Position Paper

Consensus conference on TIPS management: Techniques, indications, contraindications

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A B S T R A C T

The trans jugular intrahepatic Porto systemic shunt (TIPS) is no longer viewed as a salvage therapy or a bridge to liver transplantation and is currently indicated for a number of conditions related to portal hypertension with positive results in survival. Moreover, the availability of self-expandable polytetrafluoroethylene (PTFE) covered endoprostheses has dramatically improved the long-term patency of TIPS. However, since the last updated International guidelines have been published (year 2009) new evidence have come, which have open the field to new indications and solved areas of uncertainty. On this basis, the Italian Association of the Study of the Liver (AISF), the Italian College of Interventional Radiology—Italian Society of Medical Radiology (ICIR-SIRM), and the Italian Society of Anesthesia, Analgesia and Intensive Care (SIAARTI) promoted a Consensus Conference on TIPS. Under the auspices of the three scientific societies, the consensus process started with the review of the literature by a scientific board of experts and ended with a formal consensus meeting in Bergamo on June 4th and 5th, 2015. The final statements presented here were graded according to quality of evidence and strength of recommendations and were approved by an independent jury. By highlighting strengths and weaknesses of current indications to TIPS, the recommendations of AISF-ICIR-SIRM-SIAARTI may represent the starting point for further studies.

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Introduction

Portal hypertension (PH) is one of the major complications of cirrhosis. The trans jugular intrahepatic porto systemic shunt (TIPS) has been an established procedure in the treatment of the complications of portal hypertension, including bleeding oesophageal
varices, refractory ascites, hepatic hydrothorax, type-2 hepatorenal syndrome, and more recently, Budd–Chiari syndrome and veno-occlusive disease. However, despite these broad applications, many clinical aspects remain controversial. The multispecialistic contribute to patient selection and TIPS management have led the Italian hepatologic community to produce a consensus statements aimed to the reassessment of the technical and clinical aspects.

Methods

The goal of this document was to provide clinical guidelines for the proper management of TIPS. Promoter of this “Consensus Guidelines” was the Italian association for the Study of Liver (AISF). The Consensus was endorsed by: ICIR (Italian College of Interventional Radiology), SIRM (Italian Society of Medical Radiology) and SIAARTI (Italian Society of Anesthesia, Analgesia and Intensive Care).

According to the PNLG (National Plan for Guideline), the promoter identified a Scientific Board of Experts. The Scientific Board defined methodology, goals and acted as developer and reviewer.

The methodology chosen involved the following steps:

2. For each topic a working party was identified by both the Promoters and the Scientific Board, and was composed by a group of at least four experts guided by a chairman. The chairman, together with the promoters and the Scientific Board, selected the relevant clinical questions aiming at focusing on the clinical practice and controversial areas. The questions were circulated within the working groups to refine the topics and to avoid duplications. The members of the working parties were identified on the basis of competence, role, expertise and publication/research in the field of end stage liver diseases and liver transplantation.
3. Each working group independently carried out a systematic literature search and review, between October 2014 and May 2015, using Medline/Pub Med to support definitions and statements. Each recommendation was graded according with the Oxford grading system (Appendix 1 in Supplementary material).
4. The working groups elaborated the proposed statements, graded according with the selected grading system. They prepared the statements together with the presentation of the literature review for each topic during phone conferences, group meetings and mailing exchange before the Consensus Conference (between February and May 2015).
5. The jury members were nowhere involved in the selection, preparation and discussion of the topics and statements prior to the Consensus Conference.
6. All the promoters, members of the Scientific board, working groups, and Jury invited to participate to the Consensus conference were asked to declare any potential conflict of interests.
7. On June 4th and 5th, 2015 a Consensus Meeting was held in Bergamo. The consensus group consisted of a total of 102 participants (promoters, Scientific Board, Working Groups, and Jury). The jury was selected among Hepatologists, Radiologists, Surgeons, Methodologists, Intensive care physicians, epidemiologists, patient representatives and ethicists. During the first sessions the chairman of each group presented the selected topics and the proposed statements. A general discussion was held in order to refine the. At the end of the general session each group met independently to re-elaborate the final statements to be presented in the voting session according to the advices received by the jury. The final general session consisted in the presentation of the statement by the chairman of each working group, followed by a public vote from the jury. The agreement was reached if over 73% of the voters agreed upon a two-levels score (Agree, Disagree).
8. The format of this document, drafted by the writing committee, includes the questions, the statements, the quality comments by the working group chairmen, the percentage of agreement of the jury and the selected references.

