

Treatment of Acute Variceal Bleeding in 2021—When to Use Transjugular Intrahepatic Portosystemic Shunts?



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KEYWORDS

• TIPS • Preemptive TIPS • Portal hypertension • Acute variceal bleeding

KEY POINTS

- Preemptive transjugular intrahepatic portosystemic shunt (TIPS) should be the standard of care in patients with high-risk acute variceal bleeding (Child-Turcotte-Pugh stage B plus active bleeding on endoscopy or stage C with 10–13 points).
- The implementation of preemptive TIPS in clinical practice still requires further efforts.
- Lack of control of bleeding or early rebleeding within 5 days should be managed by rescue/salvage TIPS. Esophageal stents should be considered as the treatment of choice as a bridge until TIPS placement.

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A. Baiges and M. Magaz share first coauthorship.

Conflict of Interest Statement: V. Hernández-Gea and F. Turon receive speaker fees from Gore. J.C. García-Pagán advisory for GORE, Cook, and Shionogi. The remaining authors declare no conflicts of interests.

Financial Support Statement: This study was supported by the Ministry of Education and Science (SAF-2016-75767-R); Instituto de Salud Carlos III (ISCIII) and Fondo Europeo de Desarrollo Regional (FEDER) (PIE15/00027); and Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), funded by the Instituto de Salud Carlos III. J.C. García-Pagán also received a grant from Secretariat for Universities and Research of the Department of Economy and Knowledge (SGR17_00517). A. Baiges is a recipient of a Juan Rodés grant from Instituto de Salud Carlos III, Spain. M. Magaz is a recipient of a Río Hortega grant from Instituto de Salud Carlos III, Spain.

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Clin Liver Dis 25 (2021) 345–356

<https://doi.org/10.1016/j.cld.2021.01.001>

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- Currently, there is not enough evidence to use TIPS as a first-line treatment to prevent rebleeding.
- TIPS also may play a role in gastric varices, gastropathy of portal hypertension, and ectopic varices bleeding.

INTRODUCTION

Cirrhosis is a progressive disease that impairs liver function and decreases life expectancy.¹ The prognosis of patients with cirrhosis is highly dependent on the presence or not of portal hypertension (PH) and also on the presence or not of hepatic decompensation (mainly ascites, variceal bleeding, or hepatic encephalopathy [HE]). PH is defined by a pathologic increase in portal pressure gradient between the portal vein and inferior vena cava (portal pressure gradient), which is increased above the normal limit of 5 mm Hg in the setting of PH due to cirrhosis.¹ PH becomes clinically significant when the portal pressure gradient increases above the threshold of 10 mm Hg (formation of varices and ascites) or 12 mm Hg (variceal bleeding).^{2–4} Clinically, the development of gastroesophageal varices (GEVs) is a hallmark in the natural history of cirrhosis, given that they represent the clinical confirmation of PH and increase the risk of decompensation. Acute variceal bleeding (AVB) is due to the rupture of GEVs and represents one of the most severe medical emergencies in cirrhosis. The prognosis of AVB has improved significantly over the past decades due to better management of the hemorrhage and its associated complications. Mortality, however, still is approximately 15% to 20%.^{5,6} Moreover, variceal bleeding can trigger other complications of cirrhosis, such as bacterial infections, HE, and hepatorenal syndrome, that deteriorate prognosis further. Therefore, therapy to prevent bleeding (primary prophylaxis), to adequately control the acute bleeding episode, and to prevent rebleeding (secondary prophylaxis) is mandatory in order to improve survival. Currently, prevention and treatment of PH-related complications are based on medical treatment (nonselective β -blockers [NSBBs] administration; nitrates; diuretics; vasoactive drugs, such as somatostatin/terlipressin/octreotide; and so forth), endoscopic procedures and transjugular intrahepatic portosystemic shunt (TIPS) placement. Since the introduction of TIPS, the management of PH has been radically improved. TIPS placement is a percutaneous imaging-guided procedure that, by connecting usually the right intrahepatic portal branch and the right hepatic vein with a self-expandable metal stent, drastically reduces the portocaval pressure gradient. Although TIPS also can be used to treat other complications of PH, this review focuses on the use of TIPS in the different scenarios of cirrhotic PH bleeding, which are summarized in [Fig. 1](#).

TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNTS FOR PRIMARY PROPHYLAXIS

Different disease states encompass different risks of decompensation and, specifically, of variceal bleeding. It is considered that in patients with GEVs who never have bled that the risk of TIPS implantation outweighs its potential benefits and, therefore, currently TIPS is not indicated for primary prophylaxis. When TIPS is performed for another indication (ie, refractory ascites), however, variceal prophylaxis

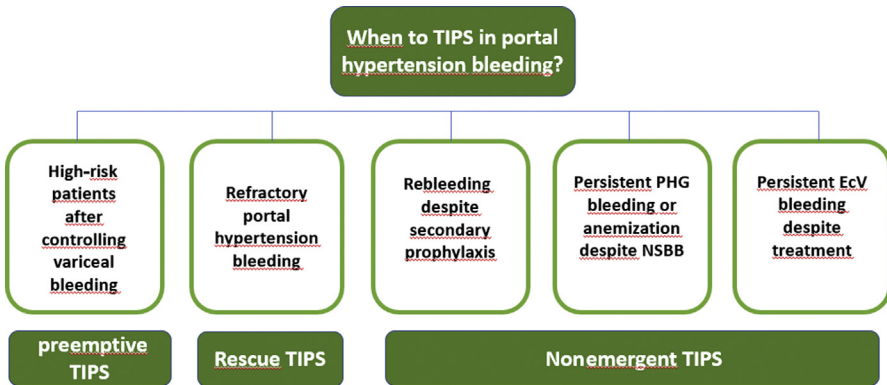


Fig. 1. When to use TIPS in the management of portal hypertension - related bleeding..

can be discontinued as long as TIPS is properly decreasing the portal pressure gradient below 12 mm Hg.

ACUTE EPISODE OF VARICEAL BLEEDING

Medical and Endoscopic Management

Vasoactive drugs, prophylactic antibiotics, and a restrictive blood transfusion constitute the cornerstone of the initial medical treatment of AVB.⁷ Vasoactive drugs should be initiated as soon as AVB is suspected, because they facilitate the subsequent endoscopy and improve bleeding control.⁸ Somatostatin, terlipressin, and octreotide currently are accepted vasoactive drugs; they require intravenous (IV) administration⁹ and should be maintained for up to 5 days, with the aim of avoiding early rebleeding.¹ A shorter administration (48–72 h) has been suggested as effective as maintaining treatment for 5 days. More data are required, however, to strongly support this short-term administration.

Active infections that are quite frequent at admission in cirrhotic patients with acute gastrointestinal bleeding must be ruled out and treated adequately. Even if these are ruled out, prophylactic antibiotics must be given to reduce the probability of infection, improve bleeding control, and survival rates.¹⁰ Also, it is important to apply antiemphalopathy measures and preserve renal function with adequate replacement of fluids and electrolytes. Red blood cell restitution must be restrictive, aiming at maintaining hemoglobin levels to a target level of 7 g/dL in order to avoid overexpansion.¹¹ Once hemodynamic stability is achieved, a gastroscopy should be performed and, if variceal bleeding is confirmed, endoscopic therapy done.^{1,12} Several studies have evaluated the best timing for endoscopy after admission with divergent results.^{12–15} The most accepted time interval to perform the gastroscopy, however, is within 12 hours after admission, especially in patients with hematemesis or hemodynamic instability. In patients with severe active bleeding or HE or in comatose patients, there is a high risk of aspiration. Thus, it is advisable to consider prophylactic orotracheal intubation prior to endoscopy to ensure airway protection.⁷

In the absence of contraindications (QT prolongation), administration of prokinetic agents, such as erythromycin, before the endoscopy (250 mg IV, 30–120 min before) has been shown to improve endoscopy performance and esophagogastric mucosa visibility.^{16,17} Endoscopic band ligation (EBL) is more effective than sclerotherapy and presents fewer adverse effects and, therefore, must be the endoscopic treatment of choice. Sclerotherapy can be used when band ligation is not feasible.

