Arroyo V, Gines P, Gerbes AL, et al. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. International Ascites Club. Hepatology 1996;23:164-76.
113. Gines P, Arroyo V, Vargas V, et al. Paracentesis with intravenous infusion of albumin as compared with peritoneovenous shunting in cirrhosis with refractory ascites. N Engl J Med 1991;325:829-35.
114. Moore KP, Wong F, Gines P, et al. The management of ascites in cirrhosis: report on the consensus conference of the International Ascites Club. Hepatology 2003;38:258-66.
115. Runyon BA. Management of adult patients with ascites due to cirrhosis: an update. Hepatology 2009;49:2087-107.
116. Bai M, Qi XS, Yang ZP, Yang M, Fan DM, Han GH. TIPS improves liver transplantation-free survival in cirrhotic patients with refractory ascites: an updated meta-analysis. World J Gastroenterol 2014;20:2704-14.
117. Gines P, Arroyo V, Quintero E, et al. Comparison of paracentesis and diuretics in the treatment of cirrhotics with tense ascites. Results of a randomized study. Gastroenterology 1987;93:234-41.
118. Salerno F, Badalamenti S, Incerti P, et al. Repeated paracentesis and i.v. albumin infusion to treat 'tense' ascites in cirrhotic patients. A safe alternative therapy. J Hepatol 1987;5:102-8.
119. Gines P, Tito L, Arroyo V, et al. Randomized comparative study of therapeutic paracentesis with and without intravenous albumin in cirrhosis. Gastroenterology 1988;94:1493-502.
120. Pozzi M, Osculati G, Boari G, et al. Time course of circulatory and humoral effects of rapid total paracentesis in cirrhotic patients with tense, refractory ascites. Gastroenterology 1994;106:709-19.

121. Ruiz-del-Arbol L, Monescillo A, Jimenez W, Garcia-Plaza A, Arroyo V, Rodes J. Paracentesis-induced circulatory dysfunction: mechanism and effect on hepatic hemodynamics in cirrhosis. Gastroenterology 1997;113:579-86.
122. Appenrodt B, Wolf A, Grunhage F, et al. Prevention of paracentesis-induced circulatory dysfunction: midodrine vs albumin. A randomized pilot study. Liver Int 2008;28:1019-25.
123. Gines A, Fernandez-Esparrach G, Monescillo A, et al. Randomized trial comparing albumin, dextran 70, and polygeline in cirrhotic patients with ascites treated by paracentesis. Gastroenterology 1996;111:1002-10.
124. Planas R, Gines P, Arroyo V, et al. Dextran-70 versus albumin as plasma expanders in cirrhotic patients with tense ascites treated with total paracentesis. Results of a randomized study. Gastroenterology 1990;99:1736-44.
125. Sola-Vera J, Minana J, Ricart E, et al. Randomized trial comparing albumin and saline in the prevention of paracentesis-induced circulatory dysfunction in cirrhotic patients with ascites. Hepatology 2003;37:1147-53.
126. Moreau R, Valla DC, Durand-Zaleski I, et al. Comparison of outcome in patients with cirrhosis and ascites following treatment with albumin or a synthetic colloid: a randomised controlled pilot trail. Liver Int 2006;26:46-54.
127. Salerno F, Guevara M, Bernardi M, et al. Refractory ascites: pathogenesis, definition and therapy of a severe complication in patients with cirrhosis. Liver Int 2010;30:937-47.
128. Lata J, Marecek Z, Fejfar T, et al. The efficacy of terlipressin in comparison with albumin in the prevention of circulatory changes after the paracentesis of tense ascites--a randomized multicentric study. Hepatogastroenterology 2007;54:1930-3.
129. Moreau R, Asselah T, Condat B, et al. Comparison of the effect of terlipressin and albumin on arterial blood volume in patients with cirrhosis and tense ascites treated by paracentesis: a randomised pilot study. Gut 2002;50:90-4.