SESSION 1—TIPS placement technique

Although no clear definition of technical skills and relative learning curve exists, only a physician with elevated knowledge in both hepatic and cardiopulmonary hemodynamic, should perform TIPS placement [1–7].

Steps required for proper TIPS placement

1. Creation of a vascular access by the puncture of the internal jugular vein, which must be performed under US guidance [2].
2. Catheterization of one of the hepatic veins, which can be also punctured percutaneously under real time US guidance when its ostium is not easily accessible [3]. When hepatic veins are occluded (Budd–Chiari syndrome), portal vein branches can be reached by direct puncture from the inferior vena cava [4–11].
3. Puncture through the liver parenchyma of one of the main branches of portal vein with or without real time ultrasound guidance [12].
4. Measurement of the portal-systemic pressure gradient (PPG) by a digital recording system properly set-up for venous pressure [13,14]. Inferior vena cava and not right atrium blood pressure should be subtracted to portal vein pressure to calculate the gradient [15].
5. Balloon dilatation of the parenchymal tract between the hepatic (or inferior vena cava) and portal vein.
6. Deployment of the stent within the parenchymal tract.
7. Hemodynamic assessment of the resultant PPG reduction followed by further balloon dilatation of the lumen to reach the desired target of pressure gradient [14,16]. PPG measurement upon recovery from deep sedation should be considered at least in patients with variceal bleeding as an indication [14,17].

The use of bare metal stents to perform TIPS has been associated with high rates of dysfunction and recurrence of portal hypertension complications [14]. Stents covered with polytetrafluoroethylene (PTFE—endoprostheses), have proven to warrant long-term patency [18]. Dysfunctions occurring with the use of new generation TIPS sets (early thrombosis, later stenosis) appear to be highly dependent upon the operative skills and the accuracy of placement technique [19–21]. Clinical and technical indications, success rates (>90%) and complications (<5%) of TIPS should be monitored periodically in each Center [22,23].

Statements: technical consideration and patients selection

1.1. Where should a TIPS procedure be performed and who should do it?

Statement 1.1

1.1.1. TIPS should only be performed in tertiary care centres by interventional radiologists or specially trained physicians experienced in: (a) portal vein catheterization either through a hepatic vein or the inferior vena cava; (b) assessment and interpretation of invasive hepatic and cardiopulmonary hemodynamic; (c) trans catheter embolization, and (d) management of procedural complications (5, D) [15,24–26].

1.1.2. The decision to perform a TIPS should be reached by an expert team made of one hepatologist (clinical indication) and an interventional radiologist (technical feasibility); in high risk patients, the decision to place a TIPS should be based on liver transplantation candidacy and a transplant surgeon should also be involved in the evaluation period (5, D) [24,27].

1.1.3. Clinical and technical indications, success rates (>90%) and complications (<5%) of TIPS should be monitored periodically in each Center (5, D) [22,23].

Votation 1.1: Votes in Favour: 96%.
1.2. Which imaging studies are needed prior to TIPS placement?

Statement 1.2
Doppler ultrasonography (Doppler-US) and cross-sectional liver imaging by computed tomography (CT) or magnetic resonance (MR) are appropriate to identify anomalies in liver anatomy, to rule out intrahepatic masses, to assess both portal and hepatic vein anatomy and patency and to plan the procedural approach (5, D) [22,24,25].

Votation 1.2: Votes in Favour: 100%
Comment: Before TIPS placement, a vascular and anatomical study of the liver should be performed in order to assess both technical feasibility and anatomical contraindications to the creation of the shunt. To this end, there is no evidence to support the use of CT or MR rather than Doppler US [22,24,25].

