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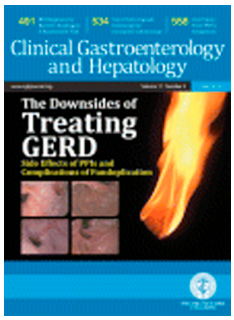

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North American Practice-Based Recommendations for Transjugular Intrahepatic Portosystemic Shunts in Portal Hypertension

Short Title: North American Guidance for TIPS use

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Abbreviations (alphabetically)

AKD: Acute Kidney Disease

AKI: Acute kidney injury

ALF: Acute liver failure

ALTA: Advancing Liver Therapeutic Approaches

ACC: American College of Cardiology

AHA: American Heart Association

BCS: Budd-Chiari Syndrome

CCM: Cirrhotic cardiomyopathy

CKD: Chronic kidney disease

CO: Cardiac output

CTP: Child-Turcotte-Pugh

DIPS: Direct intrahepatic portosystemic shunt

ECG: Electrocardiogram

ePTFE: Expanded polytetrafluoroethylene

EVL: Endoscopic variceal ligation

GFR: Glomerular filtration rate

GV: Gastric fundal varices

HE: Hepatic encephalopathy

HF: Heart failure

HH: Hepatic hydrothorax

HPS: Hepatopulmonary syndrome

HRS: Hepatorenal syndrome

INCPH: *idiopathic non-cirrhotic portal hypertension*

INR: Internationalized normal ratio

IR: Interventional radiology

IVC: Inferior vena cava

LT: Liver transplantation

LV: Left ventricular

LVEF: Left ventricular ejection fraction

LVP: Large volume paracentesis

MELD: Model for End-Stage Liver Disease

POPH: Portopulmonary hypertension

PSG: Portosystemic gradient

PVT: Portal vein thrombosis

RA: Refractory ascites

RAP: Right atrial pressure

RCTs: Randomized controlled trials

RV: Right ventricular

sCr: Serum creatinine

SPSS: Spontaneous portosystemic shunts

TFS: Transplant-free survival

TIPS: Transjugular intrahepatic portosystemic shunt

TR: Tricuspid regurgitation

VHD: Valvular Heart Disease

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L.B.V., J.R.B., E.C.V., M.B.F., B.G.T., and K.P.K. are ALTA Steering Committee members and developed the idea for the manuscript and created the structure. L.B.V., J.R.B., B.G.T., E.C.V., K.P.K., M.J.I., S.K.A., and B.F. each wrote specific sections of the manuscript. All authors participated in regular working group meetings, critical review of the literature, the Delphi voting process, and the virtual conference, commented on and revised the manuscript, and approved the final version.

DATA TRANSPARENCY STATEMENT

Not applicable

ABSTRACT

Complications of portal hypertension, including ascites, gastrointestinal bleeding, hepatic hydrothorax, and hepatic encephalopathy are associated with significant morbidity and mortality. Despite few high quality randomized controlled trials to guide therapeutic decisions, transjugular intrahepatic portosystemic shunt (TIPS) creation has emerged as a crucial therapeutic option to treat complications of portal hypertension. In North America, the decision to perform TIPS involves gastroenterologists, hepatologists, and interventional radiologists, but TIPS creation is performed by interventional radiologists. This is in contrast to other parts of the world in which TIPS creation is primarily performed by hepatologists. Thus, the successful use of TIPS in North America is dependent on a multidisciplinary approach and technical expertise, so as to optimize outcomes. Recently, new procedural techniques, TIPS stent technology, and indications for TIPS have emerged. As a result, practices and outcomes vary greatly across institutions and significant knowledge gaps exist. In this Consensus statement, the Advancing Liver Therapeutic Approaches (ALTA) group critically reviews the application of TIPS in the management of portal hypertension. ALTA convened, for the first time, a multidisciplinary group of North American experts from hepatology, interventional radiology, transplant surgery, nephrology, cardiology, pulmonology, and hematology to critically review existing literature and develop practice-based recommendations for the use of TIPS in persons with any cause of portal hypertension in terms of candidate selection, procedural best practices and post-TIPS management; and to develop areas of consensus for TIPS indications and prevention of complications. Finally, future research directions are identified related to TIPS for the management of portal hypertension.

Key Words: TIPS procedure; cirrhosis; end-stage liver disease; complications; consensus statement; guidance document; ascites; variceal bleeding

INTRODUCTION

Portal hypertension, defined as elevated pressure in the portal venous system, can lead to major clinical complications including ascites, gastrointestinal hemorrhage, hepatic hydrothorax (HH), and hepatic encephalopathy (HE), all associated with significant morbidity and mortality.[1] While medical therapies and liver transplantation (LT) are effective treatments in many scenarios, transjugular intrahepatic portosystemic shunt (TIPS) creation is a crucial therapeutic option.(Figure S1)

In North America, the decision to perform TIPS is determined by specialists in gastroenterology and hepatology who treat patients with portal hypertension, but TIPS creation is performed by interventional radiology (IR). This is in contrast to other parts of the world (e.g., Europe) in which hepatologists primarily perform TIPS. While TIPS creation is effective for management of complications of portal hypertension,[2-7] it is associated with several risks, including deterioration in liver function, new onset or worsening HE,[8] and changes in cardiopulmonary and renal hemodynamics (Figure S1).[9] Over the past decade there have been important advancements in TIPS devices, procedural techniques, and immense growth in the literature supporting the role of TIPS in the management of portal hypertension.[10, 11] However, there are few high quality randomized controlled trials (RCTs) of TIPS use. New indications for TIPS placement have also emerged, including treatment of portal vein thrombosis (PVT), which require rigorous assessment. As a result, practices and outcomes vary greatly across institutions and significant knowledge gaps exist.

The goals and objectives of the Advancing Liver Therapeutic Approaches (ALTA) Consensus Conference were to convene, for the first time, a multidisciplinary group of North American experts from hepatology, IR, transplant surgery, nephrology, cardiology, pulmonology, and hematology to critically review existing literature and develop practice-based recommendations for the use of TIPS in persons with any cause of portal hypertension in terms of candidate selection, procedural best practices and post-TIPS management across seven key topic areas: general considerations for TIPS, TIPS in the management of ascites/HH, TIPS in the management of variceal bleeding, novel

indications for TIPS, cardiopulmonary considerations of TIPS including management of hepatopulmonary syndrome (HPS), renal considerations of TIPS including management of hepatorenal syndrome (HRS), and HE and TIPS.

METHODS

A consensus-building process was conducted consistent with standards described in the Appraisal of Guidelines for Research and Evaluation II[12] and used a modified Delphi approach to achieve consensus (Supplemental Methods).[13] Practice-based recommendations were developed by 30 ALTA group members with extensive experience in the management of portal hypertension and the use of TIPS, who participated in the consensus conference held on October 23, 2020. The target users are gastroenterologists, hepatologists and sub-specialty physicians who refer for TIPS and/or provide care for patients undergoing TIPS.

PubMed, EMBASE, and Cochrane were queried for English language papers published between January 1, 1990 and July 1, 2020. The target population was persons with any cause of portal hypertension undergoing TIPS. Terms were chosen through input from participants and by consultation with a medical librarian (Supplemental Methods). We considered peer-reviewed articles in the following order of relevance: RCTs, systematic reviews and meta-analyses, and observational studies. For select topics where studies were limited, case reports were included. Between August 2020 and October 2020, literature for each topic was iteratively discussed by workgroups of physicians with expertise in the identified topics. Level of evidence for all consensus statements was graded using the Oxford Centre for Evidence-based Medicine Levels of Evidence.[14]

RESULTS AND DISCUSSION

The literature search yielded 2,116 articles, with 703 remaining after titles and abstracts were screened for relevance (Supplemental Methods). An additional 81 articles not captured by the literature search were included on the basis of panel agreement of relevance.

A total of 105 clinical statements were developed for assessment throughout the two iterations of the Delphi survey. All panelists completed all survey items. After two iterations of the Delphi survey, 87 statements met the standardized definition for consensus (Supplemental Methods and Table S1). The recommendations are outlined in Tables 1-3. The following text provides brief rationale supporting these recommendations. Expanded rationale, where indicated, is available in the supplemental material.

General Considerations for TIPS

Table 1 summarizes recommendations concerning TIPS planning, procedural best practices, and care of the TIPS recipient independent of indication for TIPS.

Pre-TIPS Considerations

Q1. Who should be involved in the decision to place a TIPS?

A team-based approach to TIPS is critical in all stages of TIPS planning and management (Figure 1).[15, 16] Initial consideration for decision on TIPS candidacy should involve the patient and caregiver as well as a gastroenterologist or hepatologist and a proceduralist with competency in TIPS. Complex cases should include consultation with additional specialties (e.g., transplant surgery, nephrology, etc.) as appropriate.

Q2. What services should be readily available at centers where TIPS is performed and what referral pathways should be established for a higher level of care?

Centers that offer TIPS creation should ensure availability of multidisciplinary services to provide high quality care for this high-risk population (Figure 1).[16] Centers should have access to expertise in IR, gastroenterology/hepatology, cardiology, surgery, nephrology, and critical care medicine. In complex cases, including patients meeting criteria for referral for transplant or requiring specific technique expertise (e.g., PVT), referral to centers with additional expertise is recommended.

Q3. Is there a Model for End-Stage Liver Disease (MELD) threshold above which elective TIPS should not be considered?

A multidisciplinary approach, rather than an absolute MELD cutoff, is recommended to assess TIPS candidacy. MELD score is the strongest predictor of 90-day mortality after TIPS when compared to MELD-Na and other scoring systems (e.g., Child-Turcotte-Pugh (CTP) score, etc.; Supplemental Discussion).[17-22] MELD score performs better in patients with TIPS for variceal bleeding compared to patients with refractory ascites (RA).[23-25] Studies have examined additional risk factors for poor outcomes with mixed results, including older age and specific numerical MELD score cutoffs.[24-30] Variability in patient population and study design limit the ability to determine firm cutoffs.[4, 31-34] Determination of TIPS candidacy using the MELD score should take into consideration the relative risk and benefit of TIPS creation, considering the TIPS indication, patient comorbidities and alternative treatment options.

Q4. What evaluation is required prior to TIPS creation?

Cross-sectional imaging and echocardiography provide important information for TIPS planning. Cross-sectional imaging should include portal venous phase imaging to adequately define portal veins, hepatic veins, and the liver parenchyma to permit planning of TIPS creation. Comprehensive echocardiography before TIPS is recommended to assess risk for cardiac decompensation after TIPS (details in cardiopulmonary section).[15] Emergent TIPS indications may not allow a complete anatomic

and cardiac evaluation; however, a liver ultrasound with doppler and a limited two-dimensional echocardiogram should still be considered.

Q5. What are absolute contraindications to elective TIPS creation?

The absolute contraindications to TIPS creation include American College of Cardiology (ACC)/American Heart Association (AHA) Stage C or D heart failure (HF, i.e., echocardiographic evidence of systolic +/- diastolic dysfunction combined with clinical features of HF),[35] AHA/ACC stage C or D untreated valvular heart disease (VHD, i.e., asymptomatic severe VHD with or without decompensation of the left or right ventricle or symptomatic VHD),[36] moderate-severe pulmonary hypertension, uncontrolled systemic infection, refractory overt HE and anatomic barriers to shunt creation (e.g., multiple hepatic lesions).[15, 16]

Q6. Should all patients undergo evaluation for LT prior to TIPS creation?

In patients undergoing elective or emergent TIPS, there is insufficient evidence to recommend universal pre-procedure LT evaluation. While patients with cirrhosis and RA or variceal bleeding undergoing TIPS have indications for a LT evaluation, not all will be LT candidates.[37] TIPS should not be delayed in order to consider a LT evaluation.

TIPS Procedural Considerations

Q7. Who should perform TIPS creation?

TIPS should be performed by a credentialed, board certified Interventional Radiologist or a certified provider with equivalent training and procedural competency, acknowledging that training pathways vary worldwide.[16, 38] According to radiology professional society guidelines, TIPS placement must be performed by a physician with board certification or accredited training as well as sufficient

experience with TIPS procedures. In the absence of certification or accredited training, TIPS placement can be performed by a competent proceduralist defined as one who has performed competent proceduralist is one who has performed a sufficient number of TIPS procedures under supervision (minimum threshold = 5), in addition to other endovascular techniques (i.e., minimum of 100 angiograms, 50 angioplasties, 10 stent placements, and 5 embolizations), has achieved expected procedure completion thresholds, and has obtained appropriate privileges at their center.[38]

Q8. What type of stent is recommended for TIPS creation?

Numerous studies have demonstrated improved patency, ascites control and rebleeding prevention with the use of expanded polytetrafluoroethylene (ePTFE) covered stent grafts versus bare metal stents at the time of TIPS creation.[39-46] The use of a specialized purpose-designed stent graft appears to yield superior patency compared with shunts created with off-label use of bare metal stent/stent graft constructs.[47] Use of a controlled-expansion stent that allows for incremental and reliable expansion of stent diameter is recommended in order to optimize the amount of portosystemic shunting based on the indication, patient risk factors, and target gradient, while potentially mitigating the risk of HE.[10] Underdilation of a self-expanding stent with a fixed diameter as a method of decreasing HE risk is not recommended because the stent will passively expand over time to its nominal diameter..[48, 49]

Q9. Should coagulopathy be corrected prior to TIPS creation?

It is unclear whether correction of coagulopathy to a specific target internationalized normal ratio (INR) or thrombocytopenia decreases complications or improves survival after TIPS.[50] INR and platelet count are poor measures of bleeding risk in patients with cirrhosis and routine transfusion of blood products prior to invasive procedures does not portend lower procedural bleeding risk.[51-55] However, these studies primarily include patients undergoing paracentesis and liver biopsy, and it is

unclear if the results can be extrapolated to patients undergoing TIPS creation, which carries a higher bleeding risk. Plasma fibrinogen levels < 100 mg/dL are associated with increased bleeding risk in critically ill patients with cirrhosis, but causal relationships are not established.[50] The role of correction to levels > 100 mg/dL and reduction of bleeding risk during TIPS creation is unknown.[50]

Q10. Should periprocedural antibiotics be routinely used in TIPS creation?

The use of periprocedural antibiotics will depend on patient (e.g., prior biliary instrumentation) or local risk factors.[56, 57] There is insufficient evidence that the routine use of periprocedural antibiotics decreases infectious complications after TIPS creation.

Q11. Should TIPS creation be performed using general anesthesia or is deep or conscious sedation appropriate?

There is no evidence that the use of any specific type of anesthetic has an impact on procedural success, complication rate, or post-procedure outcomes. The use of general anesthesia, deep sedation, or conscious sedation will depend on patient risk factors and local practices.

Q12. Is the use of intravascular ultrasound recommended to assist with the portal vein puncture?

The use of intravascular ultrasound to facilitate access into the portal vein is associated with decreased needle passes through the liver, contrast use, procedure time, time to portal access, and radiation exposure.[58, 59] However, no studies have shown that the use of intravascular ultrasound reduces complication rates or improves survival after TIPS creation.

Q13. What is the optimal location from which to measure the systemic venous pressure at the time of TIPS creation?

Either the free hepatic or IVC pressure should be used as the systemic venous pressure when measuring the PSG before and after TIPS creation. In patients with cirrhosis, the use of the free hepatic venous pressure or the inferior vena cava (IVC) pressure as the systemic venous pressure, rather than the right atrial pressure (RAP), when calculating the hepatic venous pressure gradient is well validated.[60, 61] Studies have shown the efficacy of these measurements when assessing clinical response following TIPS creation.[62-64] These studies have also demonstrated a statistically significant difference between the hepatic venous or IVC pressure compared to the RAP due to the effect of intra-abdominal pressure. This difference decreases the prognostic value of the portosystemic gradient (PSG) when the RAP is used and could potentially lead to under- or over-dilation of the TIPS stent to achieve a target gradient.[64]

Q14. Are there specific technical factors that should be considered to ensure that TIPS creation does not adversely influence liver transplant candidacy?

LT candidacy should not be impacted by creation of TIPS. The presence of a patent TIPS in patients undergoing LT is unlikely to negatively impact surgical outcomes although it may increase surgical complexity.[65-68] During LT, the presence of TIPS may cause hyperdynamic circulation and increased portal flow,[67, 69] but does not impact blood transfusion requirements, operative time, or hospital length of stay.[65-68] Operative factors are more favorable with TIPS compared to pre-transplant surgical shunts.[66] TIPS malposition may affect up to 20% of transplants;[66, 68] therefore, care should be taken to ensure that the TIPS device does not extend into the right atrium and leaves a segment of the portal vein for transplant anastomoses.

Care of the Post-TIPS Patient

Q15. What is the recommended duration of intensive post-procedure monitoring?

Most patients may be safely monitored overnight in an acute care unit after TIPS creation. Patients at high risk for TIPS-related decompensation based on patient factors (e.g., cardiac dysfunction, overt HE) or immediate complication based on intraprocedural events (e.g., trans-splenic approach) may require a higher level of care.

Q16. What early testing is recommended following TIPS creation and at what interval?

Laboratory evaluation to assess for bleeding, hepatic dysfunction and to allow calculation of MELD score prior to discharge after TIPS creation is considered standard of care (Supplemental Discussion). Because early TIPS thrombosis is rare in the era of ePTFE-covered TIPS[41, 46] and early Doppler ultrasound of ePTFE-covered TIPS flow is obscured by the presence of microbubbles,[70, 71] early post-TIPS Doppler ultrasound interrogation is unlikely to impact clinical decisions and is not routinely recommended. However, early imaging in select patients with high risk of early thrombosis (e.g., underlying thrombophilia) may be appropriate.

Q17. Should TIPS venography and intervention be based on ultrasound, clinical findings, or both?

The decision to perform TIPS venography and intervention should depend on the indication for TIPS creation due to low specificity (33-95%) and high false positive rates (50%) of Doppler ultrasound for detecting TIPS dysfunction.[70, 72] In patients who have undergone TIPS for management of varices, TIPS stenosis will increase the PSG and risk for subsequent variceal hemorrhage.[73] Clinical (e.g., ascites) or Doppler ultrasound findings suggesting stenosis in this cohort should prompt TIPS venography and manometry, where stenosis can be confirmed and intervened upon or refuted.

In patients who undergo TIPS for ascites/HH and with absence of clinically apparent ascites/HH, intervention based on Doppler ultrasound findings suggesting TIPS stenosis depends on other clinical factors. If ascites/HH is well-controlled, confirmation of TIPS stenosis by venography and manometry may not necessarily prompt intervention.

In patients who undergo TIPS to reestablish portal vein patency, routine scheduled TIPS venography and manometry +/- intervention is suggested within 1-2 months following portal vein recanalization and TIPS creation in order to assess for residual thrombus, perform additional portal vein recanalization, and embolize spontaneous competing portosystemic shunts as needed in order to help maintain portal vein patency (see Supplemental Discussion).[74]

Q18. What are the optimal techniques for altering TIPS flow when intervention is required?

When an indication to change the PSG is identified, stepwise dilation of a controlled expansion stent is the least invasive way to achieve this goal. When a TIPS has been dilated to its maximum potential diameter, the next step relies on individualized decision-making. Interventions to further decrease the PSG include parallel TIPS creation and medical therapy. Multiple techniques have been described to increase the PSG by constraining the flow lumen of pre-existing TIPS. Comparative data between TIPS reduction techniques do not exist.

Q19. Who should see patients with TIPS in follow up?

We recommend a multidisciplinary approach to post-TIPS management involving a gastroenterologist/hepatologist and a proceduralist given the need for ongoing liver care as well as monitoring for any post-procedural complications and potential need for TIPS revision (Figure 2).[15, 16]

Specific Considerations for TIPS by Indication

The approach to TIPS creation should differ depending on clinical indication, as the optimal balance between efficacy and morbidity may vary (Table 2).

TIPS in Ascites or HH

Q1. What is the optimal technical approach to TIPS creation among patients with cirrhosis and RA?

In the setting of elective TIPS for ascites, there is time to carefully titrate the amount of portal decompression obtained while monitoring for shunt morbidity, including HE. After weighing the advantages and disadvantages of various approaches (Table S1), we favor the creation of a small diameter TIPS (8 mm, based on the minimum 8 mm diameter with current generation on-label use of controlled expansion stent graft) followed by progressive dilation, if needed, based on clinical response at 6-week intervals. This approach minimizes the risks of overshunting and offers the greatest opportunity for procedural uniformity.

Q2. Is TIPS associated with better outcomes than serial large volume paracentesis (LVP) for the treatment of RA?

As compared to LVP, TIPS is associated with improved control of ascites, but increased risk of HE (Table S2).[4, 75-80] The impact of TIPS on survival has been more controversial, with some,[4, 76, 79, 80] but not all RCTs demonstrating improved transplant-free survival (TFS).[77, 78] Several subsequent meta-analyses[81-86] have confirmed the superiority of TIPS compared to serial LVP in prevention of recurrent ascites, but remained split in terms of TFS benefit, depending upon methodology and whether one potentially outlier[75] paper was included (Table S2, Supplemental Discussion).

Q3. Is there a threshold of liver dysfunction above which TIPS for RA should be contraindicated and how should it be defined?

Among patients with cirrhosis and RA, elevated bilirubin, MELD score and CTP Class C cirrhosis are associated with increased post-TIPS complications including mortality.[76, 84-86] However, strong evidence for a specific cutoff for any of these parameters is lacking (Table S2, Supplemental Discussion).