130. Singh V, Kumar R, Nain CK, Singh B, Sharma AK. Terlipressin versus albumin in paracentesis-induced circulatory dysfunction in cirrhosis: a randomized study. J Gastroenterol Hepatol 2006;21:303-7.
131. Singh V, Dheerendra PC, Singh B, et al. Midodrine versus albumin in the prevention of paracentesis-induced circulatory dysfunction in cirrhotics: a randomized pilot study. Am J Gastroenterol 2008;103:1399-405.
132. Lebrec D, Giuily N, Hadengue A, et al. Transjugular intrahepatic portosystemic shunts: comparison with paracentesis in patients with cirrhosis and refractory ascites: a randomized trial. French Group of Clinicians and a Group of Biologists. J Hepatol 1996;25:135-44.
133. Rossle M, Ochs A, Gulberg V, et al. A comparison of paracentesis and transjugular intrahepatic portosystemic shunting in patients with ascites. N Engl J Med 2000;342:1701-7.
134. Sanyal AJ, Genning C, Reddy KR, et al. The North American Study for the Treatment of Refractory Ascites. Gastroenterology 2003;124:634-41.
135. Gines P, Uriz J, Calahorra B, et al. Transjugular intrahepatic portosystemic shunting versus paracentesis plus albumin for refractory ascites in cirrhosis. Gastroenterology 2002;123:1839-47.
136. Narahara Y, Kanazawa H, Fukuda T, et al. Transjugular intrahepatic portosystemic shunt versus paracentesis plus albumin in patients with refractory ascites who have good hepatic and renal function: a prospective randomized trial. J Gastroenterol 2011;46:78-85.
137. Salerno F, Merli M, Riggio O, et al. Randomized controlled study of TIPS versus paracentesis plus albumin in cirrhosis with severe ascites. Hepatology 2004;40:629-35.
138. Leveen HH, Christoudias G, Ip M, Luft R, Falk G, Grosberg S. Peritoneo-venous shunting for ascites. Ann Surg 1974;180:580-91.
139. Martin LG. Percutaneous placement and management of the Denver shunt for portal hypertensive ascites. AJR Am J Roentgenol 2012;199:W449-53.
140. Bratby MJ, Hussain FF, Lopez AJ. Radiological insertion and management of peritoneovenous shunt. Cardiovasc Intervent Radiol 2007;30:415-8.
141. Foroulis CN, Desimonas NA. Massive pneumoperitoneum: a late complication of the Denver pleuroperitoneal shunt. Ann Thorac Surg 2005;80:e13.
142. Lopez-Viego MA, Cornell JM. Pneumoperitoneum and signs of peritonitis from a pleuroperitoneal shunt. Surgery 1992;111:228-9.

143. Rosemurgy AS, Zervos EE, Clark WC, et al. TIPS versus peritoneovenous shunt in the treatment of medically intractable ascites: a prospective randomized trial. Ann Surg 2004;239:883-9; discussion 89-91.
144. Zervos EE, Rosemurgy AS. Management of medically refractory ascites. Am J Surg 2001;181:256-64.
145. Boyer TD, Sanyal AJ, Wong F, et al. Terlipressin Plus Albumin Is More Effective Than Albumin Alone in Improving Renal Function in Patients With Cirrhosis and Hepatorenal Syndrome Type 1. Gastroenterology 2016;150:1579-89 e2.
146. Gifford FJ, Morling JR, Fallowfield JA. Systematic review with meta-analysis: vasoactive drugs for the treatment of hepatorenal syndrome type 1. Aliment Pharmacol Ther 2017;45:593-603.
147. Amin AA, Alabsawy EI, Jalan R, Davenport A. Epidemiology, Pathophysiology, and Management of Hepatorenal Syndrome. Semin Nephrol 2019;39:17-30.
148. European Association for the Study of the Liver. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. J Hepatol 2010;53:397-417.
149. Runyon BA, Aasld. Introduction to the revised American Association for the Study of Liver Diseases Practice Guideline management of adult patients with ascites due to cirrhosis 2012. Hepatology 2013;57:1651-3.
