ADVANCES IN HEPATOLOGY

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Update on Transjugular Intrahepatic Portosystemic Shunt Use in Liver Disease

Justin R. Boike, MD
Assistant Professor of Medicine
Northwestern University Feinberg School of Medicine
Chicago, Illinois

G&H Which patients should be considered for early use of a transjugular intrahepatic portosystemic shunt?

JB There has been some movement away from previous practice approximately 20 years ago when the transjugular intrahepatic portosystemic shunt (TIPS) was reserved only for patients being evaluated for liver transplant. Data now show that many patients with good or preserved liver function can tolerate TIPS as a means of the next step in managing portal hypertensive complications. The main reasons to consider TIPS are refractory ascites and recurrent bleeding varices. Specifically for patients with ascites, guidelines now recommend considering TIPS once a patient has required 3 or more large-volume paracenteses within the past 12 months despite adequate medical therapy, including a low-sodium diet as well as adequate diuretic dosing. This is anchored in robust data, most recently a 2017 paper from Bureau and colleagues in *Gastroenterology* on early use of TIPS at the onset of ascites when patients required more than 2 large-volume paracenteses and still had relatively preserved liver function. These patients had, on average, a Model for End-Stage Liver Disease (MELD) score of 12. The authors demonstrated that patients undergoing early use of TIPS had a 1-year survival of 93% compared with patients randomized to large-volume paracentesis, who had a survival of only approximately 53% in 1 year. Fairly remarkable data support the use of TIPS, which can mitigate the risks associated with ongoing ascites that requires frequent large-volume paracentesis. All of these data are reflected in multiple guidelines and guidance papers, including from the American Association for the Study of Liver Diseases (AASLD), Baveno VII, and the Advancing Liver Therapeutic Approaches (ALTA) study group, whose most recent TIPS guidance paper was published in *Clinical Gastroenterology and Hepatology* in 2022.

As for varices, TIPS is used for patients who have ongoing bleeding varices that are refractory to endoscopy and traditional band ligation. This is considered rescue TIPS, where a patient emergently undergoes the TIPS procedure as definitive treatment for bleeding esophageal varices. The use of preemptive or early TIPS is a newer concept based on an initial landmark study from García-Pagán and colleagues in 2010. This study looked specifically at patients who came to the hospital with an esophageal bleeding variceal event. Patients with Child C cirrhosis and a Child-Pugh score of 10 to 13 and patients with Child B cirrhosis and a score of 8 to 10 as well as active bleeding at the time of endoscopy despite adequate medical management were randomized for

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earlier preventative TIPS. The goal of utilizing TIPS was to prevent future rebleeding and the mortality associated with variceal bleeding. The authors found a significant reduction in the risk of rebleeding after TIPS as well as improvement in overall survival. As a result of that paper and subsequent papers demonstrating similar results, the 2023 AASLD practice guidelines as well as the most recent Baveno VII consensus guidelines in 2022 recommend the use of preemptive TIPS in this specific patient population.

Unfortunately, data from Thabut and colleagues have shown that despite approximately 30% of patients potentially qualifying for preemptive TIPS, less than 10% go on to receive it or are referred to a center that can perform it. This is likely because of a lack of overall understanding and knowledge of the use of preemptive TIPS in this select patient group. Efforts are needed to educate providers to consider preemptive TIPS when patients present to the hospital with a variceal bleeding event.

G&H How should patients be evaluated for TIPS?

JB Evaluating a patient for TIPS ideally should be multidisciplinary, under the direction of a hepatologist or gastroenterologist comfortable in managing patients with cirrhosis as well as in conjunction with discussion with interventional radiology and any other stakeholders pertinent to that patient's care. Baseline evaluation typically includes an echocardiogram as well as standard blood work to calculate the patient's MELD score, which allows providers to risk stratify the patient in terms of proceeding with TIPS. As well, it is always good practice to perform updated cross-sectional contrast-based imaging such as computed tomography triple-phase or magnetic resonance imaging of the liver. This can establish landmarks to assist the interventional radiologist with TIPS placement as well as ensure the absence of hepatocellular carcinoma, other lesions, or biliary obstruction that would potentially contraindicate TIPS.

G&H What have been some of the key findings from the ALTA study group?