Q4. What is the impact of age on candidacy for TIPS for RA?

Among patients with cirrhosis and RA, advanced age is associated with increased post-TIPS complications including HE and mortality. However, there are no studies that provide strong evidence of a specific cutoff above which TIPS should be considered contraindicated (Table S2, Supplemental Discussion).

Q5. What is the role of TIPS in patients with ascites that is not refractory?

TIPS should be considered in selected patients with at least three LVPs for tense ascites in a year despite optimal medical therapy.[1] Among RCTs comparing TIPS vs LVP, those which included patients not fulfilling strict criteria of RA showed improved TFS[4, 79] or a trend for improved TFS.[76] Among trials including patients with RA with a strict definition, only one showed an improvement in survival. The specific definitions of non-RA vary by trial (Table S3).

Q6. What is the role of TIPS in HH?

For patients with HH on maximal medical therapy requiring frequent thoracentesis or those with significant clinical symptomatology (e.g., hypoxia, resting dyspnea), TIPS should be considered.[1] TIPS creation for refractory HH leads to complete response in over 50% of patients, with partial responses observed in approximately 20%, similar to response rates for RA.[87-91] Predictors of inferior outcomes of TIPS for recurrent HH are similar to those observed in TIPS placed for RA, including older age, severity of liver disease, and renal insufficiency.[5, 17, 89]

Q7. Is prior LT a contraindication to TIPS for RA? Is TIPS superior to surgical shunt, serial LVP or splenic artery embolization in LT recipients with RA?

There is insufficient evidence to support any recommendation regarding therapy (TIPS and other modalities) in LT recipients with RA (Supplemental Discussion). The technical success for TIPS creation post-LT is similar to that observed in patients pre-transplant; however, the clinical efficacy is inferior to that observed in RA pre-LT.[92-94] Careful assessment for the underlying etiology of ascites should be undertaken prior to TIPS creation and the timing post-LT should be considered.

Q8. What is the expected timeline for TIPS to be effective for reduction of ascites/HH?

In detailed pathophysiological studies, a negative sodium balance (under a very strict low-sodium diet) is achieved at around four weeks after TIPS.[95] With a less restrictive diet this level of natriuresis might not be achieved and patients may require the use of diuretics after TIPS. If using a staged approach to TIPS (progressive stent dilation from 8 to 9 to 10 mm of diameter based upon clinical response), the decision to increase TIPS diameter should not be made before 6 weeks.

TIPS in Variceal Bleeding

Q1. When is TIPS indicated in acute variceal hemorrhage?

TIPS is recommended in patients with cirrhosis with uncontrolled acute variceal hemorrhage at endoscopy or who have successfully undergone endoscopic variceal ligation (EVL) but who rebleed at any time during admission (after endoscopy).[73] In addition, select patients with CTP Class C cirrhosis or CTP B with active bleeding at endoscopy are at highest risk for rebleeding and may benefit from early or pre-emptive TIPS within 72 hours of admission to improve survival (Supplemental Discussion)[2, 3, 96-101]

Q2. When should TIPS be used in the management of bleeding gastric fundal varices (GV)?

Variceal obliteration/embolization with or without TIPS should be considered for bleeding GV if unable to be managed endoscopically (Figure 2). TIPS combined with variceal obliteration may be associated with a decrease in rebleeding rates,[102-104] particularly when the pre-treatment PSG is less than 12 mmHg. The most appropriate management for bleeding from GV will depend on the vascular anatomy of the portal venous system and center expertise (Supplemental Discussion).[94]

Q3. What are the procedural considerations in TIPS creation for variceal hemorrhage?

The main procedural factors to consider are the target PSG, the optimal shunt diameter and whether or not to perform concurrent variceal embolization. When placing a TIPS for variceal hemorrhage, the risk of rebleeding is decreased by obtaining an absolute PSG < 12 mmHg or a relative reduction in the PSG of at least 50-60% from the pre-TIPS gradient.[10, 63, 105-107] These thresholds are best studied in bleeding from esophageal varices as GV and other ectopic varices may bleed at a lower PSG.[108] Studies using shunt diameter as a predictor of rebleeding rates have shown mixed results.[10, 31, 45] Concurrent embolization at the time of TIPS creation decreases the risk of rebleeding in variceal hemorrhage.[109-114] There is currently insufficient data to show superiority of a specific embolic agent (see Supplemental Discussion).

Q4. How should patients be monitored after TIPS creation for variceal hemorrhage?

Imaging surveillance with Doppler ultrasonography post-TIPS for variceal hemorrhage is recommended, because TIPS stenosis/occlusion can lead to recurrent variceal hemorrhage. The optimal frequency of surveillance is not known, yet typically is performed 1-6 months post-TIPS initially, and then every 6-12 months thereafter. If TIPS stenosis/occlusion is suspected based on imaging or recurrent symptomatic portal hypertension (e.g., ascites, variceal bleeding), a TIPS venogram is indicated with consideration for TIPS revision. Non-selective beta blockade can reduce the PSG even after TIPS[115] and may be considered as an adjunctive treatment.

Novel Indications for TIPS

Q1. Does preoperative TIPS creation in patients with portal hypertension improve perioperative outcomes following non-transplant abdominal surgery?

Use of prophylactic TIPS to prevent bleeding complications or improve survival after elective non-liver transplant surgery is not recommended. Specific patient and surgical factors may warrant TIPS creation in individual cases (Table S4).[116, 117] Theoretical benefits of portal decompression prior to abdominal, non-liver transplant surgery (e.g., ascites control) must be weighed against the potential risks of TIPS in the preoperative setting (e.g., overt HE, liver insufficiency).

Q2. Does TIPS creation in patients with cirrhosis and portal vein obstruction facilitate listing for LT and/or improve outcomes after LT?

The specific degree of portal vein obstruction resulting in exclusion from LT candidacy varies by center. While partially occlusive PVT can be easily extracted at surgery, this is not the case when complete obliteration of the lumen has occurred, particularly when surrounded by venous cavernoma. Increased case complexity and inferior outcomes are reported for LT in patients with extensive chronic PVT.[118] Successful recanalization of the main portal vein using a transhepatic and trans-splenic approach followed by TIPS creation in order to re-establish a patent main portal vein has been reported in a single center case series without a control population.[74]

Q3. Does TIPS creation prevent or reduce portal hypertensive complications in patients with non-cirrhotic portal hypertension due to extrahepatic portal vein obstruction?

Acute or chronic extrahepatic PVT are associated with significant morbidity and may require urgent decompression. In general, TIPS creation is technically feasible and effective in reducing portal

hypertension in patients with PVT, especially in patients with extensive PVT and bowel ischemia (Table S4).[119, 120] There are a lack of studies comparing revascularization with or without TIPS creation to anticoagulation alone in patients with PVT (Supplemental Discussion).

Q4. Does TIPS creation in patients with idiopathic non-cirrhotic portal hypertension (INCPH) and without extrahepatic portal vein obstruction prevent or reduce portal hypertensive complications?

Limited series evaluating outcomes after TIPS creation in patients with INCPH, including one case control series with a comparator group of patients with cirrhotic portal hypertension, have demonstrated similar technical outcomes and control of portal hypertensive complications compared with patients with cirrhotic portal hypertension. It is unclear whether patients with INCPH have lower rates of overt hepatic encephalopathy and mortality compared with patients with cirrhotic portal hypertension (Table S4).[121-123]

Q5. Does TIPS creation improve outcomes in patients with Budd-Chiari Syndrome (BCS)?

In patients with BCS who remain symptomatic or without improving liver function despite medical therapy and who are not candidates for percutaneous revascularization of the hepatic venous outflow tract, creation of a percutaneous portosystemic shunt, either TIPS or direct intrahepatic portosystemic shunt (DIPS), should be strongly considered.[124] TIPS creation is technically successful in 84-100% of BCS cases,[125-130] controls portal hypertensive complications and is associated with good survival (72% overall and TFS).[125-129, 131, 132] Importantly, venoplasty with or without stenting should not preclude subsequent creation of a percutaneous portosystemic shunt in patients who remain symptomatic after initial revascularization (Supplemental Discussion). Finally, in patients with BCS, re-intervention may be needed to maintain or restore TIPS patency as primary patency rates with ePTFE-covered TIPS for BCS varies widely (5-year primary patency, 45-91%).[133, 134]

Cardiopulmonary, Renal and Neurologic Considerations in TIPS

Cardiopulmonary Considerations in TIPS

Cardiac decompensation post-TIPS varies from 1% in one week[135] to 20% in one year.[136] The underlying pathophysiology is multifactorial, involving pre-TIPS subclinical cardiac dysfunction (e.g., cirrhotic cardiomyopathy; CCM) and post-TIPS worsening in hyperdynamic circulation given increased preload and cardiac output (CO) with concomitantly decreased systemic vascular resistance.[137] Recommendations for cardiopulmonary considerations in TIPS are summarized in Table 3.

Q1. What cardiopulmonary testing is indicated prior to elective TIPS?

Cardiac risk assessment prior to TIPS is essential and should incorporate contemporary echocardiographic measurements for left ventricular (LV) and right ventricular (RV) function, with particular attention to the recently updated criteria for CCM (Table S5).[138, 139] Electrocardiogram (ECG) is warranted for evaluation of arrhythmia if tachycardia or bradycardia is noted on pre-procedure assessment.

Q2. Does CCM or diastolic dysfunction confer a risk for post-TIPS heart failure (HF)?

In patients undergoing TIPS creation, evaluating the presence and severity of systolic and/or diastolic dysfunction is an important part of risk stratification for adverse cardiac outcomes. There is limited data regarding TIPS outcomes in patients with LV ejection fraction (LVEF) < 50%. Impaired global longitudinal strain, reflective of subclinical systolic dysfunction, is associated with poor post-TIPS survival.[140] Older studies have shown conflicting results about the impact of diastolic dysfunction on TIPS outcomes.[141, 142] However, the new diastolic dysfunction criteria[138] have been found to be predictive of increased mortality and cardiac events post-TIPS.[136]

Q3. Can TIPS be safely performed in patients with moderate or severe portopulmonary hypertension (POPH) (i.e., mean Pulmonary Artery Pressure > 35 mmHg, Pulmonary Vascular Resistance > 3 wood units)?

TIPS creation, if pulmonary hypertension is present, has the potential to precipitate right-sided HF and/or be ineffective at lowering portal pressure.[143, 144] There are no published data regarding TIPS in patients with POPH. TIPS acutely increases right atrial pressure (RAP) by 3-5 mmHg in those without POPH.[145-148] One study specifically demonstrated that RAP pre- and post-TIPS of > 14.5 mmHg and > 21.5 mmHg, respectively, was associated with increased post-TIPS mortality, though whether these patients had POPH specifically is unknown.[145] Thus, significant caution should be exercised when considering TIPS in patients with moderate/severe POPH on treatment or elevated RAP.

Q4. Can severe tricuspid regurgitation (TR) be prohibitive of TIPS creation?

TR usually reflects volume overload and/or pressure overload from conditions resulting in pulmonary hypertension in patients with a normal tricuspid valve. Careful assessment of TR etiology is necessary to determine if TIPS risk is prohibitive. When volume overload is suspected, volume optimization is warranted prior to reassessment. In some cases, chronic volume overload results in RV dysfunction and tricuspid annular dilatation, leading to persistent moderate to severe functional TR, which can be prohibitive of TIPS.

Q5. Can TIPS treat HPS?

Given the risks associated with TIPS creation, current evidence does not support routine use of TIPS for treatment of HPS alone (Supplemental Discussion).[149-151]

Q6. Does stent size affect risk for post-TIPS HF in high cardiac risk patients?

A recent study showed that an 8 mm stent was associated with better survival than a 10 mm stent; however, cardiac deaths were not specified.[152] Generally, larger stent size leads to higher cardiac venous return resulting in potentially higher decompensation risk. Thus, in patients with systolic and/or diastolic dysfunction or mild POPH who are undergoing TIPS, the desired PSG must be balanced with the potential risk for worsening cardiac dysfunction.

Q7. Is there a need for post-TIPS echocardiographic surveillance?

There are prompt incremental changes post-TIPS involving CO, cardiac index, RAP as well as LV and RV end diastolic and end systolic volumes.[137, 153-155] These changes peak at 3-months post-TIPS, and tend to resolve within 6-12 months post-TIPS in some, but not all, patients.[153, 156, 157] Surveillance in high-risk patients (e.g., prior HF, elevated RAP, LV dysfunction) may be beneficial to guide pre-emptive interventions (e.g., initiation of HF guideline-directed anti-remodeling therapy).

Renal Considerations in TIPS

The true incidence of acute kidney injury (AKI) or disease (AKD) following TIPS and potential benefit in persons with chronic kidney disease (CKD) is unknown given a wide spectrum of indication and urgency for TIPS, the heterogeneity in measurement of kidney function (e.g., measured versus estimated glomerular filtration rate (GFR), serum creatinine (sCr)), definitions of AKI or CKD, and patient selection. We suggest considering the primary indication, individualized risk factors, and physiologic goals of the intervention when considering TIPS creation in patients with kidney dysfunction (Table 3).

Q1. What is the best marker to assess kidney function before or after TIPS?

Kidney function should be assessed prior to TIPS either through measurement of sCr or GFR (estimated or measured).[75, 158-162] A change in GFR may best capture changes in kidney function. The limitations of sCr in cirrhosis are well documented (Supplemental Discussion).[163]

Q2. Is there an absolute cutoff for kidney function for which TIPS is contraindicated?

Kidney function (measured by sCr) is included in several predictive models of outcomes after TIPS.[17-22, 164, 165] Elevated sCr is a risk factor for post-TIPS HE.[166] However, there is insufficient evidence to recommend an absolute sCr, CKD stage, or presence/absence of renal replacement therapy where TIPS creation is contraindicated.

Q3. What can be done to prevent kidney complications after TIPS?

Data regarding kidney protection strategies surrounding TIPS are lacking (Supplemental Discussion). Maintenance of intravascular volume with albumin infusion in the setting of LVP if performed with TIPS creation may help prevent kidney dysfunction secondary to circulatory impairment.[1, 167-169] Judicious use of iodinated contrast agents may minimize risk of contrast nephropathy. Development of AKI and progression to AKD and CKD may not be immediately recognized after TIPS. Recognition-Action-Result framework for secondary prevention and follow up based on AKI/AKD severity as outlined by the Acute Disease Quality Initiative may identify those at highest risk for progression and allow for early mitigation.[170]

Q4. What is the role of TIPS for hepatorenal syndrome (HRS)?

Data on TIPS in patients with HRS is limited.[171] The quality of available studies is low due to small sample size and significant heterogeneity (Supplemental Discussion). Larger randomized trials

applying the most recent definition of HRS-AKI are needed before TIPS can be recommended for this indication.

HE and TIPS

Q1. What is the risk of overt HE after TIPS and what patient factors contribute to its development?

Incidence of overt HE is estimated between 25%-50% (Supplemental Discussion).[3, 4, 97, 98, 172-174] Notably, most studies excluded patients with a history of recurrent overt HE. Patient factors for development of post-TIPS overt HE includes prior HE, advanced liver dysfunction (CTP Class C, MELD score >18),[4, 97, 98, 175, 176] older age,[166] elevated creatinine,[166] hyponatremia and sarcopenia.[177, 178]

Q2. What social factors should be considered a contraindication to elective TIPS as it relates to overt HE?

Patients and family members should be counseled about the manifestations of overt HE.[179, 180] In patients who have poor social support, and therefore may be at greater risk of harm due to post-TIPS HE, we favor non-TIPS management options. This does not apply to urgent TIPS for variceal bleeding where survival and prevention of rebleeding remains the priority.

Q3. What is the role for formal evaluation for covert or minimal HE prior to elective TIPS?

The diagnosis of covert HE has been associated with a greater risk of post-TIPS HE,[173, 181, 182] and impaired health related quality of life (Supplemental Discussion).[183-185] In patients being considered for elective TIPS, a diagnosis of covert HE should guide discussion of the pros and cons of TIPS creation with patients, family members and clinical teams.

Q4. What TIPS stent diameter should be considered with regards to limiting post-TIPS HE?

Smaller shunts (e.g., 8mm vs. 10mm) may decrease overt HE, but may also be less effective for portal decompression (Supplemental Discussion).[10, 31, 186-188]

Q5a. Is there a role for collateral embolization at the time of TIPS to prevent HE?

In patients undergoing elective TIPS for ascites/HH, embolization of spontaneous portosystemic shunts (SPSS) > 6mm may be considered in order to reduce the risk of post-TIPS HE. Large SPSS have been associated with increased risk of overt HE and mortality in patients with cirrhosis (Supplemental Discussion).[189-192]

Q5b. Is there a role for TIPS with shunt embolization in the management of refractory HE related to presumed portosystemic shunting?

In select patients with large (> 6mm) SPSS and refractory HE, we recommend that shunt embolization be considered. In those who develop portal hypertensive-associated complications after shunt embolization, small caliber TIPS creation could be considered. The prevalence of SPSS approaches 70% among patients with cirrhosis and with persistent overt HE.[193] Evidence on retrograde transvenous obliteration or embolization of SPSS for treatment of overt HE is limited to small series but with success rates of 59-100% free of overt HE.[194-199]

Q6a. What is the role for medical prophylaxis to prevent HE after TIPS?

RCTs using uncovered TIPS stents showed no difference in the incidence of overt HE in a head to head comparison of lactulose, rifaximin, and placebo.[193] A recent RCT with a larger sample size, however, demonstrated significantly reduced incidence of first episode of HE post-TIPS (44.2% vs

59.1%, p = 0.05) in patients without a history of overt HE receiving rifaximin versus placebo as prophylaxis prior to TIPS.[200]

Q6b. What is the recommended medical therapy to treat overt HE after TIPS?

Lactulose is recommended for treatment of the first episode of overt HE followed by the addition of rifaximin if there is a subsequent episode of overt HE.[180]

Q6c. What is the role for TIPS stent reduction/occlusion for treatment of persistent or refractory HE?

Severe refractory overt HE that requires shunt reduction occurs in approximately 8% of TIPS recipients.[166] There is no consensus definition of refractory overt HE; however, shunt reduction should be considered when there is persistent HE refractory to medical therapy or at least three or more episodes of unprovoked HE requiring hospitalization in the past 3 months.[201] Shunt reduction is effective at reducing post-TIPS HE; however, recurrence of portal hypertensive complications are likely.[166, 202-207]

CONCLUSIONS AND FUTURE DIRECTIONS

Tremendous progress has been made in the application of TIPS creation for the management of portal hypertension. With such a rapid evolution of knowledge, practice-based recommendations must also evolve. These North American consensus recommendations reflect multi-disciplinary discussion required around TIPS creation, including consideration of alternatives and best practices to minimize short and long-term complications and maximize benefit. There are multiple knowledge gaps and areas in need of future research regarding the clinical effectiveness and efficacy of TIPS across indications for use (Table 4). Of particular relevance is the notion of personalized TIPS, in which the benefits and risks of TIPS are tailored to the specific needs of the patient. With the advent

of new controlled expansion stents, personalized TIPS is the future of precision medicine for the management of portal hypertension. As the field continues to develop and the research questions identified during this process are answered, the recommendations presented herein will evolve in the context of new data.

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FIGURE LEGENDS

Figure 1. Team-Based Approach to TIPS Care. A team-based approach to TIPS is of critical importance in all stages of TIPS planning and management. Initial consideration for decision on TIPS candidacy should involve the patient and corresponding caregiver as well as a gastroenterologist or hepatologist and a proceduralist with competency in TIPS. Complex cases should include consultation with additional specialties (e.g., cardiology, pulmonology, transplant surgery, hematology, nephrology) as appropriate. Once a patient is determined to meet criteria for TIPS creation, longitudinal care includes a spectrum of multi-specialty (e.g., anesthesia, critical care, IR, GI/hepatology, primary care provider), multi-practitioner (e.g., nursing, physician, pharmacy, mid-level providers) providers. Abbreviations: GI, gastroenterologist; IR, interventional radiologist; PCP, primary care provider; TIPS, transjugular intrahepatic portosystemic shunt.

Figure 2. Proposed Approach to Gastric Fundal Variceal Bleeding in Cirrhosis

Management of gastric fundal variceal bleeding depends on the admitting center's expertise as well as the patient's portal vascular anatomy and severity of their liver disease. Initial management is similar to the approach for all patients presenting with acute gastrointestinal bleeding, particularly in the setting of known portal hypertension. Once gastric varices (GV) are confirmed as the bleeding source, use of endoscopic therapy with "glue" injection can be considered depending on proceduralist's expertise. If hemostasis is not achieved, TIPS evaluation +/- variceal obliteration should then be considered. In addition, TIPS +/- variceal obliteration should be considered for secondary prophylaxis or if there is GV rebleeding. Abbreviations: BRTO, balloon-occluded retrograde transvenous obliteration; GOV, gastroesophageal varices; IGV, isolated gastric varices; NSBB, nonselective beta-blocker; TIPS, transjugular intrahepatic portosystemic shunt. *Sarin SK, Lahoti D, Saxena SP, Murthy NS, Makwana UK. Prevalence, classification and natural history of

gastric varices: a long-term follow-up study in 568 portal hypertension patients. Hepatology 1992 Dec;16(6):1343-9. doi: 10.1002/hep.1840160607.

DESCRIPTION OF SUPPORTING MATERIAL

Supplemental Methods. Expanded methods mapped to AGREE II criteria and terms used for literature search strategy.