1.3. Which are the techniques to access the portal vein for TIPS placement?

Statement 1.3
1.3a. The internal jugular vein is the first-choice peripheral vascular access for TIPS placement. For anatomical reasons, the right internal jugular vein is preferred (5, D) [2].
1.3b. US-guided puncture of the vessel is needed in order to decrease the complications (1a, A) [2].
1.3c. In case of unsuccessful trans jugular catheterization of the hepatic vein, a US-guided percutaneous puncture of the hepatic vein can be performed (4, C) [3].
1.3d. In absence of available hepatic veins, a direct puncture from the inferior vena cava can be performed (4, C) [4–6].
1.3e. The portal vein should be punctured under real time ultrason sound guidance to reduce complications due to capsule perforation or accidental puncture of arteries, ectasic bile ducts and masses (cysts, haemangioma, tumours) along the parenchymal tract of TIPS (5, D) [7,9,10,12].

Votation 1.3: Votes in Favour: 100%

1.4. Which is the technique for measuring the portal-systemic pressure gradient (PPG)?

Statement 1.4
1.4a. Baseline and post procedural portal-systemic pressure gradient (PPG) should be calculated subtracting the inferior vena cava pressure (measured at the level of the hepatic vein and TIPS outflow level, respectively) to the portal vein pressure (2b, B) [14,15].
1.4b. Deep sedation with propofol and remifentanil adds substantial variability and uncertainty to PPG measurements. This limitation needs to be considered whenever hemodynamic measurements are obtained under this condition (2b, B) [28].
1.4c. Reduction of PPG to less than 12 mmHg should be achieved when the indication is bleeding from oesophageal varices (1b, A) [14]. This is still an uncertain hemodynamic target in patients with refractory ascites (5, D) [24,25].

Votation 1.4: Votes in Favour: 100%
Comment: PPG value after TIPS placement can be underestimated in deep sedated patients: repetition of PPG measurement a few days following the procedure is advisable in case of incomplete clinical response particularly in bleeding patients. [14,28].

1.5. Which types of device are available for TIPS?

Statement 1.5
1.5a. Dedicated ePTFE-covered stents should be preferred over bare stents in order to reduce the risk of shunt dysfunction (1b, A) [18–20,29–31].

Votation 1.5: Votes in Favour: 100%
Comment: Two RCTs [32,33] and a meta-analysis [29] of six studies (one prospective and five retrospective) comparing TIPS placement with PTFE-covered stents and bare stents for portal hypertension related complications showed that the covered stent was superior in terms of shunt dysfunction (HR = 0.28; 95% CI 0.20–0.35).

1.6. Which is the proper stent diameter for TIPS?

Statement 1.6
1.6a. A step-wise procedure based on the progressive dilatation of 10-mm diameter covered stents by using balloon catheters of increasing diameter might be used. The extent of dilatation can be considered acceptable when the target PPG is reached (in case of variceal bleeding) (1a, A) [14] or an adequate clinical response is obtained (in case of refractory/recidivant ascites) (4, C) [14,25,31,32].
1.6b. There is not enough evidence to support the use of 10-mm rather than 8-mm nominal diameter PTFE-covered stents aiming to achieve a better control of portal hypertension complications (5, D) [33,34].

Votation 1.6: Votes in Favour: 100%
Comment: A randomized, single centre, open label, active control trial [33], which was aimed to demonstrate a potential benefit of 8-mm in comparison to 10-mm covered stents in reducing the risk of post-TIPS encephalopathy, was early interrupted after enrolling 39% of the calculated sample size (45 of 114 patients) due to the apparent worse control of ascites in patients treated with smaller stent grafts. Despite that, most operators perform TIPS using a 10 mm stent dilated to 8 mm (with subsequent calibration up to 10 mm depending on post-procedure portocaval gradient) [33,34]. A step-wise procedure based on the progressive dilatation of 10 mm diameter stents at TIPS positioning or at delayed time points during follow up can be also applied in ascitic patients with the goal to achieve a portal-pressure gradient <12 mmHg [14,25] and or an adequate clinical response [31,32].