JB The ALTA study group has published a variety of papers on TIPS use. Comprised of investigators from multiple academic centers, our work has focused on a large retrospective dataset of more than 1100 TIPS recipients from around 2010 to 2015. We have looked at overall survival and transplant-free survival rates among patients undergoing TIPS in a more contemporary practice. Some results have demonstrated that patients who are undergoing TIPS have different risks for mortality and transplant depending on the TIPS indication, whether ascites or variceal bleeding. We have also identified that a traditional MELD-Sodium score of greater than 20 is probably the inflection point when patients are at higher risk for decompensation and TIPS-related mortality. Several investigators have published other papers looking at post-TIPS renal dysfunction and the risk of ongoing chronic kidney disease. The ALTA study group also put together a consensus conference in 2020 where we reviewed all of the data and literature on the use of TIPS as it relates to North American practice. This guidance paper, which was created for an audience of hepatologists and gastroenterologists regarding the evaluation of candidates for TIPS as well as monitoring for it, was published in 2022 in *Clinical Gastroenterology and Hepatology*. The ALTA study group is currently enrolling TIPS recipients in a prospective registry to try to answer further questions that have been somewhat limited in retrospective studies. This includes the incidence and severity of hepatic encephalopathy, quality-of-life metrics, as well as adjudicating events such as death or need for liver transplant after TIPS to understand more clearly how TIPS is being utilized in a current contemporary practice setting.

G&H What advances have been made in TIPS technology?

JB TIPS technology has changed fairly considerably over the past 30 or so years since its introduction. The original TIPS stents were bare metal stents that were prone to dysfunction and thrombosis. Covered TIPS stents were introduced in the early 2000s and were covered in polytetrafluoroethylene, which significantly reduced the risk of TIPS thrombosis.

More recently, controlled expansion covered TIPS stents were introduced around 2016. These stents allow the interventional radiologist to control the dilation of the TIPS stent, which makes it possible to focus on controlling portal hypertension while avoiding overshunting of portal flow, which can induce hepatic encephalopathy. The stents also allow the interventional radiologist to go in and dilate the TIPS further should the patient require additional lowering of portal pressure to mitigate ascites and variceal bleeding risk. This provides another layer of adjustment that was not possible with prior stent technology.

G&H What potential complications still remain with the use of TIPS, and how can they be best reduced?

JB Hepatic encephalopathy from excessive shunting remains the Achilles' heel of TIPS. We know that TIPS

is very effective at lowering portal pressure, treating ascites, and reducing variceal bleeding risk. The caveat is that this comes with the risk of hepatic encephalopathy, both making it worse in patients who had prior episodes and increasing the risk of a first-time occurrence.

The key to mitigating future risk of hepatic encephalopathy is ideal patient selection. A variety of studies over the years have shown that there are multiple risk factors for hepatic encephalopathy development after TIPS. Patients older than 65 years tend to have higher rates of hepatic encephalopathy. Part of this is probably because of multiple medical issues as well as frailty, which is often related to sarcopenia or low muscle mass. Muscle mass is responsible for metabolism of ammonia, which is related to the risk of hepatic encephalopathy, so low muscle mass is also an important factor. Patients who are severely sarcopenic are at much higher risk of developing spontaneous hepatic encephalopathy as well as having hepatic encephalopathy after TIPS.

Therefore, it becomes important to consider TIPS early in the disease process of refractory ascites before the patient develops significant sarcopenia and frailty; an early TIPS could potentially reduce the risk of sarcopenia by preventing further paracentesis and associated muscle wasting, which could ultimately reduce the risk of hepatic encephalopathy after TIPS. Providers should always consider the patient's risk or prior episodes of hepatic encephalopathy. For example, if a patient had significant episodes of unprovoked hepatic encephalopathy prior to TIPS, that patient probably runs a significant risk of continued hepatic encephalopathy after TIPS as well. If a patient who undergoes TIPS has 3 or more episodes of hospitalization for unprovoked hepatic encephalopathy, providers should consider reducing the diameter of the TIPS to mitigate the future risk of hepatic encephalopathy given the significant impact that hepatic encephalopathy has on quality of life.

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G&H Is there a role for using rifaximin post-TIPS?

JB My suspicion is likely yes, but right now, there are no robust data to support its use arbitrarily in every patient after TIPS. A recent paper by Bureau and colleagues published in *Annals of Internal Medicine* randomized patients to initiating rifaximin 2 weeks prior to undergoing TIPS vs proceeding with standard of care, which typically involves treating hepatic encephalopathy only should it present itself after TIPS. The authors found that patients who started rifaximin and continued it after undergoing TIPS experienced a 20% reduction in their risk of hepatic encephalopathy after TIPS. The caveat is that, owing to insurance constraints, patients may be limited in their ability to afford or obtain insurance coverage for rifaximin if they have not had prior episodes of hepatic encephalopathy; currently, rifaximin is approved by the US Food and Drug Administration only for patients who have had recurrent hepatic encephalopathy despite treatment with standard-of-care lactulose. In my practice, we favor rifaximin prior to TIPS or even after it to mitigate the risk of future hepatic encephalopathy.