Supplemental Discussion. Specific comments on strengths and limitations of available literature in across specific aspects of care for patients undergoing TIPS as indicated in the main text.

Table S1.

Table S2. Technical Approaches to Elective TIPS Creation for Ascites

Table S3. Prospective randomized controlled trials and meta-analyses comparing TIPS v. large volume paracentesis for refractory ascites

Table S4: Patients with non-refractory recurrent ascites included in randomized controlled trials

Table S5: Summary of selected studies on TIPS for novel indications

Table S6. Components of a Comprehensive Echocardiographic Evaluation pre-TIPS.

*Two or more abnormalities are needed to make the diagnosis of diastolic dysfunction. The degree of diastolic dysfunction is to be determined by the cardiologist depending on additional measures such as early to late diastolic transmitral flow velocity (E/A) ratio (at rest or during Valsalva), left atrial

strain, and left ventricular strain. Guidance is adapted from the American Society for Echocardiography guidelines and the Cirrhotic Cardiomyopathy Consortium practice guidance.

Figure S1. Mechanisms of TIPS for the treatment of portal hypertension and the effect of TIPS creation on portal, cardiac and renal hemodynamics. According to the peripheral arterial vasodilation hypothesis, pooling of blood in the splanchnic/portal circulation leads to decreased effective circulating volume in cirrhosis.[208] As a means of compensation, there is increased kidney retention of sodium/water and renal vasoconstriction, which leads first to ascites formation, hyponatremia, and later, increased sCr reflecting "functional" kidney injury.[209, 210] TIPS creation for ascites and poor kidney perfusion leads to decompression of portal hypertension, restores end-organ perfusion, alleviates maladaptive vasoconstriction, and decreases retention of sodium/water.[211] Creation of TIPS is associated with transient increase in cardiac index, central blood volume, with deactivation of RAAS, lowering of renin, aldosterone and norepinephrine levels with increase in urinary sodium excretion and renal blood flow.[9, 75-77, 95, 147, 159, 212-222] TIPS is also associated with increased portosystemic shunting which can result in new or worsening hepatic encephalopathy.[166]

Abbreviations: ADH, anti-diuretic hormone; AKI, acute kidney injury; CI, cardiac index; CO, cardiac output; GFR, glomerular filtration rate; LVEDV, left ventricular end diastolic volume; LVESV, left ventricular end-systolic volume; NE, norepinephrine; RAP, right atrial pressure; RVSP, right ventricular systolic pressure; TIPS, transjugular intrahepatic portosystemic shunt

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Table 1. Clinical consensus statements for TIPS planning, procedural best practices and care of the TIPS recipient independent of indication for TIPS

Question	Statement	Level of Evidence
PRE-TIPS CONSIDERATIONS		
Q1. Who should be involved in the decision to place a TIPS and what other pre-procedure consultations are recommended?	Prior to TIPS creation, we recommend that a gastroenterologist or hepatologist should be involved in the initial decision to place an emergent or nonemergent TIPS with subsequent consultation by an interventional radiologist or other proceduralist with competency in TIPS. If center expertise is not available, we recommend referral to an expert center. Additional specialty consultations (e.g., Transplant Surgery, Cardiology, Critical Care, Hematology, Nephrology) may be considered on a case-by-case basis.	5
Q2. What services should be readily available at centers where TIPS is performed and what referral pathways should be established for a higher level of care?	For all patients undergoing TIPS creation, we recommend that TIPS should occur at a center with available Interventional Radiology (IR), Gastroenterology/Hepatology, Cardiology, Pulmonary Surgery, Hematology, Nephrology and Critical Care services in order to provide an adequate level of support for patient management before and after TIPS. In patients requiring a higher level of care, such as possible liver transplant candidates, or in whom the need for further IR expertise is indicated (e.g., extensive portal vein thrombosis), we recommend referral to centers with adequate experience in these areas.	5
Q3. Is there a MELD threshold above which elective TIPS should not be considered?	In patients with cirrhosis undergoing TIPS, a multidisciplinary approach, rather than an absolute MELD cutoff, is recommended to assess TIPS candidacy.	2a
Q4. What imaging and/or pre-procedural evaluation is required prior to TIPS creation?	Q4a. In patients undergoing elective TIPS, we recommend: • Contrast-enhanced multiphasic cross-sectional imaging (CT/MRI) to assist with TIPS planning. • Comprehensive echocardiography to assess for abnormalities in cardiac structure, function, and right ventricular systolic pressure.	2a
	Q4b. In patients with cirrhosis undergoing emergent TIPS, best clinical judgement should be applied – we suggest at least a liver ultrasound with doppler to evaluate the patency of the portal venous system and consideration of a limited (bedside) echocardiogram, evaluating left ventricular ejection fraction and right ventricular systolic pressure.	3
Q5. What are absolute contraindications (medical and	The absolute contraindications to elective TIPS include: • severe congestive heart failure (ACC/AHA Stage C or D HF) • severe untreated valvular heart disease (AHA/ACC stage C or D VHD)	2a

anatomical) to elective TIPS creation?	• moderate-severe pulmonary hypertension (based on invasive measurements) despite medical optimization • uncontrolled systemic infection • refractory overt HE • unrelieved biliary obstruction • lesions (e.g., cysts) or tumors in the liver parenchyma that preclude TIPS creation	
Q6. Should all patients being considered for TIPS undergo evaluation for liver transplantation prior to TIPS creation?	In patients with cirrhosis undergoing elective or emergent TIPS, there is insufficient evidence to recommend universal pre-procedure liver transplant evaluation.	5
TIPS PROCEDURAL CONSIDERATIONS		
Q7: Who should perform TIPS creation?	We recommend that TIPS creation should be performed by a credentialed, board certified Interventional Radiologist OR a certified provider with equivalent training and procedural competency*.	5
Q8. What type of stent is recommended for TIPS creation?	For patients undergoing TIPS placement, we recommend the use of an ePTFE lined stent graft (1b) with controlled expansion which allows the operator to tailor the amount of portosystemic shunting based on the indication, target gradient and patient comorbidities (2b).	1b and 2b
Q9. Should coagulopathy be corrected prior to TIPS placement?	Due to insufficient evidence, we do not recommend a specific target INR or platelet threshold when placing a TIPS in a patient with cirrhosis.	2b
Q10. Should periprocedural antibiotics be routinely used in TIPS creation?	There are no studies to show that the routine use of antibiotics during TIPS placement decreases infectious complications and their use should depend on patient and local risk factors.	5
Q11. Should TIPS creation be performed using general anesthesia or is deep or conscious sedation appropriate?	The use of general anesthesia, deep sedation, or conscious sedation may all be appropriate for TIPS placement and their use will vary depending on the patient risk factors and local practices.	5

Q12. Is the use of intravascular ultrasound recommended to assist with the portal vein puncture?	For patients undergoing TIPS creation, while there is insufficient evidence to recommend the universal use of intravascular ultrasound guidance, it may facilitate efficient portal access in certain situations. Its use will depend on equipment availability and operator preference.	3b
Q13. What is the optimal location from which to measure the systemic venous pressure at the time of TIPS creation (hepatic vein, IVC, right atrium)?	We recommend the use of the free hepatic vein or IVC pressure as the systemic pressure when measuring the portosystemic gradient before and after TIPS placement.	2a
Q14. Are there specific technical factors that should be considered to ensure that TIPS placement does not adversely influence liver transplant candidacy?	Q14a. In patients undergoing TIPS placement who are potentially eligible for liver transplant, we recommend positioning the stent as to not interfere with the portal and hepatic vein anastomoses, presuming that this does not detrimentally affect TIPS function or patency. This positioning includes leaving a segment of unstented main portal vein and not extending the TIPS stent into the right atrium.	5
	Q14b. Liver Transplant candidacy should not be impacted by placement of TIPS.	2a
CARE OF THE POST-TIPS PATIENT		
Q15. What is the recommended duration of intensive post-procedure monitoring?	Following TIPS creation, we recommend that all patients undergo in-hospital overnight observation at minimum. The level of care during post-TIPS observation should be dictated by the patient's condition, indication for TIPS, and intraprocedural technical complexity.	5
Q16. What early laboratory testing and/or imaging is recommended following TIPS	Q16a. In all patients undergoing TIPS creation, routine labs (complete blood count, comprehensive metabolic panel, and PT/INR) should be obtained on the day following TIPS creation. Hemoglobin/hematocrit labs may be obtained on the same day of TIPS creation, depending on institution and/or operator discretion.	5
	Q16b. Pre-discharge imaging is not indicated in most patients undergoing TIPS creation.	5

creation and at what interval?		
Q17. Should TIPS venography and intervention be based on ultrasound, clinical findings, or both?	Q17a. In patients who have undergone TIPS creation for management of varices, either Doppler ultrasound findings suggesting TIPS dysfunction, or persistence or recurrence of portal hypertensive complications should prompt TIPS venography and manometry +/- intervention. Ultrasound findings suggesting TIPS dysfunction include alterations in intrahepatic portal vein direction of flow, abnormal flow velocities within the TIPS, and persistent (e.g., > 6 weeks post-TIPS) or recurrent ascites.	2b
	Q17b. In patients who have undergone TIPS creation for management of ascites and/or hepatic hydrothorax, persistence or recurrence of portal hypertensive complications should prompt TIPS venography and manometry +/- intervention. Medical decision-making should be individualized in patients with well-controlled ascites and/or hepatic hydrothorax and ultrasound findings suggesting TIPS dysfunction.	2b
	Q17c. In select patients, scheduled TIPS venography with intervention is suggested in the early (1-2 months) post-TIPS period. An example of such a scenario would be TIPS creation in a patient with portal vein thrombosis.	5
Q18. What are the optimal techniques for increasing or decreasing TIPS flow when intervention is required?	Q18a. In patients in whom further decrease in portal pressure is desired, we recommend stepwise dilatation of TIPS to its maximum diameter. If it is already at maximum diameter, other interventions to decrease portal pressure (e.g., nonselective beta-blockers, parallel TIPS creation) should be evaluated.	5
	Q18b. In patients in whom an increase in portal pressure desired, there is insufficient evidence to recommend a specific technique to reduce portosystemic shunting through a TIPS.	5
Q19. Who should see patients with TIPS in follow up?	In patients who have undergone TIPS creation, we recommend that a gastroenterologist or hepatologist and a competent proceduralist (e.g., interventional radiologist) should follow the patient to ensure ongoing management of chronic liver disease, post-procedural complications and to determine any need for potential device revision.	5

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; CT, computed tomography; ePTFE, Polytetrafluoroethylene; HF, heart failure; INR, internationalized normal ratio; IVC, inferior vena cava; MELD, Model for End-Stage Liver Disease; MRI, magnetic resonance imaging; NYHA, New York Heart Association; PT, prothrombin time; TIPS, transjugular intrahepatic portosystemic shunt; VHD, valvular heart disease

* According to radiology professional society guidelines, TIPS placement must be performed by a physician with board certification or accredited training as well as sufficient experience with TIPS procedures. In the absence of certification or accredited training, TIPS placement can be performed by a competent proceduralist defined as one who has performed a sufficient number of TIPS procedures under supervision (minimum threshold = 5), in addition to other endovascular techniques (i.e., minimum of 100 angiograms, 50 angioplasties, 10 stent placements, and 5 embolizations), has achieved expected procedure completion thresholds, and has obtained appropriate privileges at their center.[38]

Table 2. Clinical Consensus Statements for TIPS by Indication

Question	Statement	Level of Evidence
TIPS IN ASCITES OR HEPATIC HYDROTHORAX (HHT)		
Q1. What is the optimal technical approach to TIPS creation among patients with cirrhosis and refractory ascites?	Q1a. For patients with cirrhosis and diuretic refractory or resistant ascites undergoing elective TIPS, we recommend the use of an ePTFE-covered controlled expansion stent.	2b
	Q1b. For patients with cirrhosis and diuretic refractory or resistant ascites undergoing elective TIPS, we recommend a staged approach to TIPS creation with an initial procedural stent dilation to 8mm followed by clinical assessment, and then subsequent progressive stent dilation to 9mm and then 10 mm at 6-week intervals if needed to optimize clinical response.	2b
Q2. Is TIPS associated with better outcomes (mortality, ascites control) than serial large volume paracentesis for the treatment of refractory ascites?	Q2a. For carefully selected patients with cirrhosis and refractory ascites, TIPS is recommended over LVP to prevent recurrent ascites.	1a
	Q2b. For carefully selected patients with cirrhosis and refractory ascites, TIPS is recommended over LVP to improve transplant-free survival.	1a
Q3. Is there a threshold of liver dysfunction above which TIPS for refractory ascites should be contraindicated and how should it be defined?	Among patients with cirrhosis and refractory ascites, elevated bilirubin, elevated MELD score and CTP class C cirrhosis are associated with increased post-TIPS complications including mortality. There is insufficient evidence to recommend a cutoff above which any of these measures should be considered a contraindication to TIPS.	1a
Q4. What is the impact of age on candidacy for TIPS for refractory ascites?	Among patients with cirrhosis and refractory ascites, advanced age is significantly associated with post-TIPS complications including severe hepatic encephalopathy and death. There is insufficient evidence to recommend an age cutoff that should be considered a contraindication to TIPS.	1a
Q5. What is the role of TIPS in patients with ascites that is not refractory?	In patients not fulfilling a strict definition of refractory ascites but requiring at least 3 large volume paracenteses for tense ascites in a year despite optimal medical therapy, we recommend that TIPS creation should be considered.	1a

Q6. What is the role of TIPS in HHT? Is patient selection similar for patients with ascites vs patients with HHT?	For patients with HHT requiring recurrent thoracentesis, we recommend that TIPS should be considered.	2b
Q7. Is prior liver transplantation a contraindication to TIPS for refractory ascites? Is TIPS a better treatment than surgical shunt, serial LVP or splenic artery embolization in liver transplant recipients with refractory ascites?	Unlike TIPS for ascites and HHT in cirrhosis, there is insufficient evidence to support any recommendation regarding therapy (TIPS and other modalities) in liver transplant recipients with refractory ascites.	2b
Q8. What is the expected timeline for the TIPS to be effective for reduction of Ascites/HHT?	In the setting of TIPS creation for ascites or hepatic hydrothorax, we recommend using a staged approach by starting with the TIPS stent with the smallest diameter with concomitant use of diuretics as tolerated. Reassessment for need to further dilate the TIPS stent should be performed every 6 weeks.	2b
TIPS IN VARICEAL BLEEDING		
Q1. When is TIPS indicated in Acute Variceal Hemorrhage?	For acute variceal hemorrhage, we recommend TIPS creation in the following scenarios: • Pre-emptive TIPS in patients who have been successfully banded but who meet high-risk criteria for rebleeding. High-risk criteria are CTP Class C (10-13 points) or CTP Class B >7 points with active bleeding at endoscopy. TIPS should be performed within 72 hours of admission in patients without contraindications to TIPS.	1c
	• Rescue TIPS in patients who have been successfully banded but who rebleed at any time during admission (after endoscopy).	2a

	• Salvage TIPS should be performed emergently for patients in whom endoscopic band ligation cannot be performed because of profuse bleeding or bleeding persists at endoscopy despite endoscopic band ligation.	2b
Q2. When should TIPS be used in the management of bleeding gastric fundal varices or prevention of rebleeding?	Q2a. We recommend that the initial management of bleeding gastric-fundal varices should be based on center expertise. Variceal obliteration/embolization with or without TIPS should be considered for bleeding gastric-fundal varices if unable to be managed endoscopically.	5
	Q2b. For rebleeding gastric-fundal varices after endoscopic therapy, we recommend variceal obliteration with or without TIPS creation.	2b
Q3. What are the procedural considerations in TIPS creation for variceal hemorrhage?	Q3a. When placing a TIPS for variceal hemorrhage, we recommend a goal PSG of <12 mmHg or 50-60% decrease from initial. We do not recommend using shunt diameter as a procedural endpoint.	2b
	Q3b. In cases of TIPS creation for variceal hemorrhage, we recommend concurrent obliteration of varices.	1b
Q4. How should patients be monitored after TIPS creation for variceal hemorrhage?	Q4a. In the setting of TIPS creation for variceal bleeding, we recommend surveillance with Doppler ultrasonography three months after TIPS creation and every six months thereafter in order to monitor for post TIPS stenosis or occlusion.	5
	Q4b. If TIPS stenosis/occlusion is suspected or if patient rebleeds after TIPS creation, TIPS venogram with pressure measurements is indicated with consideration of TIPS revision.	2b
NOVEL INDICATIONS FOR TIPS		
Q1. Does pre-operative TIPS creation in patients with portal hypertension reduce operative complication and/or improve perioperative outcomes following <u>non-transplant</u>	Q1a. In patients with portal hypertension requiring non-transplant surgery, there is insufficient evidence to recommend that preoperative TIPS prevents bleeding complications or the need for blood transfusion during or after invasive non-transplant surgical procedures.	1b
	Q1b. In patients with cirrhosis without clinically significant ascites, there is insufficient evidence to recommend pre-operative TIPS in abdominal surgery to prevent complications of ascites. In patients with cirrhosis with clinically significant ascites requiring abdominal surgery, a multidisciplinary team approach (hepatology and hepatobiliary surgery) is recommended to individualize the surgical/medical management.	3b
	Q1c. There is no evidence that preoperative TIPS has an impact on postoperative mortality after invasive non-transplant surgical procedures.	3b

abdominal surgery?		
Q2. Does TIPS creation in patients with cirrhosis and portal vein obstruction facilitate listing for liver transplantation and/or improve outcomes after liver transplantation?	Q2a. In patients with cirrhosis and chronic, complete portal vein thrombosis, portal vein recanalization and TIPS creation could be considered to facilitate transplant eligibility.	3b
	Q2b. Patients with cirrhosis and complete portal vein thrombosis otherwise being considered for liver transplantation or denied listing due to technical challenges associated with complete portal vein obstruction, should be considered for portal-vein reconstruction and TIPS. Referral to a center with specialized expertise may be necessary.	5
Q3. Does TIPS creation prevent or reduce portal hypertensive complications in patients with non-cirrhotic portal hypertension due to extrahepatic portal vein obstruction?	Q3a. In patients with non-cirrhotic portal hypertension and acute portal vein thrombosis, we recommend immediate anticoagulation. In those who fail or have a poor response to anticoagulation, we recommend that portal vein thrombectomy/thrombolysis using a transjugular approach with or without small caliber TIPS creation should be considered.	4
	Q3b. In patients with acute non-cirrhotic portal vein thrombosis who are not critically ill, evidence is insufficient to recommend TIPS versus anticoagulation alone. We recommend that a trial of anticoagulation be considered initially given the reported rates of venous recanalization.	2b
	Q3c. In patients with chronic portal hypertension secondary to non-cirrhotic extrahepatic portal vein obstruction that is not responsive to anticoagulation, TIPS may be considered for the same indications as cirrhotic portal hypertension.	5
Q4. Does TIPS creation in patients with non-cirrhotic portal hypertension and without extrahepatic portal vein obstruction prevent or reduce portal hypertensive complications?	In patients with chronic idiopathic portal hypertension/porto-sinusoidal vascular disease TIPS may be considered for the same indications as cirrhotic portal hypertension.	5

Q5. Does TIPS creation improve outcomes in patients with Budd-Chiari Syndrome?	Q5a. Patients with Budd-Chiari syndrome should be evaluated and managed at centers with experience and expertise in hematological evaluation, clinical management, and percutaneous intervention in this patient population. Ideally the center will also have expertise in liver transplantation, should this be warranted at initial evaluation or during subsequent follow-up. If these resources are not available at the presenting institution, strong consideration of transfer to such an institution should be given while medical management is initiated.	5
	Q5b. In patients with Budd-Chiari syndrome who remain symptomatic or without improving liver function after initiation of appropriate medical therapy and who are not candidates for percutaneous revascularization of the hepatic venous outflow tract (short segment obstruction), creation of a percutaneous portosystemic shunt, either TIPS or direct intrahepatic portosystemic shunt (DIPS), should be strongly considered.	2b
	Q5c. In patients with Budd-Chiari syndrome undergoing TIPS, we recommend close clinical monitoring and imaging follow-up.	4

Abbreviations: PFTE, polytetrafluoroethylene; LVP, large volume paracentesis; MELD, Model for End-Stage Liver Disease; CTP, Child-Turcotte-Pugh; RCT, randomized controlled trial; HHT, hepatic hydrothorax; ePTFE, Polytetrafluoroethylene; PSG, portosystemic gradient; DIPS, direct intrahepatic portosystemic shunt; TIPS, transjugular intrahepatic portosystemic shunt