150. Colle I, Laterre PF. Hepatorenal syndrome: the clinical impact of vasoactive therapy. Expert Rev Gastroenterol Hepatol 2018;12:173-88.
151. Cavallin M, Kamath PS, Merli M, et al. Terlipressin plus albumin versus midodrine and octreotide plus albumin in the treatment of hepatorenal syndrome: A randomized trial. Hepatology 2015;62:567-74.
152. Sharma P, Kumar A, Shrama BC, Sarin SK. An open label, pilot, randomized controlled trial of noradrenaline versus terlipressin in the treatment of type 1 hepatorenal syndrome and predictors of response. Am J Gastroenterol 2008;103:1689-97.
153. Ghosh S, Choudhary NS, Sharma AK, et al. Noradrenaline vs terlipressin in the treatment of type 2 hepatorenal syndrome: a randomized pilot study. Liver Int 2013;33:1187-93.
154. Sanyal AJ, Boyer TD, Frederick RT, et al. Reversal of hepatorenal syndrome type 1 with terlipressin plus albumin vs. placebo plus albumin in a pooled analysis of the OT-0401 and REVERSE randomised clinical studies. Aliment Pharmacol Ther 2017;45:1390-402.
155. Boyer TD, Sanyal AJ, Garcia-Tsao G, et al. Predictors of response to terlipressin plus albumin in hepatorenal syndrome (HRS) type 1: relationship of serum creatinine to hemodynamics. J Hepatol 2011;55:315-21.
156. Sanyal AJ, Boyer T, Garcia-Tsao G, et al. A randomized, prospective, double-blind, placebo-controlled trial of terlipressin for type 1 hepatorenal syndrome. Gastroenterology 2008;134:1360-8.
157. Neri S, Pulvirenti D, Malaguarnera M, et al. Terlipressin and albumin in patients with cirrhosis and type I hepatorenal syndrome. Dig Dis Sci 2008;53:830-5.
158. Solanki P, Chawla A, Garg R, Gupta R, Jain M, Sarin SK. Beneficial effects of terlipressin in hepatorenal syndrome: a prospective, randomized placebo-controlled clinical trial. J Gastroenterol Hepatol 2003;18:152-6.
159. Sridharan K, Sivaramakrishnan G. Vasoactive Agents for Hepatorenal Syndrome: A Mixed Treatment Comparison Network Meta-Analysis and Trial Sequential Analysis of Randomized Clinical Trials. J Gen Intern Med 2018;33:97-102.
160. Salerno F, Navickis RJ, Wilkes MM. Albumin treatment regimen for type 1 hepatorenal syndrome: a dose-response meta-analysis. BMC Gastroenterol 2015;15:167.
161. Brensing KA, Textor J, Perz J, et al. Long term outcome after transjugular intrahepatic portosystemic stent-shunt in non-transplant cirrhotics with hepatorenal syndrome: a phase II study. Gut 2000;47:288-95.
162. Guevara M, Gines P, Bandi JC, et al. Transjugular intrahepatic portosystemic shunt in hepatorenal syndrome: effects on renal function and vasoactive systems. Hepatology 1998;28:416-22.
163. Lake JR, Ring E, LaBerge J, Gordon R, Roberts J, Ascher N. Transjugular intrahepatic portacaval stent shunts in patients with renal insufficiency. Transplant Proc 1993;25:1766-7.
164. Testino G, Ferro C, Sumberaz A, et al. Type-2 hepatorenal syndrome and refractory ascites: role of transjugular intrahepatic portosystemic stent-shunt in eighteen patients with advanced cirrhosis awaiting orthotopic liver transplantation. Hepatogastroenterology 2003;50:1753-5.
165. Wong F, Pantea L, Sniderman K. Midodrine, octreotide, albumin, and TIPS in selected patients with cirrhosis and type 1 hepatorenal syndrome. Hepatology 2004;40:55-64.

166. Linas SL, Schaefer JW, Moore EE, Good JT, Jr., Giansiracusa R. Peritoneovenous shunt in the management of the hepatorenal syndrome. Kidney Int 1986;30:736-40.