Rescue Transjugular Intrahepatic Portosystemic Shunt

In 10% to 20% of patients, variceal bleeding is not controlled or reappears in a short period of time despite the application of the strategy, discussed previously. In mild rebleedings, a second endoscopic attempt finally may achieve hemostasis. In most cases, however, especially in those with more severe bleeding, a rescue/salvage TIPS is needed.¹² Balloon tamponade (BT) might be used as a bridge to rescue TIPS in unstable patients. BT is highly effective in controlling variceal bleeding. It can be used only for a short period of time (<24 h), however, due to its damage to the esophagus mucosa, and physicians always should be aware that bleeding recurs after deflation in more than half of the cases. In addition, BT frequently causes severe complications, such as bronchoaspiration, asphyxia, or esophageal perforation.^{18,19} Esophageal stents have proved to be at least as effective as BT but, importantly, they are safer than BT in the management of AVB. Moreover, stents can be left in place for longer periods of time (usually up to 7 days), thus giving more time to achieve stabilization of the patient (ie, controlling possible sepsis or aspiration pneumonias) before placing a rescue TIPS.²⁰

The studies establishing the value of TIPS as a rescue therapy were uncontrolled (due to lack of an adequate comparator) and used uncovered stents. These studies showed that rescue TIPS is associated with considerable mortality rates (30%–50%)^{21–23} despite achieving high rates of bleeding control.^{24,25} Therefore, additional studies in the era of covered stents are needed. Considering the lack of effective therapeutic alternatives, the main factor limiting the use of rescue TIPS is therapeutic futility, which should be evaluated in the light of a patient's eligibility for liver transplantation and in prognostic scores developed to predict survival after rescue TIPS: a consistent finding in the literature is that patients with a Child-Turcotte-Pugh score over 13 points requiring rescue TIPS rarely survive a TIPS.²⁶ Nevertheless, individual decisions should be taken in a case-by-case basis.

ROLE OF PREEMPTIVE TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT IN PATIENTS WITH VARICEAL BLEEDING AT HIGH RISK OF TREATMENT FAILURE AND OF MORTALITY

The high mortality associated with the use of TIPS as a rescue treatment raised the question on whether patients with poor prognostic indicators at admission might benefit from a more aggressive initial therapeutic approach. The concept of preemptive (p)-TIPS refers to the preventive insertion of a TIPS in patients who are at high risk both of failure to control bleeding (considering a period of 5 days) and of bleeding-related mortality. The rationale for placing a p-TIPS is that by preventing treatment failure (and, therefore, maneuvers associated with it, such as multiple blood transfusions, repeated endoscopies, used of BT, and high risk of aspiration pneumonia) and by promoting a marked reduction in PH, mortality would be reduced. Accordingly, the use of p-TIPS requires identifying which patients are at risk of having a poor prognosis during AVB. It has been reported that patients with hepatic venous pressure gradient (HVPG) greater than or equal to 20 mm Hg are 5 times more likely to experience failure to control AVB or to present early rebleeding, require more blood transfusions, and have higher mortality rates than patients with HVPG less than 20 mm Hg.^{2,27,28} Likewise, the Child-Turcotte-Pugh score also has been used widely to estimate prognosis in the setting of AVB: survival in Child-Turcotte-Pugh stage A patients ranges from 96% to 100% whereas mortality is very high in patients with a Child-Turcotte-Pugh score greater than 13 points. More recently, a Model for End-Stage Liver Disease score greater than or equal to 19 also has proved an accurate marker of poor prognosis.²⁹ An important randomized clinical trial (RCT) confirmed