Table 3. Cardiopulmonary, Renal and Neurologic Considerations in TIPS

Question	Statement	Level of Evidence
CARDIOPULMONARY CONSIDERATIONS IN TIPS		
Q1. What cardiopulmonary testing is indicated prior to elective TIPS?	Q1a. In patients undergoing elective TIPS creation, we recommend comprehensive echocardiographic evaluation incorporating, in addition to the assessment of left ventricular ejection fraction (LVEF), measurement of left ventricular global longitudinal strain, when feasible, and the contemporary surrogates of left ventricular diastolic function.	2b
	Q1b. In patients undergoing elective TIPS creation, we recommend assessment of right ventricular function using tricuspid annular plane systolic excursion (TAPSE) and right ventricular systolic pressure (RVSP). Right ventricular strain has not become standard of care in most centers but should be measured if available.	5
	Q1c. In patients undergoing TIPS creation who have a right ventricular systolic pressure (RVSP) exceeding 45 mmHg or TAPSE less than 1.6 cm, we recommend referral to cardiology for consideration of right heart catheterization to evaluate for RV dysfunction and pulmonary hypertension prior to TIPS creation.	5
	Q1d**.** In patients undergoing TIPS creation, who have tachycardia or bradycardia on physical examination, we recommend pre-TIPS electrocardiographic assessment to evaluate for arrhythmia.	5
Q2. Does cirrhotic cardiomyopathy or diastolic dysfunction confer a risk for post-TIPS heart failure?	Q2a. In patients undergoing elective TIPS creation, we recommend considering the presence of systolic and/or diastolic dysfunction, which may suggest cirrhotic cardiomyopathy in the absence of other cardiac history, a significant risk factor for post-TIPS heart failure.	2b
	Q2b. In patients undergoing evaluation for elective TIPS, we recommend avoiding TIPS if LVEF is < 50% or if there is grade III diastolic dysfunction, given the risk of post-TIPS cardiac decompensation.	5
Q3. Can TIPS be safely performed in patients with moderate or severe portopulmonary hypertension?	Q3a. In patients with moderate or severe portopulmonary hypertension (POPH) on treatment (i.e., mean pulmonary artery pressure (mPAP) > 35 mmHg, pulmonary vascular resistance (PVR) > 3 wood units), we recommend significant caution when considering TIPS insertion as it may precipitate right-sided heart failure.	5
	Q3b. In patients undergoing elective TIPS who do not have evidence of POPH on screening, we recommend measuring the right atrial pressure at the time of planned TIPS insertion and if > 14 mmHg, we recommend considering right heart catheterization prior to TIPS creation to exclude POPH based on the clinical situation.	5
Q4. Can tricuspid regurgitation severity be prohibitive of TIPS creation?	In patients being considered for elective TIPS who have moderate or severe tricuspid regurgitation despite optimization of volume overload, we recommend evaluation for the underlying cardiopulmonary etiology, which can prohibit proceeding with TIPS.	5
Q5. Can TIPS treat hepatopulmonary syndrome (HPS)?	We do not recommend TIPS as a therapy for HPS, but it may be considered in patients with HPS who have an established indication for TIPS.	4

Q6. Does stent size affect risk for post-TIPS HF in high cardiac risk patients?	In patients with systolic and/or diastolic dysfunction or mild POPH who are undergoing TIPS, we recommend balancing the desired portosystemic gradient with potential worsening of cardiac function by initially deploying the endoprosthesis to 8 mm diameter. If the desired gradient is achieved, no additional dilatation of the shunt should be pursued.	5
Q7. Is there a need for post-TIPS echocardiographic surveillance?	In patients with systolic and/or diastolic dysfunction, pulmonary hypertension, or moderate to severe valvular disease, we recommend echocardiographic surveillance at 3 months post-TIPS or earlier, if indicated. Surveillance beyond 3 months can be considered if there is echocardiographic worsening at 3 months (compared to baseline) or if there is clinical indication.	5
RENAL CONSIDERATIONS IN TIPS		
Q1. What is the best marker to assess kidney function before or after TIPS?	Q1a. In patients with cirrhosis undergoing TIPS, kidney function should be assessed prior to the procedure either through measurement of serum creatinine or glomerular filtration rate (GFR, estimated or measured). A change in GFR may better capture changes in kidney function, though there is insufficient evidence to recommend one equation over another.	5
	Q1b. The optimal method to assess kidney function in cirrhosis patients with sarcopenia or chronic kidney disease is not known.	5
Q2. Is there an absolute cutoff for kidney function for which TIPS is contraindicated?	There is insufficient evidence to recommend an absolute serum creatinine, CKD stage, or presence/absence of renal replacement therapy where TIPS creation is contraindicated.	5
Q3. What can be done peri-procedurally to reduce the incidence of kidney complications after TIPS? What secondary or tertiary preventive measures can be considered to avoid AKI, acute kidney disease, or de Novo or progressive CKD after TIPS?	Q3a. In patients undergoing TIPS creation for ascites, albumin infusion should be considered in all patients undergoing concurrent paracentesis, and especially for those in whom >5L are removed, to prevent paracentesis-induced circulatory dysfunction and AKI.	1a
	Q3b. LVP Large volume paracentesis with albumin infusion may be performed either within 24hrs prior to, or concomitantly during TIPS creation.	5
	Q3c. Adequate hydration and judicious use of iodinated contrast are rational strategies to help reduce the risk of contrast related injury.	2b
	Q3d. In patients with AKI/CKD prior to TIPS or in those that develop AKI after TIPS creation, kidney function should be closely followed within 1 week of discharge after TIPS creation.	5
Q4. What is the role of TIPS for hepatorenal syndrome (HRS)?	Q4a. There is insufficient evidence to recommend for or against the use of TIPS for treatment of hepatorenal syndrome; however, presence of HRS is not an absolute contraindication for TIPS creation in the presence of other indications (e.g., refractory ascites, variceal bleeding).	2a
	Q4b. Mortality in patients with HRS undergoing TIPS appears to be driven by liver function (i.e., serum bilirubin, INR), therefore, careful patient selection is recommended.	4
HEPATIC ENCEPHALOPATHY AND TIPS		

Q1. When counseling patients, what is the overall risk of overt hepatic encephalopathy after TIPS and what patient specific factors contribute to development of overt HE?	We recommend counseling patients that TIPS is associated with a risk of overt HE in approximately 25-50% of recipients (1b). Patient specific risk factors for development of post-TIPS overt HE include prior history of overt HE, advanced age, advanced liver dysfunction (CTP Class C), hyponatremia, renal dysfunction and sarcopenia (2a).	1b, 2a
Q2. What social factors should be considered a contraindication to elective TIPS as it relates to overt HE?	We recommend avoiding elective TIPS in patients with cognitive impairment and limited family or social support.	3
Q3. What is the role for formal evaluation for covert or minimal HE prior to elective TIPS?	In patients being considered for elective TIPS, testing for covert or minimal HE could be considered for prognostication and discussion with the patient.	2
Q4. What TIPS stent diameter should be considered with regards to limiting post-TIPS HE?	In patients undergoing elective TIPS for ascites, we recommend starting with a smaller diameter controlled-expansion stent to potentially reduce rates of HE.	4
Q5a. Is there a role for collateral embolization at the time of TIPS?	In patients undergoing elective TIPS for ascites and/or hepatic hydrothorax, embolization of spontaneous portosystemic shunts (SPSS) >6mm may be considered in order to reduce the risk of post-TIPS hepatic encephalopathy.	4
Q5b. Is there a role for TIPS with shunt embolization in the management of refractory HE related to presumed clinically significant portosystemic shunting?	In select patients with large (>6mm) SPSS and refractory HE, we recommend that shunt embolization be considered. For select patients who develop portal hypertensive-associated complications (ascites, varices) after shunt embolization, we recommend that small caliber TIPS creation could be considered.	4
Q6a. What is the role for medical prophylaxis to prevent HE after TIPS?	In patients without a history of overt HE undergoing TIPS, we do not recommend medical prophylaxis to prevent HE after TIPS.	3

Q6b. What is the recommended medical therapy to treat overt HE after TIPS?	We recommend medical management of post-TIPS overt HE based on current guidelines with the use of lactulose and rifaximin.	1
Q6c. What is the role for TIPS stent reduction/occlusion as the treatment of persistent or refractory HE?	We recommend consideration of TIPS stent diameter reduction in patients with persistent or refractory HE post-TIPS.	2b

Abbreviations: CTP, Child-Turcotte-Pugh; LVEF, left ventricular ejection fraction; TAPSE, tricuspid annular plane systolic excursion; HF, heart failure; RVSP, right ventricular systolic pressure; mPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; POPH, portopulmonary hypertension; HPS, hepatopulmonary syndrome; GFR, glomerular filtration rate; CKD, chronic kidney disease; AKI, acute kidney injury; LVP, large volume paracentesis; HRS, hepatorenal syndrome; INR, internationalized normal ratio; HE, hepatic encephalopathy; SPSS spontaneous portosystemic shunt; TIPS, transjugular intrahepatic portosystemic shunt

Table 4. Future Research Directions Related to TIPS

Area	Knowledge Gap/Future Research
Standard setting in TIPS	• Prospective data are needed to establish threshold INR and platelet levels for safe TIPS creation as well as to investigate the role of fibrinogen and thromboelastography in the assessment of procedural bleeding risk. • Prospective data could validate societal recommendations regarding the use of periprocedural antibiotics. Currently these recommendations are based on expert consensus rather than studies demonstrating improved outcomes or decreased infectious complications. • Prospective data are needed to assess whether the use of intravascular ultrasound to assist with the portal vein puncture leads to decreased complications or improved survival. • Is there a MELD threshold for TIPS? Future studies require a large size, diverse geographic regions/multi-center studies, increased representation of populations with ascites, higher MELD scores, and standardized procedural techniques. • Prospective data are needed to determine and assess quality indicators throughout the course of TIPS planning and for long-term management of post-TIPS patients.
Ascites/Hepatic Hydrothorax	• Prospective data to understand the best approach to elective TIPS creation for refractory ascites, which balances safety and efficacy; in particular, more data are are needed to understand whether a staged approach is safest, and whether the best target during the procedure should be stent diameter, decreases in HVPG or changes in portal flow. • Better refinement of parameters of liver function, such as MELD or total bilirubin, that should be utilized in risk stratification or as a contraindication to elective TIPS creation is needed. • The role of TIPS creation in patients with ascites that is not refractory requires further study in prospective randomize controlled trials. • Prospective data are needed to determine whether there is a clinical benefit to universal post-TIPS surveillance doppler ultrasound to monitor for TIPS stenosis in patients who undergo TIPS for refractory ascites. • A better understanding of the role of TIPS creation in transplant recipients with ascites is needed, including refinement of candidate selection criteria and comparison to other therapeutic strategies.
Variceal Bleeding	• Prospective data are needed to further refine criteria for preemptive TIPS, particularly studies which include a range of CTP Class and stratify by etiology of cirrhosis. • The timing of rescue TIPS creation and futility (or not) of the procedure in advanced CTP Class C cirrhosis (score 14-15) remains to be established. • The timing of TIPS creation in patients with PVT diagnosed at the time of variceal hemorrhage needs to be established. • Prospective data are needed on endoscopic therapy vs covered TIPS with/without variceal obliteration vs variceal obliteration alone to prevent GV rebleeding.

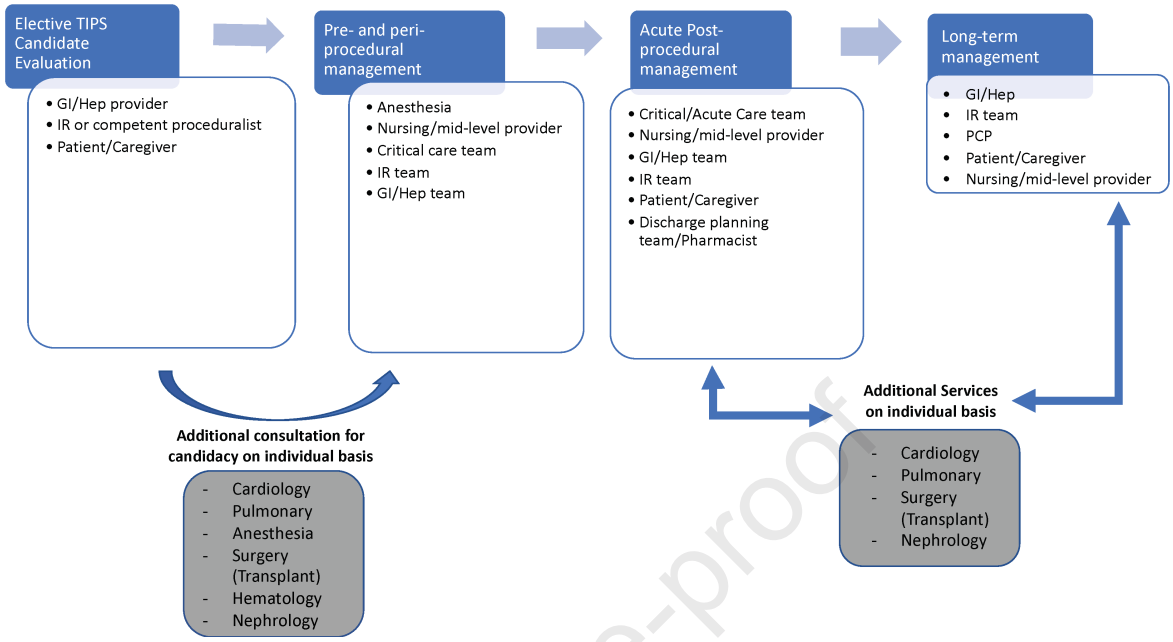
	• Prospective data are needed to establish whether use of a small diameter covered TIPS stent with and without variceal obliteration to control bleeding is efficacious in order to reduce HE. • Prospective data are needed to determine predictors of GV rebleeding and HE after TIPS both with and without variceal obliteration. • Data are needed to support standardization of surveillance protocols after GV treatment. • Prospective data are needed to identify the target PSG after intervention in order to prevent GV rebleeding. • Data are needed to determine the optimal frequency of surveillance for TIPS stenosis/occlusion. • Prospective data are needed to determine whether long term use of non-selective beta blockers after TIPS reduces risk for recurrent variceal hemorrhage.

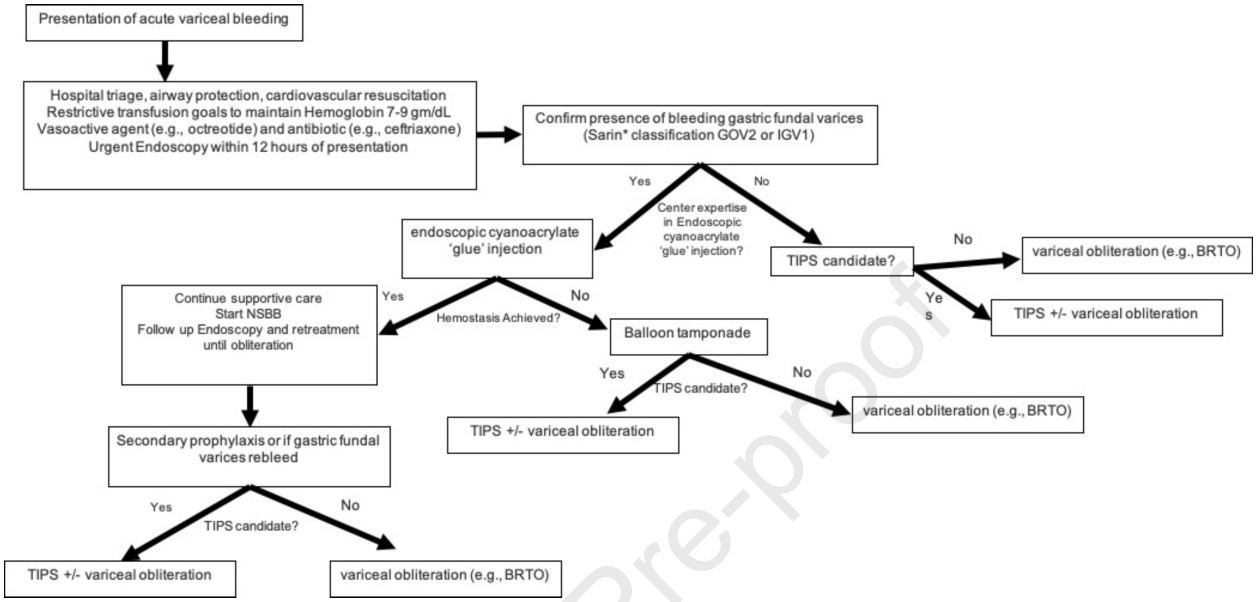
Novel Indications for TIPS	• Multicenter studies, ideally controlled, evaluating portal hypertensive complications and post-liver transplant outcomes in patients with portal vein obstruction pre-LT who undergo portal vein reconstruction and TIPS creation prior to LT.
	• Multicenter controlled studies evaluating safety and efficacy of medical and invasive interventions (including TIPS) in patients with symptomatic non-cirrhotic portal hypertension due to extrahepatic portal vein obstruction.
	• Budd-Chiari Syndrome
	  ○ In the minority of patients in whom anticoagulation alone improves liver function and results in resolution of portal hypertensive complications, does a risk for progressive liver failure persist? If so, can this be avoided by earlier percutaneous intervention?
	  ○ Over what timeframe and based on what specific criteria should progression between stepwise management progress?
	  ○ What factors predict failure of anticoagulation alone, such that a patient presenting with BCS would proceed to venoplasty/stenting or TIPS (based on anatomy) immediately?
	  ○ In which patients should transjugular portosytemic shunting be avoided and urgent liver transplantation be the primary non-medical therapy employed?
	• Long-term PV Access
	  ○ Safety and efficacy of creating TIPS as an easily accessible intermediate or long-term route for portal infusion therapy (i.e., portal chemoperfusion)

Cardiopulmonary Considerations	• Utility of new cardiac imaging modalities (e.g., MRI and PET) in pre-TIPS cardiac risk assessment and post-TIPS cardiac surveillance • Post TIPS changes in cirrhotic cardiomyopathy, its components, and severity • Evolution of right heart function and pulmonary vascular hemodynamics after TIPS in patients with mild portopulmonary hypertension • Role of cardiac biomarkers in post TIPS surveillance • Impact of post TIPS echocardiographic surveillance on cardiac decompensation and survival • Effect of TIPS on cardiac function after the first year post TIPS • The interplay between stent size and cardiac function post TIPS

	• Impact of valvular heart disease on TIPS outcomes
Renal Considerations	• What drivers of MELD or MELD-Na dictate outcomes? For the same MELD/MELD-Na score, does a creatinine predominant MELD or MELD-Na have different outcomes compared to other drivers of MELD/MELD-Na score? • What is the role of novel biomarkers in prediction of kidney outcomes after liver transplantation? • What is the of role of TIPS in patients with CKD, and those with sarcopenia? • What is the role of peri-procedure vasoconstrictor use to prevent kidney dysfunction?
Hepatic Encephalopathy and TIPS	• Objective metrics beyond patient characteristics and laboratory values are needed to better predict post-TIPS HE. • Future studies investigating the effect of medically controlled covert HE on post-TIPS OHE are necessary. • Future prospective RCTs are needed to investigate the role for medical prophylaxis to prevent post-TIPS OHE. • The indication of TIPS for embolization of large portosystemic shunts in the management of uncontrolled OHE requires further study.

Abbreviations: GV, gastric varices; MRI, magnetic resonance imaging; OHE, occult hepatic encephalopathy; PET, positron emission tomography; pTIPS, preemptive TIPS; PSG, portosystemic gradient; PVT, portal vein thrombosis; RCT, randomized controlled trial; TIPS, transjugular portosystemic shunt





Supplemental Methods

Scope and Purpose

A consensus-building process was conducted consistent with standards described in the Appraisal of Guidelines for Research and Evaluation II.[1] The consensus meeting used a modified Delphi approach to achieve consensus.[2] This is a formal group method in which an expert panel discusses and iteratively rates candidate recommendations. In the first round, the experts rated the proposed recommendations individually without meeting as a single group. After a face-to-face meeting in which the preliminary ratings were discussed, a second round of voting was held to re-rate statements through equally weighted voting.

The authors of the Consensus statement are members of the ALTA Group. The group is independent of any other organization and, at the time of the conference, was run by a Steering Committee who convened the diverse expert panel of clinicians and researchers from North America to discuss issues relating to the use of TIPS in the management of portal hypertension at the ALTA consensus conference on October 23, 2020. The broad objective of the conference was to produce expert-based statements and a summary of current knowledge pertaining to the use of TIPS in the clinical management of portal hypertension in adults, and identify evidence gaps to establish research priorities. Conference participants were divided into seven work groups, which were tasked with formulating strategies related to three overall domains related to TIPS (1) candidate selection, (2) procedural best practices and (3) post-TIPS management across seven key topic areas: General considerations for TIPS, TIPS in the management of ascites/HH, TIPS in the management of variceal bleeding, novel indications for TIPS, cardiopulmonary considerations of TIPS including management of hepatopulmonary syndrome (HPS), renal considerations of TIPS including management of hepatorenal syndrome (HRS), and HE and TIPS. Each work group determined the scope of their assigned topic by developing a list of targeted questions, which were used to direct the literature review.

Methods of Review

Stakeholder Involvement. These practice-based recommendations were developed by 30 physicians and researchers with extensive experience in clinical care and research activities related to the diagnosis or management of complications of portal hypertension and the use of TIPS. The target users are gastroenterologists involved in referring adult patients for consultation for TIPS and sub-specialty physicians who provide longitudinal care for adult patients undergoing TIPS creation.

Rigor of Development. PubMed, EMBASE and Cochrane were queried for English language papers published between January 1, 1990 and July 1, 2020, using keywords along with terms specific to each working group. Terms were chosen through input from working group leaders and by consultation with a medical librarian. For most groups, results were limited to controlled trials, prospective and retrospective studies, reviews and meta-analyses, and technical papers. However, for some working groups where the number of studies was limited, case reports were included. This resulted in a total of 2,116 papers; 1,413 were excluded by working group leaders, and 81 were added based on review of reference lists by the experts for a final total of 784 articles that were reviewed. Due to the broad scope of the PubMed database and the type of articles selected for this review, it should be noted that EMBASE and Cochrane did not supply additional articles beyond what the PubMed search strategy provided.