G&H Currently, how can patients be best followed after undergoing TIPS?

JB First of all, patients with cirrhosis who undergo TIPS should still be followed at routine intervals. That is partly because there can be a risk of decompensation in the future and those patients should be monitored to make sure they do not require referral for liver transplant evaluation. Patients with cirrhosis also require screening for hepatocellular carcinoma every 6 months. It is important that if patients undergo TIPS, they are not otherwise discharged from the gastroenterology or hepatology clinic; these patients should still follow standard-of-care cirrhosis management.

Regarding complications specifically involving TIPS, the risk of hepatic encephalopathy can persist for many patients and can increase as patients become older or develop worsening sarcopenia. Therefore, it is important that patients still follow up with their care team.

As far as the risk of TIPS dysfunction, meaning that the TIPS stent becomes either thrombosed or narrowed, the indication for the procedure should be taken into account when considering surveillance ultrasound. For example, if a patient undergoes TIPS for ascites, guidelines recommend that they be monitored for their need for ongoing paracentesis. If a patient's ascites is controlled several weeks after TIPS, the patient likely does not require TIPS surveillance ultrasound as long as their ascites remains resolved and they do not require paracentesis.

Contrary to that, patients who had bleeding esophageal or gastric varices should undergo TIPS ultrasounds to ensure TIPS patency at least at an interval of every 6 months. That is because TIPS thromboses or narrowing will not be evident to the provider otherwise and patients may develop variceal bleeding.

G&H Have there been any other changes in the use of TIPS?

JB There is another important use of TIPS, in patients with portal vein thrombosis. Traditionally, TIPS was not technically feasible in patients with cirrhosis who developed portal vein thrombosis because there was no open portal vein to facilitate placement. Our group at Northwestern demonstrated a novel technique of portal vein reconstruction whereby through the use of TIPS and cannulating the portal vein through access across the spleen, it was possible to restore patency and blood flow to the portal vein. Ultimately, we published a report on a group of patients who underwent TIPS with portal vein reconstruction who eventually had restoration of blood flow to the portal vein and were able to go on to receive a liver transplant; historically, portal vein thrombosis was a relative contraindication to liver transplant and added to the surgical complexity if transplant was offered.

This is a novel approach and technique that utilizes TIPS to restore portal blood flow in patients who have had chronic portal vein thrombosis. This has now moved into AASLD guidelines, especially if a patient is being considered for liver transplant. Our group has also expanded this use outside of patients with cirrhosis to noncirrhotic patients who develop portal vein thrombosis and specifically develop portal hypertension complications mostly in the form of bleeding esophageal or gastric varices. We have published reports on our experience in noncirrhotic patients undergoing TIPS with portal vein reconstruction with good patency of TIPS as well as restoration of portal blood flow. That has expanded the framework as well as utilization of TIPS in this patient population.

G&H What are the priorities of research involving TIPS?

JB There is always a desire to move the field forward. As mentioned, the ALTA study group is looking at a prospective registry of patients undergoing TIPS to understand the pattern of referral as well as risk of hepatic encephalopathy after TIPS in structured interviews and follow-up. One area that continues to warrant further research is the use of TIPS to manage portal hypertension prior to a patient undergoing abdominal surgery. Historically, patients with cirrhosis who have portal hypertension are not surgical candidates for abdominal surgery because of the risk of bleeding as well as the risk of complications associated with portal hypertension. This remains an area that is relatively understudied. One of the benefits of the ALTA study group is that we can pull in practice patterns from multiple centers regarding the use of TIPS in patients prior to abdominal surgery to gain additional information regarding patient selection. Right now, determining whether a patient should be considered for TIPS prior to abdominal surgery should be an individual, case-by-case discussion with the hepatologist as well as the surgeon with a clear understanding of the patient's portal hypertension and degree of liver function to guide the decision-making process.

Disclosures

Dr Boike has received investigator-initiated funding from WL Gore and Associates, manufacturer of TIPS endoprosthesis.

Suggested Reading

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