1.7. Is there a need for US-Doppler follow up immediately after TIPS placement?

Statement 1.7
Doppler-US follow up surveillance should not be routinely performed in properly placed ePTFE-covered stents (4, C) [35–39].

Votation 1.7: Votes in Favour: 87%
Comment: A single evaluation within the first 7 days should be performed when bare metal stents are implanted, technical difficulties occurred or in case of incomplete clinical response. The evaluation of flow direction in the intrahepatic portal vein branches is a reliable qualitative indicator of TIPS malfunction [35,36,38,39].

1.8–11. Sedation and patient monitoring

Statement 1.8
Monitored anesthesia care (MAC) should be administered by an anaesthesiologist (4, C) [40].

Votation 1.8: Votes in Favour: 100%

Statement 1.9
Monitored anesthesia care (MAC) and moderate sedation should be adopted as routine procedures during TIPS (4, C) [24].

Votation 1.9: Votes in Favour: 96%

Statement 1.10
Propofol and remifentanil, which enable a fast recovery after sedation in cirrhotic patients, represent the first choices for sedation or GA (2b, B) [41–44].

Votation 1.10: Votes in Favour: 100%

Statement 1.11
1.11a. All patients undergoing general anesthesia or deep or moderate sedation require continuous monitoring of vital parameters (level of consciousness, ventilation, oxygenation status, and hemodynamic variables) (2a, B) [40].
1.11b. Patients who have received GA or MAC shall receive appropriate post-Anesthesia care (2b,B) [45].
1.11c. Discharge of the patients should be upon anaesthesiologist care (4, C) [45].

Votation 1.11: Votes in Favour: 100%
Comment: Patients undergoing TIPS placement often present with critical conditions (liver dysfunction, large amount of ascites, recent
haemorrhagic shock) with a mental status that can indeed influence the cooperation and the tolerance of the procedure. Moreover TIPS positioning can be an uncomfortable and prolonged procedure requiring analgesics and sedatives administration, which could facilitate the transition to (GA) with or without intention, and could precipitate adverse physiological responses in particularly frail patients [45]. The choice between GA and MAC depends on the patient physical conditions, mental state and ability to collaborate during the procedure. In the absence of randomized controlled trials, GA with endotracheal intubation represents the ideal option for critical patients who are at risk for aspiration during the procedure [46–48]. Chronic liver diseases are associated with variable and non-uniform reductions in drug-metabolizing activities. These conditions make it difficult to define the ideal dosages of drugs in cirrhotic patients. To avoid respiratory depression and to reduce their hemodynamic impact, anaesthetic and analgesic drugs used during TIPS placement should be easily titratable and/or rapidly antagonized [22,40]. The anaesthetist, depending on the type, will define the frequency of monitoring and its invasiveness and amount of medication administered, the length of the procedure, and the general condition of the patient. Particular attention should be given to monitoring oxygenation, ventilation, circulation, level of consciousness and temperature [45,49].

1.12. Which are the contraindications to TIPS positioning?

Statements 1.12

1.12a. The absence of vascular accesses represents the only technical contraindication to TIPS positioning (4, C) [3].

1.12b. The presence of portal vein thrombosis resulting in a portal cavernoma is not an absolute contraindication in presence of a “portal” landing zone with adequate flow and caliber to receive the device (4, C) [9,10]. See statements on PVT.

1.12c. Clinical contraindications to TIPS placement are:

- Severe liver failure (Child–Pugh > 11, serum bilirubin > 5 mg/dL, MELD > 18) (1a) [50].
- Severe organic renal failure (serum creatinine > 3 mg/dL) (1a).
- Heart failure (1a).
- Severe porto-pulmonary hypertension (mPAP > 45 mmHg at RHC) (1a).
- Recurrent or persistent overt hepatic encephalopathy grade ≥ 2 (West-Heaven scale) despite adequate treatment (1a).
- Uncontrolled sepsis (1a).

Votation 1.12: Votes in Favour: a–b 87%, c 96%.