PubMed Search Strings

General TIPS String

(TIPS[Title] OR TIPSS[Title] OR "Portasystemic Shunt, Transjugular Intrahepatic"[Majr] OR “transjugular intrahepatic portosystemic stent-shunt"[Title/Abstract] OR "transjugular intrahepatic portosystemic shunt"[Title/Abstract] OR "transjugular intrahepatic portasystemic shunt"[Title/Abstract] OR "transjugular intrahepatic porto-systemic shunt"[Title/Abstract] OR "transjugular intrahepatic portal-systemic shunt"[Title/Abstract] OR "transjugular intrahepatic shunt"[Title/Abstract]) AND ("1990/01/01"[Date - Publication] : "2020/07/01"[Date - Publication]) AND (English[Language])

TIPS in Ascites

(ascites[mesh] OR ascites[tw] OR ascites[tiab] OR hydrothorax[mesh] OR hydrothorax[tiab] OR "hepatic hydrothorax"[tw])

TIPS in Variceal Bleeding

("Esophageal and Gastric Varices"[Mesh]) AND (hemorrhage[Mesh] OR bleeding[TW] OR bleed[TW])

Novel Indications in TIPS

“abdominal surgery”[TW] OR (Abdomen[Majr] AND surgery[TW]) OR (“chronic liver disease”[TW] AND (“portal vein obstruction”[TW] OR (“Portal vein”[Mesh] AND obstruction[TW]))) OR “portal vein recanalization”[TW] OR “Budd-Chiari”[TW] OR “Budd Chiari”[TW] OR “VOD”[TW] OR “veno-occlusive”[TW] OR “venoocclusive”[TW] OR “veno occlusive”[TW]

Cardiopulmonary Implications of TIPS

(Heart[Majr] OR cardiac[TW] OR cardiopulmonary[TW] OR "cardiac function"[TW] OR "cardiac implications"[TW] OR "heart failure"[TW] OR "cardiac failure"[TW] OR "heart failure"[Majr] OR MACE[TW] OR "preserved ejection fraction" [TW] OR "reduced ejection fraction" [TW] OR "systolic dysfunction"[TIAB] OR "diastolic dysfunction"[TW] OR "myocardial strain"[TW] OR "global longitudinal strain"[TW] OR "pulmonary hypertension"[TW] OR "Hypertension, Pulmonary"[Mesh] OR "portopulmonary hypertension"[TW] OR “heart catheterization”[TW] OR “coronary catheterization”[TW] OR “swanz-ganz catheter”[TW] OR "Electrocardiography"[Mesh] OR “pulmonary function test”[TW] OR “myocardial energy expenditure”[TW] OR “exercise testing”[TW] OR "Hypoxia"[Mesh] OR "atrial fibrillation"[MeSH] OR "atrial flutter"[MeSH] OR "Arrhythmias, Cardiac"[Mesh] OR "prolonged QT"[TW] OR "Aortic Valve Stenosis"[Mesh] OR "aortic stenosis"[TW] OR "Aortic Valve Insufficiency"[Mesh] OR "aortic regurgitation"[TW] OR "Mitral Valve Stenosis"[Mesh] OR "mitral stenosis"[TW] OR "Mitral Valve Insufficiency"[Mesh] OR "mitral regurgitation"[TW] OR "Tricuspid Valve Insufficiency"[Mesh] OR "tricuspid regurgitation"[TW] OR "coronary artery disease"[Majr] OR “systemic hemodynamics”[TW] OR “systemic haemodynamics”[TW] OR "Natriuretic Peptide, Brain"[Mesh] OR “hyperdynamic circulation”[TW] OR "Echocardiography"[Mesh] OR “cardiac magnetic resonance imaging”[TW] OR “highly sensitive troponin”[TW])

Renal Implications of TIPS

("Renal Insufficiency, Chronic"[Mesh] OR "Renal Insufficiency"[Mesh] OR "Hepatorenal Syndrome"[Mesh] OR “Acute kidney injury”[Mesh])

Hepatic Encephalopathy and TIPS

("encephalopathy" [Keyword] OR "encephalopathy" [TIAB] OR "hepatic encephalopathy" [Mesh])

Members of the work groups performed reviews of the available literature in an organized manner and developed a consensus of opinion to distill literature and articulate a research agenda to address important unanswered questions. Level of evidence for all consensus statements was graded using the Oxford Centre for Evidence-based Medicine Levels of Evidence.[3] Between August 2020 and October 2020, each topic was iteratively discussed by a work group of physicians (5-6 physicians per topic) with expertise in the identified topics. Literature was distributed electronically to each work group, assessed with respect to ability to address the proposed topic, evaluated for quality, and then discussed electronically and by teleconference (3-5 meetings per group). Over this series of teleconferences, initial consensus was achieved (100% agreement of working group participants) after ongoing discussions regarding the assigned topic.

Delphi Survey Method Process and Administration

Draft consensus recommendations from the individual work groups were compiled into a single survey for distribution to conference participants. Surveys were administered via Northwestern's Research Electronic Data Capture (REDCap).[4] Individuals were asked to rate agreement with each statement based on a nine-point scale, with 1 being Strongly Disagree and 9 being Strongly Agree; a "not qualified to answer" option was also available. Participants were also given a free text space for each statement to provide comments and questions. Statements were considered to reach consensus if they achieved a mean of score of greater than 7 (agree) with at least 80% (N=24) of participants responding to the statement. The decision to require at least 80% of participants ranking a proposed statement was determined by the conference organizers. The rationale for this requirement was that due to the multidisciplinary training of participants (e.g., proceduralists and non-proceduralists) there were some items in which respondents did not feel they had the

expertise in which to rate the statement (e.g., procedural aspects rated by medical practitioners or vice versa). Thus, an 80% response threshold was set in an attempt to represent the target audience which includes a range of practitioners in both procedural and non-procedural specialties. All statements receiving a mean score below 7 were reviewed during the face-to-face meeting. The final product was then assessed and aggregated at the face-to-face meeting attended by all participants. Statements with clear non-consensus or overlap with other statements based on discussions during the face-to-face meeting were discarded or combined. All remaining statements were formally voted on in a second round of post-meeting voting using the same methodology as above. All post-meeting statements reached consensus in the second round of voting. This manuscript was then drafted based on the final recommendations.

Clarity of Presentation. The recommendations provided are specific because they clearly identify the target population and provide the level of evidence on which the recommendation is based.

Applicability. Results from this conference provide advice and a practical approach for the clinical assessment and management of patients undergoing consideration for TIPS creation. Facilitators and barriers relate primarily to distribution of these recommendations to the broad range of clinicians involved in the care of patients with portal hypertension. Monitoring and auditing of recommendations will be addressed in future studies.

Editorial Independence. The views of the funders have not influenced the content of the guidance. Competing interests of ALTA team members have been recorded.

Supplemental Discussion

General Considerations for TIPS

Pre-TIPS Considerations

Q3. Is there a Model for End-Stage Liver Disease (MELD) threshold above which elective TIPS should not be considered?

A multidisciplinary approach, rather than an absolute MELD cutoff, is recommended to assess TIPS candidacy. MELD score is the strongest predictor of 90-day mortality after TIPS when compared to MELD-Na and other scoring systems (e.g., Chronic Liver Failure Consortium Acute on Chronic Liver Failure (CLIF-C ACLF) score, Child-Turcotte-Pugh (CTP) score, Emory score, Bonn TIPS Early Mortality (BOTEM) score, and Platelet-Albumin-Bilirubin (PALBI) score).[5-10] MELD score performs better in patients with TIPS for variceal bleeding compared to patients with refractory ascites (RA).[11-13] Other studies have examined additional risk factors for poor outcomes with mixed results, including older age and specific numerical MELD score cut-offs.[12-18] Overall, it is difficult to generate definitive conclusions about additional risk factors for death after TIPS from these data. Limitations of studies include sample size, variation in center practices, spectrum of MELD score or selective diagnosis (e.g., ascites or variceal bleed), as well as heterogeneous procedural techniques (e.g., covered versus uncovered stents, stent diameter and dilation choices, variable volume/type of contrast agents used).[19-23] Thus, determination of TIPS candidacy using the MELD score should take into consideration the relative risk and benefit of TIPS creation to the specific patient under consideration in the context of clinical indication for performing TIPS, comorbidities and alternative treatment options.

Care of the Post-TIPS Patient

Q16. What early laboratory testing and/or imaging is recommended following TIPS creation and at what interval?

In all patients undergoing TIPS creation, routine labs (complete blood count, comprehensive metabolic panel, and PT/INR) should be obtained on the day following TIPS creation. Of note, liver chemistries are often elevated the day after TIPS and typically return to pre-procedure levels over the ensuing week. Hemoglobin/hematocrit measurement may be obtained on the same day of TIPS creation, particularly when patient or procedural factors increase procedure-related bleeding risk or when clinical findings suggest procedure-related bleeding has occurred.

Q17. Should TIPS venography and intervention be based on ultrasound, clinical findings, or both?

The decision to perform TIPS venography and intervention is dependent on the indication for TIPS creation. In patients who have undergone TIPS creation for management of varices, either Doppler ultrasound findings suggesting TIPS dysfunction, or persistence or recurrence of portal hypertensive complications should prompt TIPS venography and manometry +/- intervention. Ultrasound findings suggesting TIPS dysfunction include alterations in intrahepatic portal vein direction of flow, abnormal flow velocities within the TIPS, and persistent (e.g., > 6 weeks post-TIPS) or recurrent ascites. In patients who have undergone TIPS creation for management of ascites and/or hepatic hydrothorax, persistence or recurrence of portal hypertensive complications should prompt TIPS venography and manometry +/- intervention. Medical decision-making should be individualized in patients with well-controlled ascites and/or hepatic hydrothorax and ultrasound findings suggesting TIPS dysfunction. In select patients, such as those who have undergone TIPS creation

for management of portal vein thrombosis, scheduled TIPS venography with intervention is suggested in the early (1-2 months) post-TIPS period.

Notably, TIPS stenosis can be a precursor to TIPS occlusion or thrombosis.[24] From a procedural standpoint, intervening upon TIPS stenosis is technically simpler than intervening upon TIPS thrombosis. Detecting TIPS stenosis with non-invasive ultrasound and performing TIPS angioplasty may be beneficial if the patient would otherwise progress to TIPS thrombosis prior to developing clinical symptoms from the recurrent portal hypertension. On the other hand, if invasive TIPS venography is performed based on ultrasound findings only and without regard to clinical status (e.g., ascites/HH control), it is possible that TIPS angioplasty may increase the patient's risk of HE without providing clinical benefit.

Specific Considerations for TIPS by Indication

TIPS in Ascites or HH

Q2. Is TIPS associated with better outcomes (ascites control, mortality) than serial large volume paracentesis (LVP) for the treatment of RA?

RA, or diuretic-resistant ascites, is a severe manifestation of portal hypertension that impacts about 10% of patients with cirrhosis and ascites.[25] There have been seven RCTs evaluating the impact of TIPS versus serial LVP (Table S2).[19, 26-31] These trials have been heterogeneous in their definition of RA, whether non-refractory but recurrent ascites was included, the technical approach, stent type (only one with ePTFE-covered stents[19]), and the definition of treatment response. Overall, studies have consistently demonstrated improved control of ascites with TIPS compared to LVP, but increased risk of HE (Table S2).[19, 26-31] The impact of TIPS on survival has

been more controversial. Of seven trials, four demonstrated improved transplant-free survival (TFS) with TIPS vs. LVP in uni- and/or multivariable analyses[19, 27, 30, 31], two with no differences in TFS between groups[28, 29], and the earliest trial revealed decreased TFS at two years.[26] The most recent study, which notably utilized non-expandable PFTE-covered stents and also had less strict criteria for RA, showed the most significant benefit.[19] There have been several subsequent meta-analyses[32-37] that confirmed the superiority of TIPS compared to serial LVP in prevention of recurrent ascites, but remained split in terms of TFS benefit, again depending upon methodology and whether one potentially outlier[26] paper was included (Table S2). The most recent meta-analyses, which used time to event analysis, both demonstrated improved TFS.[36]

Q3. Is there a threshold of liver dysfunction above which TIPS for RA should be contraindicated and how should it be defined?

Among patients with cirrhosis and RA, elevated bilirubin, elevated MELD score and CTP Class C cirrhosis are associated with increased post-TIPS complications including mortality.[27, 35-37] However, there are no studies that provide strong evidence of a specific cutoff for any of these parameters above which TIPS should be considered contraindicated. It is important to note that patients with CTP > 11, MELD score > 15 and total bilirubin level > 3-5 mg/dL were generally not included in prospective randomized trials (Table S2).

Q4. What is the impact of age on candidacy for TIPS for RA?

Among patients with cirrhosis and RA, advanced age is associated with increased post-TIPS complications including HE and mortality. However, there are no studies that provide strong evidence of a specific cutoff above which TIPS should be considered contraindicated. It is important to note

Q7. Is prior LT a contraindication to TIPS for RA? Is TIPS a better treatment than surgical shunt, serial LVP or splenic artery embolization in LT recipients with RA?

Unlike TIPS for ascites and HHT in cirrhosis, there is insufficient evidence to support any recommendation regarding therapy (TIPS and other modalities) in LT recipients with refractory ascites. Predictors of clinical success in treating RA post-LT with TIPS include recurrent graft fibrosis and presence of a significant PSG.[38] When alternative sources are identified, including early caval or hepatic venous outflow obstruction, alternative operative and interventional strategies should be considered. In patients without outflow obstruction, there is also limited data on the use of splenic artery embolization and mesocaval surgical shunts, but no significant studies that compare these approaches.[38-40]

TIPS in Variceal Bleeding

Q1. When is TIPS indicated in Acute Variceal Hemorrhage?

Rescue TIPS is recommended in patients with cirrhosis who have been successfully banded but who rebleed at any time during admission (after endoscopy). Standard of care in patients admitted with suspected acute variceal hemorrhage consists of cautious volume resuscitation, ceftriaxone and intravenous infusion of octreotide.[41] Endoscopy is performed within 12 hours and endoscopic

variceal ligation (EVL) is performed if esophageal variceal source is confirmed.[41] Octreotide/ceftriaxone is continued for 5 days and TIPS is recommended if bleeding recurs during this period.[41] However, patients with advanced (mostly CTP Class C) cirrhosis who rebleed and have rescue TIPS placed have a very high mortality.[42-44] This led to the concept of "pre-emptive TIPS," by which patients at high risk of failing standard of care undergo TIPS creation as soon as EVL is successfully performed and within 72 hours of admission. Individual meta-analysis of three RCTs[45-47] and five observational studies[48-52] have identified patients with CTP Class C (10-13 points) and CTP Class B (8-9 points) with active bleeding at endoscopy as being at highest risk for rebleeding and most likely to benefit from pre-emptive TIPS. Patients not meeting these criteria should be considered for rescue TIPS in case of rebleeding during admission. Any patient (independent of CTP Class) with uncontrolled acute variceal hemorrhage at endoscopy should be considered for salvage TIPS. Balloon tamponade or stent should be used as bridge to TIPS in rescue/salvage TIPS.[53]

Q2. When should TIPS be used in the management of bleeding gastric fundal varices or prevention of rebleeding due to cirrhosis?

Based on limited current data, the panel developed a consensus approach to GV bleeding and timing of TIPS in cirrhosis (Figure S3). While endoscopic injection of N-butyl-2-cyanoacrylate, "glue", is efficacious in the acute setting in order to obtain initial hemostasis, use of endovascular variceal obliteration (e.g., balloon-retrograde transvenous obliteration, BRTO), or TIPS creation result in lower short- and long-term rebleeding rates.[54, 55] However, TIPS in GV bleeding is not as effective compared to TIPS in esophageal variceal bleeding as GV hemorrhage can occur at a lower PSG.[56] Based on limited data, as compared with variceal obliteration (mostly BRTO), TIPS is associated with higher rebleeding risk (20-50%) and significantly higher risk for HE (20-40%) without differences in survival.[57-64] Nevertheless, BRTO requires the presence of a spontaneous portosystemic shunt (e.g., gastro or splenorenal shunt) and may be associated with increased ascites and bleeding from esophageal varices. TIPS combined with variceal obliteration appears to be

associated with a potential decrease in rebleeding rates (0-15%),[65-67] particularly when the pre-treatment PSG is less than 12 mmHg. In addition to above considerations, the most appropriate management for bleeding from GV will depend on vascular anatomy of the portal venous system in addition to center and operator expertise.[68]

Q3. What are the procedural considerations in TIPS creation for variceal hemorrhage?

Based on moderate quality data, when placing a TIPS for variceal hemorrhage, we recommend a goal PSG of <12 mmHg or 50-60% decrease from initial.[69-73] Studies using shunt diameter as a predictor of rebleeding rates have shown mixed results and therefore we do not recommend using shunt diameter as a procedural endpoint.[20, 74] Notably, a prospective trial of the controlled expansion stent demonstrated that serial dilation of the stent from 8 mm to 10 mm to obtain a goal PSG <12 mmHg led to control of variceal bleeding while mitigating the risk of HE.[70]

In cases of TIPS creation for variceal hemorrhage, we recommend concurrent obliteration of varices based on moderate-high quality evidence.[75-80] An RCT that showed reduced rebleeding rates with concurrent embolization demonstrated improved TIPS patency when embolization was performed.[78] Studies have shown efficacy of embolization coils and vascular plugs for variceal embolization.[81, 82] Liquid embolic agents have also been shown to be effective in this setting.[80, 83] There is currently insufficient data to show superiority of one embolic agent and the use of each will depend on operator expertise.

Novel Indications for TIPS

Q3. Does TIPS creation prevent or reduce portal hypertensive complications in patients with non-cirrhotic portal hypertension due to extrahepatic portal vein obstruction?

Four uncontrolled retrospective cohort studies described the use of TIPS in this patient population (encompassing both acute and chronic thrombosis, with and without various forms of thrombolysis, Table S4).[84-87] In general, TIPS creation was found to be technically feasible and effective in reducing portal hypertension in patients with acute and chronic PVT, especially in patients with extensive PVT and bowel ischemia. The evidence level remains low due to the lack of prospective studies and a paucity of studies comparing direct intervention to anticoagulation alone. One cohort (n=330) described a high rate of venous recanalization with anticoagulation monotherapy, particularly with direct oral anticoagulants, suggesting this approach should be considered initially in patients who are not critically ill.[88] However, 23% of patients who developed chronic portal hypertensive symptoms (n=104) went on to receive a TIPS.[88] Based on available data, in patients with non-cirrhotic portal hypertension and acute portal vein thrombosis, we recommend immediate anticoagulation. In those who fail or have a poor response to anticoagulation, we recommend that portal vein thrombectomy/thrombolysis using a transjugular approach with or without small caliber TIPS creation should be considered. In patients with acute non-cirrhotic portal vein thrombosis who are not critically ill, evidence is insufficient to recommend TIPS versus anticoagulation alone. We recommend that a trial of anticoagulation be considered initially given the reported rates of venous recanalization. In patients with chronic portal hypertension secondary to non-cirrhotic extrahepatic portal vein obstruction that is not responsive to anticoagulation, TIPS may be considered for the same indications as cirrhotic portal hypertension.

Q5. Does TIPS creation improve outcomes in patients with BCS?

Cohort studies of patients with BCS (hepatic venous outflow tract obstruction) have demonstrated technically successful creation of TIPS in 84-100% of cases,[89-94] excellent control of portal hypertensive complications and good survival (72% overall and TFS).[89-93, 95, 96] The majority of published literature in BCS and on the use of TIPS in this disease comes from referral centers experienced in the complex management of BCS. However, whether patient outcomes in BCS differ based on treatment center experience is not reported in the literature.

Prospective cohort series and retrospective case series have demonstrated favorable long-term outcomes after percutaneous revascularization of short segment hepatic venous outflow tract obstruction with venoplasty and/or stent placement, with technical success rates of 78.6-100%.[92, 97-102] Technically successful creation of a percutaneous portosystemic shunt, either TIPS or direct intrahepatic portosystemic shunt (DIPS), after hepatic venous outflow tract revascularization has been demonstrated in multiple series.[91, 103-107] These data indicate that venoplasty with or without stenting does not preclude subsequent creation of TIPS or DIPS in patients who remain symptomatic after initial revascularization.

The rare presentation of BCS with acute liver failure (ALF) deserves special consideration. In-hospital mortality in ALF due to BCS is between 58-62%.[108] The BCS-TIPS prognostic index (PI) was designed to predict 1-year TFS after TIPS for BCS.[109] Among 124 patients with BCS in the original multicenter retrospective cohort study used to derive the BCS-TIPS PI score, nine (7.3%) met ALF criteria. Of these, four had BCS-TIPS PI scores > 7, all of whom died as a consequence of progressive liver failure (mean 9 days, range 2-15 days). The other five patients with BCS and ALF had BCS-TIPS PI scores ≤ 7 and all survived without LT to the end of follow-up. The prognostic value of the BCS-TIPS PI score in ALF has not been externally validated, however these findings support multidisciplinary discussion of whether to pursue TIPS or whether to proceed directly to LT in BCS patients with ALF and BCS-TIPS PI scores > 7.

Finally, one common element in the management of BCS patients is the need for re-intervention to maintain or restore TIPS patency in a portion of patients undergoing TIPS. Reported primary patency rates with ePTFE-covered TIPS vary ranging from 45% to 91% 5-year primary patency.[110, 111] Secondary patency rates range from 85-100% over follow-up periods of 20-82 months in most series, signifying that even with TIPS occlusion salvage is often possible, precluding the need for LT.[96, 97, 99, 110-113]

Cardiopulmonary Considerations in TIPS

Q1. What cardiopulmonary testing is indicated prior to elective TIPS?