the concept of better bleeding control and better survival in patients receiving p-TIPS in high-risk patients, defined as an HVPG greater than or equal to 20 mm Hg, as opposed to those receiving endoscopic treatment.³⁰ Nevertheless, this study was criticized because the high-risk criteria used (HVPG measurement) were not widely available and difficult to apply in many centers. More importantly, in this RCT, both arms were undertreated, according to current standards (TIPSs were placed using uncovered stents and patients in the control arm received sclerotherapy instead of band ligation). This study was followed by 2 other RCTs^{29,31} and 4 observational studies,^{32–35} however, that were performed using easy clinical criteria to define high-risk patients, such as (1) Child-Turcotte-Pugh stage B patients with active bleeding at diagnostic endoscopy despite receiving vasoactive drugs and (2) Child-Turcotte-Pugh stage C patients up to 13 points (regardless of endoscopy findings). All these studies used covered stents and proved that p-TIPS increases bleeding control, decreases rebleeding, improves ascites control without worsening HE, and, more importantly, reduces mortality. Mortality is reduced from 30% to 41% in patients receiving NSBBs plus EBL to 14% to 22% in the p-TIPS arm.^{33–36} In the control arm (NSBBs plus EBL group), mortality is lower in Child-Turcotte-Pugh stage B plus active bleeding than in Child-Turcotte-Pugh stage C patients. Accordingly, the effects of p-TIPS on survival are more marked in Child-Turcotte-Pugh stage C patients than on the Child-Turcotte-Pugh stage B plus active bleeding group, which present more variable and heterogeneous survival results among the different studies.³³ Most of these studies, however, have limited sample size and more data are needed. In any case, also in Child-Turcotte-Pugh stage B patients, p-TIPS clearly has been shown to improve bleeding and ascites control without worsening HE, therefore making its use advisable in this setting.

Despite this evidence and despite clinical guidelines currently recommending the implementation of p-TIPS,¹ prospective surveys demonstrate that only 7% to 13%^{33,34} of eligible patients currently are treated with p-TIPS, which highlights that physicians still need to incorporate p-TIPS in real-world practice. Supporting its implementation, it has been estimated that 4 high-risk patients need to be treated with p-TIPS to save 1 life, a number that is comparable to other very well-accepted invasive therapeutic strategies applied in other severe diseases, such as myocardial infarction. Also, Child-Turcotte-Pugh stage C patients have been shown to benefit from early intervention due to their higher risk of treatment failure and early death; patients with Child-Turcotte-Pugh stage B disease, even with active bleeding at the time of endoscopy, do not seem to universally benefit from preemptive intervention with TIPS; however a recent meta-analysis of individual patient data reveals improving survival and control of bleeding in both subgroups.³⁷

TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT IN SECONDARY PROPHYLAXIS AFTER ACUTE VARICEAL BLEEDING

A combination of NSBBs plus EBL is highly effective in the secondary prevention of rebleeding and currently is the treatment of choice.¹ Several studies have compared this strategy with the initial use of TIPS in secondary prophylaxis.^{23,38–40} Overall, in these studies, TIPS has been proved more effective than combination therapy in terms of preventing rebleeding but at expenses of a higher incidence of HE and no improvement in survival.^{23,38–40} Although in most of these studies TIPS was performed using uncovered stents, 2 of them used covered stents^{38,39} and showed similar results. Therefore, based on available data, TIPS currently cannot be recommended as a first-line treatment in secondary prophylaxis,²³ although it must be used to prevent further rebleeding when combination therapy fails.

Following the same rationale than that applied for AVB and p-TIPS, if the subpopulation of patients in whom combination therapy (NSBBs plus EBL) would fail to prevent rebleeding could be identified accurately and promptly, it might be worthy to test whether TIPS may be a better secondary prophylaxis strategy than NSBBs plus EBL in this selected group. In that regard, it already is known that patients undergoing secondary prophylaxis with EBL alone presents a higher rate of rebleeding and higher mortality than patients receiving combination therapy with NSBBs plus EBL.⁴¹ Therefore, patients who cannot tolerate NSBBs or who present other conditions contraindicating NSBBs would be a potential high-risk population in whom other therapeutic strategies, such as TIPS, should be explored. Consequently, studies aiming at identifying patients with poor prognosis despite the use of the current standard of care for secondary prophylaxis are needed.