Comment: Relative technical contraindications are anatomical conditions associated with a reduction in technical success rate or with an increased risk of complications, such as liver tumours, the presence of multiple hepatic cysts. The clinical appropriateness of TIPS positioning should be evaluated on a case-by-case basis according with the relevance of the indication and the presence of general contraindications. Indeed, in the context of a life threatening condition such as acute variceal bleeding (with a trickier assessment of liver failure), a broader range can be adopted (Child C score <14).

1.13. How to prevent post-TIPS complications (contrast induced nephropathy—CIN)?

Statements 1.13

1.13a. Fluid hydration with normal saline should be considered in patients at risk of renal impairment when undergoing TIPS placement (3, B).

1.13b. The efficacy of NAC or other drugs in reducing the incidence of CIN remains unproven and their use cannot be recommended (1a, A).

Votation 1.13: Votes in Favour 100%.

Comment: Contrast-induced nephropathy (CIN) identifies an acute renal failure developed after administration of radio contrast in the absence of other identifiable cause. It is defined as an absolute increase of serum creatinine of 0.5 mg/dL or of 25% from baseline. The rate of CIN is extremely low in patients with eGFR > 60 mL/min. It increases in patients with pre-existing renal impairment, diabetes, many intra-arterial contrast procedures and eGFR < 45 mL/m [51,52]. A cautious use of saline should be made in patients treated by TIPS for recurrent ascites with covert diastolic dysfunction, due to the increased risk of cardiac overload after the procedure.


Statements 1.14

1.14a. Routine antibiotic prophylaxis should not be performed prior to TIPS placement (4, C) [53].

1.14b. If long or complex TIPS placement procedure is anticipated (portal vein thrombosis, multiple stenting, trans parietal punctures, etc.), antibiotic prophylaxis (single dose of ceftriaxone or ampicillin/sulbactam) should be considered (3, D) [54–57].

Votation 1.14: Votes in Favour: 100%.

Comment: Early events: Bacteremia after TIPS (defined by fever >38.5 °C, or leucocytosis >15,000³ and positive blood cultures) ranges between 2–25% (54–56, 58) and in a prospective RCT was not influenced by antibiotic prophylaxis [53]. A longer duration of procedure, multiple stenting and the maintenance of a central venous line are associated with a higher risk of infection after TIPS. In patients with uncomplicated procedure, the trans jugular venous access should be removed at the end of the intervention [53,57]. A single dose of long acting cephaloridine reduces the incidence of bacterial infection (20–26%) justifying its use in anticipated complex procedures [54]. Late events: Endotipsitis is defined by the presence of sustained bacteremia associated with the evidence of thrombus or vegetations inside the TIPS. This clinical condition is rare (1%). Early endotipsitis (<120 days of the procedure) is usually related to Gram-positive organisms and the antibiotic therapy must be long-lasting (at least 3 months) to avoid recurrence [58]. In patients with uncontrolled or recurrent infection liver transplant should be considered [59]. There is no evidence for adopting long-term prophylaxis for the prevention of endotipsitis.

1.15. Are blood products routinely required during TIPS placement?

Statement 1.15

1.15a. Fresh frozen plasma, or pro-haemostatic agents are not required in cirrhotic patients undergoing TIPS, irrespective of INR value (2a, C) [60,61].

1.15b. Although the threshold of platelet count needed to ensure normal primary haemostasis in cirrhosis is not clearly defined, the 50 × 10³/L cut-off can be utilized for platelets infusion before TIPS (4, C) [62].

Votation 1.15: Votes in Favour: 100%.

Comment: A specific evaluation of the bleeding risk in patients undergoing TIPS has never been reported. In cirrhotos, routine coagulation tests cannot define the coagulation status and the bleeding risk. Several observational and randomized placebo-controlled studies have shown that prothrombin time (PT) is a poor predictor of peri- or post-operative bleeding in patients with cirrhosis [60,61,63]. In most invasive procedures, a 50 × 10³/L platelets cut-off is utilized for defining the need for blood product to correct preoperative laboratory values. However, the proper cut-off number for platelets has never been identified (even though a number >60 × 10³/L has been proven adequate, but in experimental models only [62,64]. Close monitoring for evidence of bleeding during the procedure rather than a prophylactic attitude represents the most adequate approach.