In patients undergoing elective TIPS creation, we recommend comprehensive echocardiographic evaluation to detect subclinical cardiac dysfunction (e.g., cirrhotic cardiomyopathy, CCM). CCM describes systolic and/or diastolic dysfunction in patients with cirrhosis without known heart disease.[114] Systolic function should be assessed not only by ejection fraction, but also with other echocardiographic markers of LV function, including myocardial strain imaging according to contemporary practice guidelines.[114, 115] RV systolic pressure (RVSP) > 45 mmHg is conventionally considered the threshold for considering right heart catheterization. Decreased tricuspid annular plane excursion (TAPSE, <1.6 cm) and RV strain indicate impaired RV function.[115] Baseline RV indices are particularly important to assess the possibility of post-TIPS increased preload causing cardiopulmonary decompensation. In patients undergoing TIPS creation who have a RVSP exceeding 45 mmHg or TAPSE less than 1.6 cm, we recommend referral to cardiology for consideration of right heart catheterization to evaluate for RV dysfunction and pulmonary hypertension prior to TIPS creation. Electrocardiogram (ECG) is warranted for evaluation of arrhythmia if tachycardia or bradycardia is noted on pre-procedure assessment. Historically, prolonged QTc interval was a CCM criterion but updated guidance has removed it given its variability and multifactorial etiology.[114]

Q5. Can TIPS treat HPS?

A recent systematic review of 12 case reports found some transient improvement in oxygenation in 9 patients post-TIPS with most having persistent intrapulmonary shunting.[116] Two single-center retrospective studies of patients with HPS undergoing TIPS, (one in 7 patients with HPS and BCS[117] and another in 81 patients with moderate HPS[118]), found only modest transient improvement in oxygenation after portal decompression over 3-months follow-up. Thus, we do not recommend TIPS as a therapy for HPS, but it may be considered in patients with HPS who have an established indication for TIPS.

Renal Considerations in TIPS

The true incidence of acute kidney injury (AKI) following TIPS is unknown given a wide spectrum of indication and urgency for TIPS, the heterogeneity in measurement of kidney function (e.g., measured versus estimated glomerular filtration rate (GFR), serum creatinine (sCr)), definitions of AKI (based on change in creatinine versus absolute cutoffs) and patient selection. In single center studies, the incidence of post-TIPS AKI was 16% though this may be overestimated and may not account for pre-TIPS AKI or chronic kidney disease (CKD).[119-121] Presence of AKI after TIPS creation is associated with increased odds (Odds Ratio (OR), 4.3) of inpatient mortality.[122]

Creation of TIPS and resultant reduction in PSG is associated with improvement in kidney function especially when measuring GFR.[123-130] As compared to serial paracentesis, incidence of AKI and HRS may be lower in patients with TIPS.[28, 36] Change in estimated GFR is evident over 3-4 months after TIPS creation with a potential benefit in patients with CKD (GFR<60)[123, 126] suggesting that TIPS

interrupts the natural history of decline in kidney function related to decreased effective circulating volume. Despite these physiologic improvements, there is insufficient evidence regarding clinical outcomes when considering TIPS in patients with advanced kidney dysfunction (e.g., sCr > 3mg/dL) as these patients were often excluded from studies.[27-30, 131] Additionally, TIPS is not well studied in the dialysis population, with only case reports in the literature.[132] The panel suggests considering the primary indication, predictive models like MELD score, individualized risk factors, and physiologic goals of the intervention when considering TIPS creation in patients with a degree of kidney dysfunction (Table 3).

Q1. What is the best marker to assess kidney function before or after TIPS?

Kidney function assessment in TIPS is varied with some studies reporting changes in sCr, creatinine clearance, measured (using inulin clearance) or estimated GFR (modification of diet in renal disease (MDRD), Chronic Kidney Disease Epidemiology Collaboration (CKD EPI)).[26, 123, 125, 126, 133, 134] Serum creatinine is usually used as a predictor of post-TIPS kidney dysfunction and mortality, along with other risk factors, such as age, presence of HE, and poor control of ascites [135-138] Though sCr is easy to measure and obtain, sCr may underestimate degree of kidney dysfunction, especially among women, decompensated cirrhosis patients or those with low muscle mass.[139] The role of estimating GFR using equations that include both sCr and cystatin has not been studied in patients with TIPS.[140] Measured GFR may be preferable but is impractical to obtain. Though several biomarkers have been described, these have been inadequately examined in patients with cirrhosis undergoing TIPS.[141, 142] GFR equations developed in patients with cirrhosis and biomarkers that capture structural and functional changes in kidney function may be preferable.[141, 143] In patients undergoing TIPS, sCr predicted mortality better for men whereas cystatin C predicted mortality better in women. However, GFR was not assessed in this study.[144] Assessment of kidney function is poor in patients with cirrhosis that are frail, sarcopenic and/or have underlying CKD (without

hemodialysis dependence) and are undergoing TIPS. Other biologic determinants of health, including sex, race, and ethnicity have not been well studied in TIPS populations as it relates to kidney function.

Q3. What can be done peri-procedurally to reduce the incidence of kidney complications after TIPS? What secondary or tertiary preventive measures can be considered to avoid AKI, acute kidney disease, or de Novo or progressive CKD after TIPS?

Data regarding pertinent kidney protection strategies in the TIPS population are lacking, therefore the panel extrapolated data from related clinical scenarios in order to suggest relevant rational strategies. In patients undergoing TIPS creation for ascites, albumin infusion should be considered in all patients undergoing concurrent paracentesis, and especially for those in whom >5L are removed, to prevent paracentesis-induced circulatory dysfunction and AKI.[25, 145-147] The role of vasoconstrictors at the time of LVP or in addition to albumin use during TIPS creation is unclear.[148-151]

Judicious use of intravascular iodinated contrast agents may minimize risk of contrast nephropathy after TIPS creation. In an observational study, post-TIPS AKI (defined as ≥ 0.3 mg/dL increase in sCr within 48 hours after TIPS) increased with 50 mL increases in contrast load and elevated baseline sCr (pre–TIPS AKI or CKD) levels.[120] The true incidence of, and risks for, contrast-induced nephropathy in the era of low-osmolality contrast agents is unknown. Rates of AKI in patients undergoing CT scans with low-osmolality iodinated contrast agents compared with those having CT scans without contrast may be equivalent.[152, 153] Given the limitations of studies (patient selection and study design), the influence of iodinated contrast on inducing nephropathy cannot be entirely ignored, particularly in those with more severe kidney impairment.[154, 155] Oral acetylcysteine is not recommended.[156] The risk of contrast nephropathy is extrapolated from the contrast literature; risk factors include baseline CKD, elevated serum glucose levels (> 200 mg/dL) and serum total bilirubin levels > 2.0 mg/dL.[157, 158]

Q4. What is the role of TIPS for hepatorenal syndrome (HRS)?

The quality of available studies on TIPS for management of HRS is low due to small sample size and significant heterogeneity. For example, in a small prospective study (n=7), kidney function improved in 6 out of 7, with a decline in median sCr level (5 mg/dL to 1.8 mg/dL) within 30 days post-TIPS. However, 90-day mortality was high (58%) and driven mostly by liver failure and sepsis.[124] In a subsequent study with 14 patients with type 1 HRS (50% on renal replacement therapy) and 17 patients with type 2 HRS, improvement in kidney function was observed in 77% of patients and discontinuation of hemodialysis was possible in 57% of patients. [130] High survival rates were observed (90% in HRS-2, 55% in HRS-1 at 12 weeks) likely related to strict patient selection. Both studies were conducted in the pre-MELD era and, while this data may seem encouraging, it is heavily limited by a non-randomized design and a strong selection bias. TIPS creation prevented HRS-1 recurrence in responders to vasoconstrictive therapy (n=5) with normalization of sCr without HRS recurrence up to 17 ± 5 months post-TIPS.[159] In addition, TIPS creation may reduce the incidence of HRS in patients with diuretic-RA.[28] Finally, a meta-analysis of nine studies[128] showed significant improvement in kidney function, as measured by sCr, with a pooled response rate of 93% in HRS-1 and 83% overall.[160]

Hepatic Encephalopathy and TIPS

Q1. When counseling patients, what is the overall risk of overt HE after TIPS and what patient specific factors contribute to development of overt HE?

Incidence of overt HE in uncovered (non-PTFE) stents is 33% for variceal bleeding and 53% for ascites compared to 19% and 32%, respectively, in patients who received standard medical management.[161, 162] In direct comparative studies of uncovered and covered stents, there was no difference in incidence of overt HE. Hence it is reasonable to apply the incidence data for overt HE from uncovered stents to contemporary covered stents.[161-163] The only RCT in covered TIPS stents vs. LVP for ascites demonstrated similar rates of 35% in new incidence of overt HE.[19] In several RCTs investigating pre-emptive TIPS for acute variceal hemorrhage, incidence rates of overt HE were similar in the pre-emptive TIPS groups compared to endoscopic therapy and ranged from 35-50%.[46-48] It should be noted that these studies had selective inclusion criteria and excluded patients with history of recurrent overt HE.

In a meta-analysis, the strongest independent predictors of post-TIPS HE included pre-TIPS HE (OR 3.07, 95% CI 1.75-5.40) and CTP Class C cirrhosis (OR 4.0, 95% CI 1.4-11.1).[164] In RCT multivariate analyses, MELD score pre-TIPS is not predictive of post-TIPS HE compared to incidence of HE in medical management control arms.[19, 47, 48] These RCTs however are limited based on narrow ranges of MELD scores (e.g., MELD range 10-20) among TIPS recipients. Limited single center studies suggest a MELD score > 18 is associated with an increased incidence of post-TIPS overt HE.[165] Other risk factors for post-TIPS HE include older age (Hazard Ratio (HR) 1.09, 95% CI 1.05-1.13) and elevated creatinine (HR 1.52, 95% CI 1.02-2.26).[166] More recent prospective data demonstrated sarcopenia, as evident on lumbar or psoas computed tomography measurements, is strongly associated with development of HE (HR 31.3, 95% CI 4.5-218).[167, 168]

Q3. What is the role for formal evaluation for covert or minimal HE prior to elective TIPS?

The diagnosis of covert HE has been associated with a greater risk of post-TIPS HE.[162, 169, 170] Covert HE is associated with poor daily function and impaired health related quality of life (HRQoL) and is associated with development of overt HE even in patients who do not

undergo TIPS.[171-173] However, there is no recommendation to treat patients with covert HE with medical interventions (e.g., lactulose, rifaximin) prior to TIPS. Recommendations for testing to detect covert HE include psychometric hepatic encephalopathy score, EncephalApp Stroop, or Critical Flicker frequency testing.[174] Few studies have determined the role of oral glutamine challenge in prognostication for overt HE post-TIPS.[175-177] Cognitive testing by and large worsens after TIPS, which can contribute to the further worsening of HRQoL.[162, 178] In patients being considered for elective TIPS, a diagnosis of covert HE should guide discussion of the pros and cons of TIPS creation with patients, family members and clinical teams. Future studies investigating the effect of covert HE with and without treatment on incidence of post-TIPS overt HE are necessary.

Q4. What TIPS stent diameter should be considered with regards to limiting post-TIPS HE?

While potentially providing less portal decompression, smaller shunts have been proposed as a way to decrease overt HE. In a multi-center RCT of elective TIPS for ascites, 8 mm diameter TIPS led to a PSG < 12 mmHg in only 61% of patients, but the rate of OHE was only 18%.[179] Several other studies showed significantly less overt HE in 8 mm compared to 10 mm TIPS.[20, 180, 181] In a recent prospective single arm trial of the controlled expansion stent dilated to 8 mm, the shunts did not self-expand beyond 8 mm and the rate of grade II-III HE was only 6%.[70] However, 17% of patients required dilation up to 10 mm in order to achieve adequate clinical response.[70]

Q5a. Is there a role for collateral embolization at the time of TIPS?

In patients undergoing elective TIPS for ascites and/or hepatic hydrothorax, embolization of spontaneous portosystemic shunts (SPSS) >6mm is recommended in order to reduce the risk of post-TIPS hepatic encephalopathy. Large spontaneous portosystemic shunts (SPSS) have been associated with increased risk of overt HE and mortality in patients with cirrhosis.[182, 183] Hence, embolization of SPSS could be beneficial to patients undergoing TIPS to prevent post-TIPS HE. In a retrospective cohort of 903 patients utilizing covered TIPS stents, 51% of patients with an identified SPSS > 6mm left in place at the time of TIPS developed overt HE compared to 39% among those with an embolized SPSS.[184] A smaller study comparing 33 TIPS patients with SPSS embolization and 33 TIPS patients without SPSS embolization showed no significant difference in post-TIPS HE rates.[185]

Q6a. What is the role for medical prophylaxis to prevent HE after TIPS?

Early RCTs using uncovered TIPS stents showed no difference in the incidence of overt HE in a head to head comparison of lactulose, rifaximin, and placebo.[186] However, a recent RCT with a larger sample size demonstrated significantly reduced incidence of first episode of HE post-TIPS (44.2% vs 59.1%, p = 0.05) in patients without a history of overt HE receiving rifaximin versus placebo as prophylaxis prior to TIPS.[187] The major limitation to the newer study is that lactulose was not allowed in the trial prior to TIPS, even among those with history of overt HE (12% prevalence in both arms) although could be used for treatment of overt HE if it developed. Thus, standard of care was not met in the pre-TIPS population with a history of HE who had an indication for lactulose, dampening enthusiasm for the study findings.

Table S1. Final Voting Results for the Full List of Candidate Guidance Statements related to use of TIPS in the Management of Portal Hypertension Stratified by Topic Area.

Question	Statement	Mean	SD	% response
PRE-TIPS CONSIDERATIONS				
Q1. Who should be involved in the decision to place a TIPS and what other pre-procedure consultations are recommended?	Prior to TIPS creation, we recommend that a gastroenterologist or hepatologist should be involved in the initial decision to place an emergent or nonemergent TIPS with subsequent consultation by an interventional radiologist or other proceduralist with competency in TIPS. If center expertise is not available, we recommend referral to an expert center. Additional specialty consultations (e.g., Transplant Surgery, Cardiology, Critical Care, Hematology, Nephrology) may be considered on a case-by-case basis.	8.33	0.92	90.0%
Q2. What services should be readily available at centers where TIPS is performed and what referral pathways should be established for a higher level of care?	For all patients undergoing TIPS creation, we recommend that TIPS should occur at a center with available Interventional Radiology (IR), Gastroenterology/Hepatology, Cardiology, Pulmonary Surgery, Hematology, Nephrology and Critical Care services in order to provide an adequate level of support for patient management before and after TIPS. In patients requiring a higher level of care, such as possible liver transplant candidates, or in whom the need for further IR expertise is indicated (e.g., extensive portal vein thrombosis), we recommend referral to centers with adequate experience in these areas.	8.5	0.69	93.3%
Q3. Is there a MELD threshold above which elective TIPS should not be considered?	In patients with cirrhosis undergoing TIPS, a multidisciplinary approach, rather than an absolute MELD cutoff, is recommended to assess TIPS candidacy.	8.73	0.53	86.7%
Q4. What imaging and/or pre-procedural evaluation is required prior to TIPS creation?	Q4a. In patients undergoing elective TIPS, we recommend: • Contrast-enhanced multiphasic cross-sectional imaging (CT/MRI) to assist with TIPS planning. • Comprehensive echocardiography to assess for abnormalities in cardiac structure, function, and right ventricular systolic pressure.	8.19	1.27	90.0%
	Q4b. In patients with cirrhosis undergoing emergent TIPS, best clinical judgement should be applied – we suggest at least a liver ultrasound with doppler to evaluate the patency of the portal venous system and consideration of a limited (bedside) echocardiogram, evaluating left ventricular ejection fraction and right ventricular systolic pressure.	8.52	0.64	90.0%

Q5. What are absolute contraindications (medical and anatomical) to elective TIPS creation?	In patients undergoing elective TIPS, the absolute contraindications to TIPS creation are severe cardiac dysfunction (right or left sided), moderate-severe pulmonary hypertension (based on invasive measurements) despite medical optimization, severe valvular heart disease, uncontrolled systemic infection, unrelieved biliary obstruction, or masses/tumors in the liver parenchymal that would preclude TIPS creation.	8.32	1.25	93.3%
Q6. Should all patients being considered for TIPS undergo evaluation for liver transplantation prior to TIPS creation?	In patients with cirrhosis undergoing elective or emergent TIPS, there is insufficient evidence to recommend universal pre-procedure liver transplant evaluation.	8.19	1.27	90.0%
TIPS PROCEDURAL CONSIDERATIONS				
Q7: Who should perform TIPS creation?	We recommend that TIPS creation should be performed by a credentialed, board certified Interventional Radiologist OR a certified provider with equivalent training and procedural competency*.	8.35	1.13	90.0%
Q8. What type of stent is recommended for TIPS creation?	For patients undergoing TIPS placement, we recommend the use of an ePTFE lined stent graft (1b) with controlled expansion which allows the operator to tailor the amount of portosystemic shunting based on the indication, target gradient and patient comorbidities (2b).	8.56	1.26	83.3%
Q9. Should coagulopathy be corrected prior to TIPS placement?	Due to insufficient evidence, we do not recommend a specific target INR or platelet threshold when placing a TIPS in a patient with cirrhosis.	7.88	1.63	86.7%
Q10. Should periprocedural antibiotics be routinely used in TIPS creation?	There are no studies to show that the routine use of antibiotics during TIPS placement decreases infectious complications and their use should depend on patient and local risk factors.	8.04	1.11	86.7%
Q11. Should TIPS creation be performed using general anesthesia or is	The use of general anesthesia, deep sedation, or conscious sedation may all be appropriate for TIPS placement and their use will vary depending on the patient risk factors and local practices.	8.15	1.26	86.7%

deep or conscious sedation appropriate?				
Q12. Is the use of intravascular ultrasound recommended to assist with the portal vein puncture?	For patients undergoing TIPS creation, while there is insufficient evidence to recommend the universal use of intravascular ultrasound guidance, it may facilitate efficient portal access in certain situations. Its use will depend on equipment availability and operator preference.	7.8	1.55	83.3%
Q13. What is the optimal location from which to measure the systemic venous pressure at the time of TIPS creation (hepatic vein, IVC, right atrium)?	We recommend the use of the free hepatic vein or IVC pressure as the systemic pressure when measuring the portosystemic gradient before and after TIPS placement.	7.65	1.81	83.3%
Q14. Are there specific technical factors that should be considered to ensure that TIPS placement does not adversely influence liver transplant candidacy?	Q14a. In patients undergoing TIPS placement who are potentially eligible for liver transplant, we recommend positioning the stent as to not interfere with the portal and hepatic vein anastomoses, presuming that this does not detrimentally affect TIPS function or patency. This positioning includes leaving a segment of unstented main portal vein and not extending the TIPS stent into the right atrium.	8.35	1.06	83.3%
	Q14b. Liver Transplant candidacy should not be impacted by placement of TIPS.	8.19	1.27	90.0%
CARE OF THE POST-TIPS PATIENT				
Q15. What is the recommended duration of intensive post-procedure monitoring?	Following TIPS creation, we recommend that all patients undergo in-hospital overnight observation at minimum. The level of care during post-TIPS observation should be dictated by the patient's condition, indication for TIPS, and intraprocedural technical complexity.	8.0	1.55	86.7%