Probably the characteristics of the population requiring secondary prophylaxis will drastically change in the coming years if most centers adopt the use of the p-TIPS strategy for treating high-risk patients with AVB, because only the less severe patients will undergo secondary prophylaxis with NSBBs plus EBL. Future research needs to focus on exploring whether certain subgroups of patients initially considered not high-risk patients or patients who did not undergo p-TIPS for logistical reasons still may benefit from elective TIPS implantation for secondary prophylaxis.

MANAGEMENT OF GASTRIC VARICES

The prevalence of gastric varices (GVs) is lower (15%–20%) than esophageal varices (EVs) and they seem to bleed less frequently. When they do bleed, however, the bleeding usually is more severe and with a higher mortality than in EV.⁴² According to Sarin and colleagues'⁴³ classification, there are 4 subtypes of GV that have been shown to have different prognosis: GEVs associated with EVs along the lesser curve (gastroesophageal varices type 1 [GOV1]), GEVs associated with EVs along the along the fundus (gastroesophageal varices type 2 [GOV2]), isolated GV (IGVs) located in the fundus (isolated gastroesophageal varices type 1 [IGV1]), and IGVs located at ectopic sites in the stomach/duodenum (isolated gastroesophageal varices type 2 [IGV2]).⁴³ Unfortunately, the management strategy for this subtype of varices is not as well established as in EV bleeding, given their lower prevalence and the scarce number of RCTs.⁴⁴ Additionally, in most studies, the different types of GV are mixed and, therefore, the results are of difficult interpretation.

The initial treatment of GV bleeding is like that of EV bleeding (vasoactive drugs, volume resuscitation, and antibiotics prior to endoscopy). In a massive GV bleeding, a careful tamponade with a Linton-Nachlas balloon plays an important role as a bridge to further definitive therapy. It may achieve hemostasis in up to 80% of patients, although rebleeding may occur frequently when deflating the balloon.⁴⁵

Studies evaluating the best endoscopic therapy for GV are scarce and, as discussed previously, mix different GV types. Tissue adhesives, such as cyanoacrylate injection, are the more frequently endoscopic technique used,^{46,47} although other possible endoscopic treatments are thrombin injection, sclerotherapy, band ligation, and their combinations. A recent RCT comparing cyanoacrylate injection versus thrombin injection for the acute management of GV hemorrhage found that, although both techniques present a similar rate of successful hemostasis, thrombin injection had a lower incidence of complications.⁴⁸ A significant percentage of patients included in this study presented GOV1 varices, which, according to current guidelines, should be treated as EV (including the use of p-TIPS in high-risk patients).^{7,12,49} Remarkably, there is no consensus on the management of GOV2 and IGV1: although

the American guidelines recommend TIPS as first-line therapy without prior use of endoscopic therapy,¹² Baveno VI criteria counsels cyanoacrylate injection plus NSBBs as first-line secondary prophylaxis,¹ reserving TIPS for treatment failure. Although admittedly no IGV1 or IGV2 patients were included in the p-TIPS studies, it seems reasonable to also apply the p-TIPS strategy in high-risk patients with AVB from GOV2, IGV1, and IGV2.

In experienced centers, patients with cardio-fundal varices (GOV-2 and IGV-1) and presence of an anatomic gastroduodenal shunt can be treated with balloon-occluded retrograde transvenous obliteration (BRTO).⁵⁰ BRTO is a radiological procedure that aims at sclerosing the shunt feeding the varix: a balloon catheter is inserted, usually via the right femoral vein, and wedged into the left adrenal vein, achieving variceal obliteration. This technique is effective for treating bleeding fundic GVs. Patients may be at risk, however, of developing EVs after occlusion of the gastroduodenal shunt⁵¹ as well as thrombosis of the splanchnic axis. Despite the possibility of this side effects, among the BRTO advantages are lower rates of failure to control bleeding and rebleeding⁵² and diminished incidence of HE. Thus, BRTO may be a good option for patients who have bled from fundic varices and are at high risk of HE or cardiac failure after TIPS.⁵³

In recent studies, a modified BRTO strategy (balloon-assisted antegrade transvenous obliteration), combined with TIPS placement, has proved useful for the treatment of cardio-fundal varices (GOV2 or IGV1). This combined technique seems effective and may diminish the complications of PH, such as ascites and portal vein thrombosis.⁵⁴ These results must be interpreted with caution, however, due to the low number of patients reported and the need of more standardized studies addressing this approach.