Cardiac dysfunction

1.16. Which is the role of pulmonary arterial hypertension (PAH) and how to perform a pre-TIPS cardiac assessment and?

Statement 1.16

1.16a. Doppler echocardiography (ECHO) is suggested in ALL CANDIDATES TO TIPS (5, D) [65–69].

1.16b. A systolic pulmonary artery pressure (sPAP) > 50 mmHg at ECHO or history of congestive heart failure, tricuspid regurgitation and cardiomyopathy justify the execution of a right heart catheterization (RHC) to confirm and properly define pulmonary hypertension (PAH):
a) Severe PAH (mean pulmonary artery pressure, mPAP, >45 mmHg at RHC) represents an absolute contraindication to TIPS (5, D) [24,70–74].
b) Moderate PAH (mPAP between 35–45 mmHg) with elevated pulmonary capillary wedge pressure (PCWV >15 mmHg) on right heart catheterization is a relative contraindication and requires particular attention for the indication (only in patients with variceal bleeding refractory to endoscopic/pharmacologic treatment), the procedure (small calibre TIPS) and the management (prevention of cardiac overload) (5, D) [68,75–77].
c) Mild PAH (mPAP between 25–34 mmHg) does not represent a contraindication to TIPS (5, D) [68,75–77].

Votation 1.16. Votes in Favour: 100%.
Comment: New-onset chronic cardiac dysfunction have been recognized in cirrhotic patients in the absence of known cardiac disease, irrespective of the aetiology of cirrhosis and related, at least in part, to the hyper dynamic circulation [68,75]. The disease is generally unapparent at rest and becomes manifest under pharmacological or physical stress as infection, haemorrhage, large volume paracentesis, and exercise. Left ventricular (diastolic) dysfunction may be a significant factor in the development of ascites and hepatic encephalopathy [65,66,68,77,78] as well as pulmonary arterial hypertension (PAH, defined as mPAP ≥25 mmHg). This condition is not frequent in cirrhotic patients with portal hypertension (up to 16% in transplant candidates).

The incidence of cardiac dysfunction after TIPS is unknown and no reliable predictors are available at the individual patient level. Pulmonary oedema occurs in 10–12% of patients receiving TIPS for ascites and some cases of ascites recurrence after TIPS may be due to heart failure rather than portal hypertension [66,68,75,77,78]. From the haemodynamic stand point, liver transplantation shares similarities with TIPS. Data from liver transplantation indicate that severe pulmonary arterial hypertension is an absolute contraindication because of poor outcome [71–73]. In this setting, moderate or severe PAH is expected when sPAP by ECHO is >50 mmHg. Therefore, a sPAP greater than 50 mmHg at ECHO represents the cut-off point for executing a RHC. At RHC, a mPAP greater than 45 mmHg represents a contraindication to TIPS [24,70–74,79].

1.17. Is there a risk for hepatic encephalopathy after TIPS?

Statement 1.17

TIPS is associated to an increased incidence of severe HE. (1a) Thus, the risk factors for HE should be always considered before TIPS placement (A)(Table 1).

Votation 1.17: Votes in Favour: 100%.
Comment: Hepatic encephalopathy (HE) is one of the major complications of TIPS. Notwithstanding, scarce are the studies directly aiming at the assessment of HE in relation to TIPS placement. Bearing in mind these limitations, the incidence of overt episodic or recurrent HE post-TIPS varies between 15 and 67% in a 2-year follow-up. The incidence of persistent overt HE is around 8% [80] and that of de-novo, covert HE around 35% [14,26,81–88].

1.18. Is there a need for routine prophylaxis of hepatic encephalopathy post TIPS placement?

Statement 1.18

1.18a. Prophylaxis of post-TIPS HE with either lactulos or rifaximin is not routinely recommended (1b) [88].
1.18b. Stent lumen reduction or occlusion is effective in case of persistent overt post-TIPS HE (2b, B) [89,90].