Q16. What early laboratory testing and/or imaging is recommended following TIPS creation and at what interval?	Q16a. In all patients undergoing TIPS creation, routine labs (complete blood count, comprehensive metabolic panel, and PT/INR) should be obtained on the day following TIPS creation. Hemoglobin/hematocrit labs may be obtained on the same day of TIPS creation, depending on institution and/or operator discretion.	7.77	1.21	86.7%
	Q16b. Pre-discharge imaging is not indicated in most patients undergoing TIPS creation.	8.08	1.41	86.7%
Q17. Should TIPS venography and intervention be based on ultrasound, clinical findings, or both?	Q17a. In patients who have undergone TIPS creation for management of varices, either Doppler ultrasound findings suggesting TIPS dysfunction, or persistence or recurrence of portal hypertensive complications should prompt TIPS venography and manometry +/- intervention. Ultrasound findings suggesting TIPS dysfunction include alterations in intrahepatic portal vein direction of flow, abnormal flow velocities within the TIPS, and persistent (e.g., > 6 weeks post-TIPS) or recurrent ascites.	8.33	0.82	80.0%
	Q17b. In patients who have undergone TIPS creation for management of ascites and/or hepatic hydrothorax, persistence or recurrence of portal hypertensive complications should prompt TIPS venography and manometry +/- intervention. Medical decision-making should be individualized in patients with well-controlled ascites and/or hepatic hydrothorax and ultrasound findings suggesting TIPS dysfunction.	8.21	0.78	80.0%
	Q17c. In select patients, scheduled TIPS venography with intervention is suggested in the early (1-2 months) post-TIPS period. An example of such a scenario would be TIPS creation in a patient with portal vein thrombosis.	7.22	2.21	80.0%
Q18. What are the optimal techniques for increasing or decreasing TIPS flow when intervention is required?	Q18a. In patients in whom further decrease in portal pressure is desired, we recommend stepwise dilatation of TIPS to its maximum diameter. If it is already at maximum diameter, other interventions to decrease portal pressure (e.g., nonselective beta-blockers, parallel TIPS creation) should be evaluated.	8.04	1.19	80.0%
	Q18b. In patients in whom an increase in portal pressure desired, there is insufficient evidence to recommend a specific technique to reduce portosystemic shunting through a TIPS.	8.23	0.81	80.0%
Q19. Who should see patients with TIPS in follow up?	In patients who have undergone TIPS creation, we recommend that a gastroenterologist or hepatologist and a competent proceduralist (e.g., interventional radiologist) should follow the patient to ensure ongoing management of chronic liver disease, post-procedural complications and to determine any need for potential device revision.	8.0	1.33	90.0%
TIPS IN ASCITES OR HEPATIC HYDROTHORAX (HHT)				
Q1. What is the optimal technical	Q1a. For patients with cirrhosis and diuretic refractory or resistant ascites undergoing elective TIPS, we recommend the use of an ePTFE-covered controlled expansion stent.	8.04	1.73	80.0%

approach to TIPS creation among patients with cirrhosis and refractory ascites?	Q1b. For patients with cirrhosis and diuretic refractory or resistant ascites undergoing elective TIPS, we recommend a staged approach to TIPS creation with an initial procedural stent dilation to 8mm followed by clinical assessment, and then subsequent progressive stent dilation to 9mm and then 10 mm at 6-week intervals if needed to optimize clinical response.	7.92	1.93	83.3%
Q2. Is TIPS associated with better outcomes (mortality, ascites control) than serial large volume paracentesis for the treatment of refractory ascites?	Q2a. For carefully selected patients with cirrhosis and refractory ascites, TIPS is recommended over LVP to prevent recurrent ascites.	8.26	1.02	90.0%
	Q2b. For carefully selected patients with cirrhosis and refractory ascites, TIPS is recommended over LVP to improve transplant-free survival.	8.11	1.15	90.0%
Q3. Is there a threshold of liver dysfunction above which TIPS for refractory ascites should be contraindicated and how should it be defined?	Among patients with cirrhosis and refractory ascites, elevated bilirubin, elevated MELD score and CTP class C cirrhosis are associated with increased post-TIPS complications including mortality. There is insufficient evidence to recommend a cutoff above which any of these measures should be considered a contraindication to TIPS.	7.30	1.92	90.0%
Q4. What is the impact of age on candidacy for TIPS for refractory ascites?	Among patients with cirrhosis and refractory ascites, advanced age is significantly associated with post-TIPS complications including severe hepatic encephalopathy and death. There is insufficient evidence to recommend an age cutoff that should be considered a contraindication to TIPS.	7.44	1.5	90.0%
Q5. What is the role of TIPS in patients with ascites that is not refractory?	In patients not fulfilling a strict definition of refractory ascites but requiring at least 3 large volume paracenteses for tense ascites in a year despite optimal medical therapy, we recommend that TIPS creation should be considered.	8	1.17	86.7%
Q6. What is the role of TIPS in HHT? Is patient selection similar for patients with ascites vs patients with HHT?	For patients with HHT requiring recurrent thoracentesis, we recommend that TIPS should be considered.	7.74	1.32	90.0%

Q7. Is prior liver transplantation a contraindication to TIPS for refractory ascites? Is TIPS a better treatment than surgical shunt, serial LVP or splenic artery embolization in liver transplant recipients with refractory ascites?	Unlike TIPS for ascites and HHT in cirrhosis, there is insufficient evidence to support any recommendation regarding therapy (TIPS and other modalities) in liver transplant recipients with refractory ascites.	7.23	1.73	86.7%
Q8. What is the expected timeline for the TIPS to be effective for reduction of Ascites/HHT?	In the setting of TIPS creation for ascites or hepatic hydrothorax, we recommend using a staged approach by starting with the TIPS stent with the smallest diameter with concomitant use of diuretics as tolerated. Reassessment for need to further dilate the TIPS stent should be performed every 6 weeks.	8.29	1.04	80.0%
TIPS IN VARICEAL BLEEDING				
Q1. When is TIPS indicated in Acute Variceal Hemorrhage?	For acute variceal hemorrhage, we recommend TIPS creation in the following scenarios: • Pre-emptive TIPS in patients who have been successfully banded but who meet high-risk criteria for rebleeding. High-risk criteria are CTP Class C (10-13 points) or CTP Class B >7 points with active bleeding at endoscopy. TIPS should be performed within 72 hours of admission in patients without contraindications to TIPS.	7.46	1.07	86.7%
	• Rescue TIPS in patients who have been successfully banded but who rebleed at any time during admission (after endoscopy).	7.72	1.14	83.3%
	• Salvage TIPS should be performed emergently for patients in whom endoscopic band ligation cannot be performed because of profuse bleeding or bleeding persists at endoscopy despite endoscopic band ligation.	7.04	1.8	86.7%
Q2. When should TIPS be used in the management of bleeding gastric fundal varices or prevention of rebleeding?	Q2a. We recommend that the initial management of bleeding gastric-fundal varices should be based on center expertise. Variceal obliteration/embolization with or without TIPS should be considered for bleeding gastric-fundal varices if unable to be managed endoscopically.	8.04	1	86.7%
	Q2b. For rebleeding gastric-fundal varices after endoscopic therapy, we recommend variceal obliteration with or without TIPS creation.	7.8	1.85	83.3%

Q3. What are the procedural considerations in TIPS creation for variceal hemorrhage?	Q3a. When placing a TIPS for variceal hemorrhage, we recommend a goal PSG of <12 mmHg or 50-60% decrease from initial. We do not recommend using shunt diameter as a procedural endpoint.	7.64	1.11	83.3%
	Q3b. In cases of TIPS creation for variceal hemorrhage, we recommend concurrent obliteration of varices.	7.33	1.59	83.3%
Q4. How should patients be monitored after TIPS creation for variceal hemorrhage?	Q4a. In the setting of TIPS creation for variceal bleeding, we recommend surveillance with Doppler ultrasonography three months after TIPS creation and every six months thereafter in order to monitor for post TIPS stenosis or occlusion.	8.4	0.87	83.3%
	Q4b. If TIPS stenosis/occlusion is suspected or if patient rebleeds after TIPS creation, TIPS venogram with pressure measurements is indicated with consideration of TIPS revision.	8.04	1.29	90%
NOVEL INDICATIONS FOR TIPS				
Q1. Does pre-operative TIPS creation in patients with portal hypertension reduce operative complication and/or improve perioperative outcomes following <u>non-transplant abdominal surgery</u>?	Q1a. In patients with portal hypertension requiring non-transplant surgery, there is insufficient evidence to recommend that preoperative TIPS prevents bleeding complications or the need for blood transfusion during or after invasive non-transplant surgical procedures.	7.88	1.28	83.3%
	Q1b. In patients with cirrhosis without clinically significant ascites, there is insufficient evidence to recommend pre-operative TIPS in abdominal surgery to prevent complications of ascites. In patients with cirrhosis with clinically significant ascites requiring abdominal surgery, a multidisciplinary team approach (hepatology and hepatobiliary surgery) is recommended to individualize the surgical/medical management.	7.92	1.26	83.3%
	Q1c. There is no evidence that preoperative TIPS has an impact on postoperative mortality after invasive non-transplant surgical procedures.	7.08	1.81	86.7%
Q2. Does TIPS creation in patients with <u>cirrhosis and portal vein obstruction</u> facilitate listing for liver transplantation and/or improve	Q2a. In patients with cirrhosis and chronic, complete portal vein thrombosis, portal vein recanalization and TIPS creation could be considered to facilitate transplant eligibility.	8.08	1.13	86.7%
	Q2b. Patients with cirrhosis and complete portal vein thrombosis otherwise being considered for liver transplantation or denied listing due to technical challenges associated with complete portal vein obstruction, should be considered for portal-vein reconstruction and TIPS. Referral to a center with specialized expertise may be necessary.	7.26	1.46	90.0%

outcomes after liver transplantation?				
Q3. Does TIPS creation prevent or reduce portal hypertensive complications in patients with non-cirrhotic portal hypertension due to extrahepatic portal vein obstruction?	Q3a. In patients with non-cirrhotic portal hypertension and acute portal vein thrombosis, we recommend immediate anticoagulation. In those who fail or have a poor response to anticoagulation, we recommend that portal vein thrombectomy/thrombolysis using a transjugular approach with or without small caliber TIPS creation should be considered.	7.85	0.97	86.7%
	Q3b. In patients with acute non-cirrhotic portal vein thrombosis who are not critically ill, evidence is insufficient to recommend TIPS versus anticoagulation alone. We recommend that a trial of anticoagulation be considered initially given the reported rates of venous recanalization.	7.56	1.15	90.0%
	Q3c. In patients with chronic portal hypertension secondary to non-cirrhotic extrahepatic portal vein obstruction that is not responsive to anticoagulation, TIPS may be considered for the same indications as cirrhotic portal hypertension.	7.35	1.35	86.7%
Q4. Does TIPS creation in patients with non-cirrhotic portal hypertension and without extrahepatic portal vein obstruction prevent or reduce portal hypertensive complications?	In patients with chronic idiopathic portal hypertension/porto-sinusoidal vascular disease TIPS may be considered for the same indications as cirrhotic portal hypertension.	7.38	1.39	86.7%
Q5. Does TIPS creation improve outcomes in patients with Budd-Chiari Syndrome?	Q5a. Patients with Budd-Chiari syndrome should be evaluated and managed at centers with experience and expertise in hematological evaluation, clinical management, and percutaneous intervention in this patient population. Ideally the center will also have expertise in liver transplantation, should this be warranted at initial evaluation or during subsequent follow-up. If these resources are not available at the presenting institution, strong consideration of transfer to such an institution should be given while medical management is initiated.	8.04	1.32	90.0%
	Q5b. In patients with Budd-Chiari syndrome who remain symptomatic or without improving liver function after initiation of appropriate medical therapy and who are not candidates for percutaneous revascularization of the hepatic venous outflow tract (short segment obstruction), creation of a percutaneous portosystemic shunt, either TIPS or direct intrahepatic portosystemic shunt (DIPS), should be strongly considered.	8.04	1.02	90.0%
	Q5c. In patients with Budd-Chiari syndrome undergoing TIPS, we recommend close clinical monitoring and imaging follow-up.	7.52	1.42	90.0%

CARDIOPULMONARY CONSIDERATIONS IN TIPS				
Q1. What cardiopulmonary testing is indicated prior to elective TIPS?	Q1a. In patients undergoing elective TIPS creation, we recommend comprehensive echocardiographic evaluation incorporating, in addition to the assessment of left ventricular ejection fraction (LVEF), measurement of left ventricular global longitudinal strain, when feasible, and the contemporary surrogates of left ventricular diastolic function.	7.7	1.29	90.0%
	Q1b. In patients undergoing elective TIPS creation, we recommend assessment of right ventricular function using tricuspid annular plane systolic excursion (TAPSE) and right ventricular systolic pressure (RVSP). Right ventricular strain has not become standard of care in most centers but should be measured if available.	7.12	1.61	86.7%
	Q1c. In patients undergoing TIPS creation who have a right ventricular systolic pressure (RVSP) exceeding 45 mmHg or TAPSE less than 1.6 cm, we recommend referral to cardiology for consideration of right heart catheterization to evaluate for RV dysfunction and pulmonary hypertension prior to TIPS creation.	7.32	1.68	93.3%
	Q1d**.** In patients undergoing TIPS creation, who have tachycardia or bradycardia on physical examination, we recommend pre-TIPS electrocardiographic assessment to evaluate for arrhythmia.	7.46	1.98	90.0%
Q2. Does cirrhotic cardiomyopathy or diastolic dysfunction confer a risk for post-TIPS heart failure?	Q2a. In patients undergoing elective TIPS creation, we recommend considering the presence of systolic and/or diastolic dysfunction, which may suggest cirrhotic cardiomyopathy in the absence of other cardiac history, a significant risk factor for post-TIPS heart failure.	7.92	1.15	80.0%
	Q2b. In patients undergoing evaluation for elective TIPS, we recommend avoiding TIPS if LVEF is < 50% or if there is grade III diastolic dysfunction, given the risk of post-TIPS cardiac decompensation.	7.21	1.71	93.3%
Q3. Can TIPS be safely performed in patients with moderate or severe portopulmonary hypertension?	Q3a. In patients with moderate or severe portopulmonary hypertension (POPH) on treatment (i.e., mean pulmonary artery pressure (mPAP) > 35 mmHg, pulmonary vascular resistance (PVR) > 3 wood units), we recommend significant caution when considering TIPS insertion as it may precipitate right-sided heart failure.	7.64	1.31	93.3%
	Q3b. In patients undergoing elective TIPS who do not have evidence of POPH on screening, we recommend measuring the right atrial pressure at the time of planned TIPS insertion and if > 14 mmHg, we recommend considering right heart catheterization prior to TIPS creation to exclude POPH based on the clinical situation.	7.46	1.28	80.0%
Q4. Can tricuspid regurgitation severity be prohibitive of TIPS creation?	In patients being considered for elective TIPS who have moderate or severe tricuspid regurgitation despite optimization of volume overload, we recommend evaluation for the underlying cardiopulmonary etiology, which can prohibit proceeding with TIPS.	7.56	1.08	83.3%
Q5. Can TIPS treat hepatopulmonary syndrome (HPS)?	We do not recommend TIPS as a therapy for HPS, but it may be considered in patients with HPS who have an established indication for TIPS.	7.7	1.3	90.0%

Q6. Does stent size affect risk for post-TIPS HF in high cardiac risk patients?	In patients with systolic and/or diastolic dysfunction or mild POPH who are undergoing TIPS, we recommend balancing the desired portosystemic gradient with potential worsening of cardiac function by initially deploying the endoprosthesis to 8 mm diameter. If the desired gradient is achieved, no additional dilatation of the shunt should be pursued.	7.36	1.68	83.3%
Q7. Is there a need for post-TIPS echocardiographic surveillance?	In patients with systolic and/or diastolic dysfunction, pulmonary hypertension, or moderate to severe valvular disease, we recommend echocardiographic surveillance at 3 months post-TIPS or earlier, if indicated. Surveillance beyond 3 months can be considered if there is echocardiographic worsening at 3 months (compared to baseline) or if there is clinical indication.	7.0	1.89	93.3%
RENAL CONSIDERATIONS IN TIPS				
Q1. What is the best marker to assess kidney function before or after TIPS?	Q1a. In patients with cirrhosis undergoing TIPS, kidney function should be assessed prior to the procedure either through measurement of serum creatinine or glomerular filtration rate (GFR, estimated or measured). A change in GFR may better capture changes in kidney function, though there is insufficient evidence to recommend one equation over another.	7.37	1.52	90.0%
	Q1b. The optimal method to assess kidney function in cirrhosis patients with sarcopenia or chronic kidney disease is not known.	7.44	1.4	90.0%
Q2. Is there an absolute cutoff for kidney function for which TIPS is contraindicated?	There is insufficient evidence to recommend an absolute serum creatinine, CKD stage, or presence/absence of renal replacement therapy where TIPS creation is contraindicated.	7.19	1.55	90.0%
Q3. What can be done peri-procedurally to reduce the incidence of kidney complications after TIPS? What secondary or tertiary preventive measures can be considered to avoid AKI, acute kidney disease, or de Novo or progressive CKD after TIPS?	Q3a. In patients undergoing TIPS creation for ascites, albumin infusion should be considered in all patients undergoing concurrent paracentesis, and especially for those in whom >5L are removed, to prevent paracentesis-induced circulatory dysfunction and AKI.	7.96	1.7	90.0%
	Q3b. Large volume paracentesis with albumin infusion may be performed either within 24hrs prior to, or concomitantly during TIPS creation.	7.42	1.79	86.7%
	Q3c. Adequate hydration and judicious use of iodinated contrast are rational strategies to help reduce the risk of contrast related injury.	7.96	1.06	90.0%
	Q3d. In patients with AKI/CKD prior to TIPS or in those that develop AKI after TIPS creation, kidney function should be closely followed within 1 week of discharge after TIPS creation.	7.85	1.12	86.7%

Q4. What is the role of TIPS for hepatorenal syndrome (HRS)?	Q4a. There is insufficient evidence to recommend for or against the use of TIPS for treatment of hepatorenal syndrome; however, presence of HRS is not an absolute contraindication for TIPS creation in the presence of other indications (e.g., refractory ascites, variceal bleeding).	7.56	1.31	90.0%
	Q4b. Mortality in patients with HRS undergoing TIPS appears to be driven by liver function (i.e., serum bilirubin, INR), therefore, careful patient selection is recommended.	7.56	1.05	90.0%
HEPATIC ENCEPHALOPATHY AND TIPS				
Q1. When counseling patients, what is the overall risk of overt hepatic encephalopathy after TIPS and what patient specific factors contribute to development of overt HE?	We recommend counseling patients that TIPS is associated with a risk of overt HE in approximately 25-50% of recipients (1b). Patient specific risk factors for development of post-TIPS overt HE include prior history of overt HE, advanced age, advanced liver dysfunction (CTP Class C), hyponatremia, renal dysfunction and sarcopenia (2a).	7.96	1.09	90.0%
Q2. What social factors should be considered a contraindication to elective TIPS as it relates to overt HE?	We recommend avoiding elective TIPS in patients with cognitive impairment and limited family or social support.	7.59	1.25	90.0%
Q3. What is the role for formal evaluation for covert or minimal HE prior to elective TIPS?	In patients being considered for elective TIPS, testing for covert or minimal HE could be considered for prognostication and discussion with the patient.	7.58	1.36	83.3%
Q4. What TIPS stent diameter should be considered with regards to limiting post-TIPS HE?	In patients undergoing elective TIPS for ascites, we recommend starting with a smaller diameter controlled-expansion stent to potentially reduce rates of HE.	7.24	1.33	83.3%
Q5a. Is there a role for collateral	In patients undergoing elective TIPS for ascites and/or hepatic hydrothorax, embolization of spontaneous portosystemic shunts (SPSS) >6mm may be considered in order to reduce the risk of post-TIPS hepatic encephalopathy.	7.52	1.27	80.0%

embolization at the time of TIPS?				
Q5b. Is there a role for TIPS with shunt embolization in the management of refractory HE related to presumed clinically significant portosystemic shunting?	In select patients with large (>6mm) SPSS and refractory HE, we recommend that shunt embolization be considered. For select patients who develop portal hypertensive-associated complications (ascites, varices) after shunt embolization, we recommend that small caliber TIPS creation could be considered.	7.56	1.08	83.3%
Q6a. What is the role for medical prophylaxis to prevent HE after TIPS?	In patients without a history of overt HE undergoing TIPS, we do not recommend medical prophylaxis to prevent HE after TIPS.	7.15	1.56	90.0%
Q6b. What is the recommended medical therapy to treat overt HE after TIPS?	We recommend medical management of post-TIPS overt HE based on current guidelines with the use of lactulose and rifaximin.	8.0	1.07	90.0%
Q6c. What is the role for TIPS stent reduction/occlusion as the treatment of persistent or refractory HE?	We recommend consideration of TIPS stent diameter reduction in patients with persistent or refractory HE post-TIPS.	8.08	0.93	86.7%

Abbreviations: CTP, Child-Turcotte-Pugh; LVEF, left ventricular ejection fraction; TAPSE, tricuspid annular plane systolic excursion; HF, heart failure; RVSP, right ventricular systolic pressure; mPAP, mean pulmonary artery pressure; PFTE, polytetrafluoroethylene; PVR, pulmonary vascular resistance; POPH, portopulmonary hypertension; HPS, hepatopulmonary syndrome; GFR, glomerular filtration rate; CKD, chronic kidney disease; AKI, acute kidney injury; LVP, large volume paracentesis; HRS, hepatorenal syndrome; INR, internationalized normal ratio; HE, hepatic encephalopathy; SPSS spontaneous portosystemic shunt; TIPS, transjugular intrahepatic portosystemic shunt; LVP, large volume paracentesis; MELD, Model for End-Stage Liver Disease; CTP, Child-Turcotte-Pugh; RCT, randomized controlled trial; HHT, hepatic hydrothorax; ePTFE, Polytetrafluoroethylene; PSG, portosystemic gradient; DIPS, direct intrahepatic portosystemic shunt;

Table S2. Technical Approaches to Elective TIPS Creation for Ascites

Approach/Target	Advantages	Disadvantages
Initial dilation to 8mm without consideration of PSG	• The most uniform and reproducible technique across operators and institutions. • Uniform initial use of an 8mm stent is likely to minimize complications of encephalopathy and liver failure	• Does not take into consideration individual patient hemodynamics and thus may be less effective in treating ascites • May delay successful treatment of ascites in some patients
Base the stent diameter on a target PSG; dilate progressively from 8mm to 9mm to 10mm until the PSG reaches a specified value	• TIPS operators are comfortable using PSG as a target value for creating TIPS • There is some support in the literature for using a target values of <12 mmHG or <10mmHg as thresholds for clinical success	• PSG measurements vary based on the definitions operators use, the conditions under which TIPS is performed and the precision and quality of the measurement
Base the stent diameter on a target % reduction in PSG	• % reduction is more targeted to individual patient hemodynamics than an absolute final PSG • Minimizes the concern about PSG measurement definitions and accuracy since the value is “normalized” and is obtained the same way for the pre- and post-measurements	• Requires a % calculation during the procedure that is not intuitive and not commonly performed in real time • Little data for % PSG reduction in TIPS for ascites (more commonly applied to TIPS for bleeding).