MANAGEMENT OF ECTOPIC VARICES

Ectopic varices (EcVs) are composed of dilated portosystemic collaterals placed along the gastrointestinal tract instead of the common gastroesophageal region and account for 1% to 5% of all varices.⁵⁵ Their most frequent locations are around the insertion of stomas (40%), duodenum (23%), and rectum (17%), whereas the remaining 20% are located at other sites (20%). EcVs have a 4-fold increased risk, however, of bleeding when compared with EVs and, remarkably, can have a mortality rate as high as 40%.⁵⁶ Besides, difficulty in localizing the bleeding makes the management of these patients challenging, which can be solved by performing a computed tomographic angiography.⁵⁵

TIPS employment in the management of EcV bleeding is based on case series.^{57–59} The largest cohort published is a multicentric retrospective study that included 53 patients. The investigators concluded that TIPS may provide long-term control of bleeding in most cirrhotic patients with EcV and is effective particularly in stomal EcV, although might not be as effective in duodenal EcV (50% of rebleeding risk). A British study, including 21 patients with cirrhosis and EcV bleeding, who underwent TIPS, showed that embolization stopped the bleeding in most subjects. Therefore, combining TIPS and embolization may be a good approach in this setting.⁵⁷ In any case, therapeutic approach in EcV should be individualized based on the bleeding site and the vascular anatomy, taking into account the different points of view of a multidisciplinary team.¹²

PORTAL HYPERTENSION GASTROPATHY

PH gastropathy (PHG) is a cause of morbidity in patients with PH. Its diagnosis relies in the typical endoscopic findings of polygonal areas of variable erythema and, although

not necessary for diagnosis, histologic findings may include venule and capillary dilatation, congestion, and tortuosity.⁶⁰ PHG may manifest both as chronic and overt bleeding,⁶¹ sometimes even requiring repeated blood transfusions.⁶²

The initial treatment of acute PHG bleeding should be based on vasoactive drugs, followed by NSBBs for secondary prophylaxis.⁶² TIPS should be considered in patients who rebleed or continue to bleed despite adequate β -blocker therapy and in those who present persistent anemia despite iron supplementation. Unfortunately, the evidence for TIPS in the management of PHG is limited to reduced case reports and small series.^{63–65} TIPS placement, however, may improve PHG and reduce the need of transfusions in most of the patients.⁶⁶

It is important to differentiate PHG from gastric antral vascular ectasia (GAVE), which may be present in patients without PH. GAVE is characterized by red spots without a mosaic pattern, characteristically located in the antrum with a linear distribution, hence the name, *watermelon stomach*. GAVE's gold standard treatment is argon plasma coagulation and TIPS does not play a role in its management, although it could be considered in cases where PHG and GAVE coexist.⁶⁷

CLINICS CARE POINTS

- Primary prophylaxis for AVB should be based on non-selective betablockers or endoscopic band ligation.
- The first approach to AVB is a prompt administration of vasoactive drugs, endoscopic treatment and prevention of other complications (use of antibiotics and anti-encephalopathy measures).
- In Child-Turcotte-Pugh stage B patients with active bleeding at endoscopy, and in all Child-Turcotte-Pugh stage C patients, preemptive TIPS should be considered.
- In patients presenting a rebleeding episode despite adequate secondary prophylaxis TIPS should be considered.
- TIPS \pm embolization would be recommended in the setting of gastric variceal bleeding if patients rebleed despite medical and endoscopic therapy.
- In ectopic varices refractory to local therapy, TIPS could be an effective tool.
- In patients with persistent anemization and bleeding from portal hypertensive gastropathy refractory to iron and beta-blockers treatment, TIPS could also be considered.

ACKNOWLEDGMENTS

Administrative support by Oliva Ros Fargas.

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