PSG: portosystemic pressure gradient; TIPS: Transjugular intrahepatic portosystemic shunt

Table S3. Prospective randomized controlled trials and meta-analyses comparing TIPS v. LVP for refractory ascites (RA)

Prospective Randomized Controlled Trials						
Paper	**N**	**Patient Population**	**Technical details**	**Ascites Outcomes**	**Mortality Outcome**	**Comments**
Lebrec 1996[26]	25 (12 TIPS, 13 LVP) CTP B:17 CTP C: 8	Refractory ascites	Uncovered stents Expanded to a diameter of 10mm 2-3 stents placed per patient	4 month: CTP B: improved in 5/9 TIPS v. 0/8 LVP CTP C: improved in 0% in both groups	2-year survival 29% with TIPS v. 56% in LVP (p<0.05) In CTP B, no difference in mortality	Increased HE in TIPS
Rossle 2000[27]	60 (29 TIPS, 31 LVP)	Refractory ascites or recurrent ascites	Uncovered stents	3 months: 61% v 18% no acsites (p=0.006)	TFS at 1 year 69% TIPS v 52% LVP (p=ns) In multivariable analysis, TIPS associated with TFS (adjusting for age <60, sex, bilirubin < 3 and Na > 125)	HE similar between groups
Gines 2002[28]	70 (35 TIPS, 35 LVP)	Refractory ascites	Uncovered stents Strategy: to reduce PPG < 12	Ascites recurrences 49% TIPS and 83% LVP (p=0.003)	TFS at 1 year 41% TIPS v 35% (n.s)	HE no significant difference except severe
Sanyal 2003[29]	109 (52 TIPS, 57 LVP)	Refractory ascites	Uncovered stents	TIPs superior to LVP in preventing recurrent	No difference in deaths (identical in 2 groups)	Non-significant higher rate of moderate to severe HE

				ascites (p<0.001)	Median TFS times longer in TIPS (19.6 v. 12.4 months) but log rank of TFS overall not significant	
Salerno 2004[30]	66 (33 TIPS, 33 LVP)	Refractory or recidivant ascites	Uncovered stents Strategy: to reduce PPG < 12	TIPs (39%) superior to LVP (97%) in preventing recurrent ascites (p=0.0012)	1 year TFS 77% TIPS v. 52% LVP (p=0.021), TIPS predictive of survival in MVA controlling for MELD	Higher rates of HE
Narahara 2011[31]	60 (30 TIPS, 30 LVP)	Refractory ascites	Uncovered stents Strategy: to reduce PPG < 12 Initially dilated to 6 or 8 mm, then further dilated if PPG > 12	TIPs superior to LVP in control of ascites (p<0.005)	1-year survival 80% TIPS v. 49% LVP (p<0.005)	TIPS associated with increased HE
Bureau 2017[19]	62 (29 TIPS, 33 LVP)	Recurrence tense ascites	Viatorr 10mm covered stent	Decreased LVPs needed in f/u	1 year TFS 93% TIPS and 52% LVP (p=0.003)	No difference on overt HE
Meta-analyses						
Paper	**N**	**Trials included**	**Technical details**	**Recurrent Ascites**	**Mortality**	**Comments**
Deltenre 2005[32]	330	Lebrec Rossle Gines Sanyal Salerno	Uncovered	4 months: 66% v. 23.8%, p<0.001 12 months:	1 year: 61.7% v. 56.5% (ns) 2 years: 50% v. 42.8%	Increased HE

				54.8% v 18.9%, p<0.001		
D'Amico 2005[33]	330	Lebrec Rossle Gines Sanyal Salerno	Uncovered	Pooled OR 0.14 (0.07-0.27)	Pooled OR 0.74 (0.40-1.37)	Metaregression to exclude outlier trial (Lebrec)
Albillos 2005[34]	330	Lebrec Rossle Gines Sanyal Salerno	Uncovered	Pooled RR 0.56 (0.47-0.66)	Pooled RR 0.93 (0.67-1.28)	Random effects model
Saab 2006[37]	330	Lebrec Rossle Gines Sanyal Salerno	Uncovered	3-months OR 0.07 (0.03 to 0.18, P < 0.01) 12-months OR 0.14 (0.06 to 0.28, P < 0.01)	30-days OR 1.00 (0.10 to 10.06, P = 1.0) 24-months OR 1.29, (0.65 to 2.56, P = 0.5)	Cochrane
Salerno 2007[35]	305	Rossle Gines Sanyal Salerno	Uncovered	Tense ascites 42% v 89% (p<0.001)	Actuarial probability of TFS significantly better in TIPS (p=0.035) TIPS associated with better TFS in MVA including ago, TB, Na	Did not include Lebrec study Time to event analysis included Requires IAC criteria for RA
Bai 2014[36]	390	Lebrec Rossle Gines Sanyal Salerno Narahara	Uncovered	OR 0.15 (p<0.001)	TFS HR 0.61 (p<0.001)	Additional study included Time to event analysis included Lebrec study not included in main TFS estimation

CTP: Child-Turcotte-Pugh; TIPS: transjugular intrahepatic portosystemic shunt; HE: hepatic encephalopathy; TFS: transplant-free survival; LVP: large volume paracentesis; PPG: portal pressure gradient; RA: refractory ascites; IAC, International Ascites Club

Table S4: Patients with non-refractory recurrent ascites included in randomized controlled trials

Trial	Definition used
Rossle 2000[188]	Tense ascites that recurred on at least three occasions within a 12-month period despite standard treatment
Salerno 2004[30]	"Recidivant" ascites was defined as recurrence of at least 3 episodes of tense ascites within a 12-month period despite prescription of low sodium diet and adequate diuretic doses
Bureau 2017[19]	Recurrent tense ascites (requiring ≥2 LVP in the previous 3 weeks), but excluding patients who had required >6 LVPs within the previous 3 months

Abbreviations; LVP, large volume paracentesis

Table S5. Summary of selected studies on TIPS for novel indications

TIPS prior to non-liver transplant surgery							
Paper	**Study Design**	**N**	**Follow up Time**	**Indication(s) for TIPS**	**Technical details**	**Outcomes**	**Comments**
Vinet 2006[189]	Retrospective case series with historical controls	35		Elective abdominal operations • Colectomy n=10 • Antrectomy n=5 • Other n=3		• No difference in survival, bleeding, HE, or surgical outcomes	CTP 8 in TIPS group versus 6 in non-TIPS Selection bias an issue Small sample size
Tabchouri 2019[190]	Retrospective case series with concomitant controls	124		Elective abdominal operations; Good selection of operations including colon resection and cholecystectomy		• No difference in severe post op complications or mortality at 90 days • Less ascites post-op in TIPS group • TIPS patients actually required numerically more blood during the operations and post-op	Propensity score analysis helped balance groups, but selection bias still an issue
TIPS in non-cirrhotic portal hypertension due to extrahepatic portal vein obstruction							
Paper	**Study Design**	**N**	**Follow up Time**	**Indication(s) for TIPS**	**Technical details**	**Outcomes**	**Comments**
Fanelli 2011[191]	Retrospective case series	13	Mean 17.4 months	Portal cavernoma • Recurrent variceal	Transjugular portal vein recanalization and ePFTE TIPS	TIPS Technical success 83.3% (10/12)	• 1 patient with shunt failure within 24 hours requiring emergent surgical shunt

				bleeding (n = 8) • Intestinal ischemia (n=2) • High-risk varices with need for anticoagulation (n = 2) • Refractory ascites (n = 1)	placement +/- manual aspiration thrombectomy PSG: 22.9 +/-6 -> 8 +/- 2.7 mmHg	Primary patency through followup: 70% Secondary patency through follow-up: 90% Survival 70% through follow-up (deaths = acute sepsis 6 mo, ischemic stroke 24 mo, neoplasm 6 mo)	• 2 patients with late TIPS dysfunction managed with TIPS revision • 2 patients with isolated single episodes of hepatic encephalopathy during follow up
Qi 2012[192]	Retrospective case series	20	Median 19.9 months	Portal cavernoma with variceal rebleeding or refractory ascites, with absence of cirrhosis and malignancy	Transjugular (n =1), transjugular/transhepatic (n = 4), or transjgular/transplenic (n = 2) portal vein recanalization and bare metal stent TIPS PSG: 26.3 +/- 1.1 -> 12.4 +/- 1.1 mmHg	TIPS technical success 35% (7/20) Primary patency through follow-up: 71% Secondary patency through follow-up: 86% Variceal rebleeding (p = 0.057) • 14% TIPS success • 69% TIPS failure Mortality (p = 0.587)	• No episodes of post-TIPS hepatic encephalopathy

						• 29% TIPS failure • 15% TIPS success	
Klinger 2017[85]	Retrospective case series	17	Median 28.6 months	Acute PVT with imminent intestinal infarction (n=10)	Combination of transjugular thrombectomy, local fibrinolysis and- depending on thrombus resolution- TIPS	Recanalization: 94.1% 1- and 2-year patency: 88.2%	• Major complications (n=3) resolved spontaneously in all but one patient (heparin induced thrombocytopenia type 2 with intestinal infarction) • Symptoms improved in all patients • Segmental bowel resection performed in 11.8% (n=2)
Klinger 2018[86]	Retrospective case series	17 (n=15 with cavernous transformation		Chronic PVT • Variceal bleeding (n=13) • RA (n=2) • Portal biliopathy with recurrent cholangitis (n=1) • Abdominal pain (n=1)	Combo of transjugular balloon angioplasty, mechanical thrombectomy, and depending on extent of residual thrombosis- TIPS and additional stenting of portal venous system	Recanalization: 76.5% Secondary patency: 1-year 69.5% 2-year 69.5%	Complications (n=3): • Intraperitoneal bleeding (n=1) • Liver hematoma, (n=1) • Nosocomial pneumonia (n=1)
Rosenqvist 2016[84]	Retrospective case series	10	Median 17 months (range 1.5 to 72 months)	Acute and chronic PVT • Bowel ischemia (n=4)	Local thrombolysis combined with TIPS	Recanalization: 70% 2-year patency: 70%	

				• Variceal bleeding (n=6)	utilized in 6 of 10	1 death, remaining 9 patients asymptomatic at last follow-up	
Marot 2018[87]	Retrospective case series	15	Mean 42 ± 28 months	Chronic PVT • GI bleeding (n=6) • Portal biliopathy (n=2) • Reduce portal pressure before surgery (n=4) • other (n=3)		Recanalization: 87% 1- and 2-year patency: 77% (87% vs. 60% in patients who received anticoagulation or not, respectively; P=0.3).	PVR is feasible in most patients with non-cirrhotic, non-tumoral portal vein occlusion when there is no extension of the occlusion to distal branches.
TIPS for Idiopathic Non-Cirrhotic Portal Hypertension (INCPH)							
Paper	**Study Design**	**N (TIPS)**	**Follow up Time**	**Indication(s) for TIPS**	**Technical details**	**Outcomes**	**Comments**
Bissonnette 2016[193]	Retrospective multicenter case series	41	Mean 27 +/- 28 months	Biopsy-confirmed INCPH • Refractory variceal bleeding (n = 25) • Refractory ascites (n = 16)	Standard TIPS technique with ePTFE TIPS in 80%, bare metal stent TIPS in 20% PSG: 19 +/- 6 mmHg -> 7 +/- 3 mmHg	Primary patency through follow-up: 73% Secondary patency through follow-up: 100% Variceal rebleeding: 28% Ascites (n = 9 alive at last follow up)	Early mortality 5/41 (1 peritoneal bleeding, 1 heart failure, 2 liver disease, 1 renal failure) Post-TIPS overt hepatic encephalopathy 34% (14/41) Serum creatinine (p = 0.005), ascites as indication (p = 0.04), and significant comorbidities (p = 0.01) associated with death

						• 67% no residual ascites • 33% low-dose diuretic controlled	
Regnault 2018[194]	Retrospective single center series	25	Mean 39 +/- 37 months	Biopsy-confirmed non-cirrhotic portal HTN; if cavernoma, liver histology showed pathology excluding simple extension of extrahepatic PV obstruction • Varices rebleeding prevention (n = 14) • Refractory ascites (n = 5) • Varices and ascites (n = 5) • Prior to cholecystectomy (n = 1)	TIPS prosthesis: • ePTFE (Viatorr) n = 22 • Bare metal stent n = 3 PSG: 14.7 +/- 3.8 -> 5.0 +/- 2.3 mmHg	Patency: • 2 early stent thrombosis Patency Through Follow-Up (n = 20) • Primary 80% • Secondary 100% N = 4 recurrence of presenting symptoms (3 ascites, 1 hemorrhage) between 1-5 months post-TIPS	Mortality 24% (n = 6) over follow-up • n = 1 TIPS-related (stent malposition, liver failure) • n = 2 portal HTN related (1 bleeding, 1 ascites with complications) Overt HE 40% (n = 10) through follow-up • 5/10 responed medical tx • 3/10 TIPS reduction • 2/10 death from complications of hepatic coma

Lv 2019[195]	Retrospective case control series	76 (INCPH TIPS group)	Median 36.4 mo (INCPH group) and 34.3 mo (Cirrhosis group)	Biopsy-confirmed INCPH and variceal bleeding • Emergency TIPS n = 10 • Elective TIPS n = 66	Prosthesis: ePTFE TIPS 78% PSG: 25.5 +/- 4.7 mmHg -> 8.8 +/- 3.5 mmHg	5-year outcomes c/w matched cirrhotic patients: Shunt dysfunction: INPCH 35% CPH 36% (p = 0.627) Rebleeding: INCPH 33% CPH 32% (p = 0.358) Overt HE: INCPH 16% CPH 33% (HR 0.35, p = 0.007) Mortality: INCPH 11% CPH 36% (HR 0.37, p = 0.022)	Single center case-control series demonstrating TIPS in INCPH has similar efficacy for variceal hemorrhage and similar rates of TIPS dysfunction compared with matched patients with CPH undergoing TIPS. However patients with INCPH undergoing TIPS for variceal bleeding had less HE and overall less mortality over 5 years compared with CPH group.
TIPS for Budd-Chiari Syndrome							
Paper	**Study Design**	**N (TIPS)**	**Follow up Time**	**Indication(s) for TIPS**	**Technical details**	**Outcomes**	**Comments**
Plessier 2006[92]	Prospective single center cohort	21	Median 35 months (cohort, n =51)	*Data for full cohort (n=51)* Acute 6% Chronic 69% Acute-on-chronic 25%	BMS 48% ePTFE stent graft 52%	TIPS primary patency 62% through follow-up (30% bare metal stent, 91% ePTFE stent graft)	Clearest criteria for progression through stepwise management algorithm amongst cohort of BCS patients

				Ascites 71% Asymptomatic 6%		TIPS complete clinical response 95%	
Garcia-Pagan 2008[109]	Retrospective single center case series	124	Mean 36.7 months	Ascites 98%	BMS 49% ePTFE stent graft 39% Both 12%	Primary patency 59% over follow-up OS: 87% through follow-up TFS: 1-year 88% 5-year 78% 10-year 69%	Large high quality multicenter retrospective study; BCS-TIPS score developed from cohort as predictor of 1-year OS after TIPS in BCS
Seijo 2013[95]	Prospective multicenter cohort	62	Median 50 months (cohort, n = 157)	*Data for full cohort:* Ascites 82%	BMS versus ePTFE stent graft not reported	TIPS OS: 1-year 88% 3-year 83% 5-year 72% TIPS TFS: 1-year 85% 3-year 78% 5-year 72%	Large, multicenter, prospective cohort study providing highest level of evidence available in BCS
Eldorry 2011[96]	Prospective single center cohort	13	Mean 20 months (cohort, n = 25)	*Data for full cohort:* Fulminant 4% Acute 12% Chronic 84% Ascites 96%	BMS 100%	TIPS Primary Patency: 1-year 62% End of follow-up 62% TIPS Secondary Patency: 1-year 92% End of follow-up 85% TIPS OS:	Small prospective cohort study, TIPS all performed with bare metal stents with expected loss of primary patency, excellent survival

						1-year 100% End of follow-up 100%	
Hayek 2017[110]	Retrospective single center case series	54	Mean 56 months	Subacute 2% Chronic 76% Acute-on-chronic 22% Ascites 93%	ePTFE stent graft 100%	TIPS Primary Patency: 1-year 64% 5-year 45% 10-year 45% TIPS Secondary Patency: Final follow-up 96% OS: 1-year 96% 2-year 88% 5-year 83% 10-year 76%	Large retrospective series with clearly defined management algorithm, follow-up protocol, and outcome definition.
Shalimar 2016[93]	Retrospective single center case series	80	Median 600 days	Acute 8% Subacute 28% Chronic 65% Ascites 86%	BMS + ePTFE stent graft 100%	Primary Patency: 1-year 91% 3-year 86% 5-year 86% OS: 1-year 94% 3-year 89% 5-year 84%	Large modern series using alternative ePTFE construct (BMS + stent graft) with very high primary patency rates and OS. Data did not validate BCS-TIPS PI score as predictor of 1-year survival after TIPS in BCS, although patient population with overall low BCS-TIPS PI scores at baseline
Tripathi 2017[102]	Retrospective single center case series	67	Mean 82 months	Ascites 80%	BMS 30% ePTFE stent graft 70%	Primary patency 5-year BMS 27% 5-hyear ePTFE stent graft 70%	Large retrospective series with exceptionally long mean follow-up;

						Secondary patency 99% OS: 1-year 92% 5-year 80% 10-year 72%	Patency ePTFE stent graft > BMS
Qi 2014[105]	Retrospective single center case series	51	Mean 732 days	Ascites 94%	BMS 65% ePTFE stent graft 35%	Primary patency: 1-year 62% 2-year 44% 5-year 24% OS: 1-year 84% 3-year 77% 5-year 56%	Large series from China confirming technical feasibility of TIPS/DIPS following prior hepatic venous outflow tract obstruction BCS-TIPS PI score was found to predict OS in this series
Rathod 2017[101]	Retrospective single center case series	106	Median 42 mo	Acute 7% Subacute 35% Chronic 58% Ascites 79%	ePTFE stent graft 100%	TIPS patency through follow-up: Primary 87% Secondary 100%	Large retrospective series showing high patency rates over intermediate term with ePTFE stent graft
Sakr 2017[196]	Retrospective single center cohort study	106	1 year	Acute/subcu ate 30% Chronic 79%	BMS versus ePTFE stent graft not specified	TIPS primary patency: 1-year 80% OS TIPS: 1-year 90%	Large retrospective series with good patency and high OS rates at 1-year BCS-TIPS PI score was found to predict OS in this series

Abbreviations: CTP, Child-Turcotte-Pugh; HE, hepatic encephalopathy; TIPS, transjugular intrahepatic portosystemic shunt; PVT, portal vein thrombosis; RA, refractory ascites; PVR, portal vein recanalization; BMS, bare metal stent; ePTFE, expanded polytetrafluoroethylene; BCS, Budd-Chiari Syndrome; OS; overall survival; TFS, transplant free survival; PI, prognostic index; DIPS, direct intrahepatic portosystemic shunt

Table S6. Components of a Comprehensive Echocardiographic Evaluation pre-TIPS.

Left Ventricular Function Assessment	Right Ventricular Function Assessment
• **Systolic Function** ➢ Ejection Fraction (Normal: > 50%) ➢ Global Longitudinal Strain (Normal: absolute value ≥ 18%) • **Diastolic Function*** ➢ Early diastolic transmitral flow to early diastolic mitral annular tissue velocity (E/e′) ratio (Normal: ≤ 14 cm/second) ➢ Septal e′ velocity (Normal: ≥ 7 cm/second) ➢ Left Atrial Volume Index (Normal: ≤ 34 mL/m2) ➢ Tricuspid Regurgitation Velocity (Normal: ≤ 2.8 m/second)	➢ Right Ventricular Systolic Pressure (Normal: Age-dependent, up to 45 mmHg) ➢ Tricuspid Annular Plane Systolic Excursion (Normal: > 1.6 cm)

*Two or more abnormalities are needed to make the diagnosis of diastolic dysfunction. The degree of diastolic dysfunction is to be determined by the cardiologist depending on additional measures such as early to late diastolic transmitral flow velocity (E/A) ratio (at rest or during Valsalva), left atrial strain, and left ventricular strain. Guidance is adapted from the American Society for Echocardiography guidelines and the Cirrhotic Cardiomyopathy Consortium practice guidance.[114, 115]

Figure S1. Mechanisms of TIPS for the treatment of portal hypertension and the effect of TIPS creation on portal, cardiac and renal hemodynamics. According to the peripheral arterial vasodilation hypothesis, pooling of blood in the splanchnic/portal circulation leads to decreased effective circulating volume in cirrhosis.[197] As a means of compensation, there is increased kidney retention of sodium/water and renal vasoconstriction, which leads first to ascites formation, hyponatremia, and later, increased sCr reflecting "functional" kidney injury.[198, 199] TIPS creation for ascites and poor kidney perfusion leads to decompression of portal hypertension, restores end-organ perfusion, alleviates maladaptive vasoconstriction, and decreases retention of sodium/water.[200] Creation of TIPS is associated with transient increase in cardiac index, central blood volume, with deactivation of RAAS, lowering of renin, aldosterone and norepinephrine levels with increase in urinary sodium excretion and renal blood flow.[26-28, 124, 133, 137, 201-212] TIPS is also associated with increased portosystemic shunting which can result in new or worsening hepatic encephalopathy.[166]

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