Votation 1.18: Votes in Favour: 100%.
Comment: The diagnosis and the treatment of post-TIPS overt and covert HE is not different from that of overt or covert HE occurring independently of the procedure and should be performed according to the joint EASL/AASLD guidelines. Stent lumen reduction/occlusion should be performed only in case of persistent overt HE [89–91].

Table 1

<table>
<thead>
<tr>
<th>Main risk factors for post-TIPS HE.</th>
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<tbody>
<tr>
<td>• Advanced age (1a)[48,39,91]</td>
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<tr>
<td>• High Child-Pugh and MELD score (1a)[48,81,85]</td>
</tr>
<tr>
<td>• History of hepatic encephalopathy (1b)[31,81,82,84]</td>
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<tr>
<td>• Baseline arterial hypertension (1a)[48,33]</td>
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<tr>
<td>• High serum creatinine and hyponatraemia (Na &lt; 130) (1a)[48,80,82]</td>
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<tr>
<td>• Low serum albumin levels (1b)[80]</td>
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<tr>
<td>• Bare vs. covered stent (2b)[85]</td>
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<tr>
<td>• Very low porto-systemic pressure gradient after TIPS (&lt;5 mmHg) (1a)[25,78–83,87]</td>
</tr>
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</table>

4 Child A risk of HE close to 0, in Child B up to 33%, in Child C up to 80%.

SESSION 2: TIPS for portal hypertension complications: portal hypertension-related bleeding in cirrhotic patients

The management of bleeding complications differs according to severity of the underlying liver disease and the stage of PH, ranging from primary prophylaxis of variceal bleeding to treatments aimed at controlling acute variceal bleeding or to prevent rebleeding. HVPG measurements in these settings has clearly been established as a clinically relevant diagnostic and prognostic tool [92]. The management of PH-related bleeding in cirrhotic patients includes endoscopic techniques, vasoactive drugs (somatostatin and vasopressin analogues), and TIPS.

2.1. Is TIPS indicated for primary prophylaxis of first variceal bleeding?

Statement 2.1.

2.1.2 TIPS is not indicated for the prophylaxis of first variceal bleeding (1a,A).

Votation: 2.1 Votes in Favour 100%.

Comment: The incidence of first bleeding in cirrhotic patients with oesophageal varices (EV) ranges from 5% to 15% per year and the associated mortality is about 15–20%. A meta-analysis of shunt surgery trials has conclusively shown an unacceptable burden of mortality and HE [93] in primary prophylaxis. Until RCTs are available for TIPS in this setting, results from derivative surgery must be extrapolated to percutaneous shunting as primary prophylaxis [24].

2.2. How should acute bleeding treatment failure be managed?

Statement 2.2

2.2a. Persistent bleeding and rebleeding taking place within the first five days from the index bleeding, despite appropriate combined pharmacological and endoscopic treatments, should be managed by covered-TIPS (2b,B).

Votation 2.2 Votes in Favour 91%.

Comment: Variceal bleeding is unresponsive to initial combined pharmacological and endoscopic treatments in 10–20% of cirrhotic patients. If treatment failure leads to mild bleeding and the patient is stable, a further endoscopic haemostasis may be attempted. In case of severe bleeding, derivative treatment must be considered [92,94–97]. Both TIPS and surgical shunts are extremely effective in controlling variceal bleeding (control rate approaching 95%). TIPS represents the first choice due to the intolerable surgical risk in decompensated cirrhotic patients [18,98]. Regrettably, following development of systemic complications or deterioration of liver function, mortality remains high even when TIPS is applied as a rescue therapy. Prognostic scores are helpful in the decision-making in order to accelerate TIPS referral in high-risk subjects [99] before a further deterioration of the patient’s clinical status occurs, affecting the outcome of derivative treatments. In more compromised cases it is advisable to perform TIPS in accordance with the liver transplantation team.

2.3. Which is the role of “early TIPS” in acute bleeding high-risk patients?

Statement 2.3

Early TIPS (within 72 h, ideally <24 h from bleeding, and after initial combined pharmacological and endoscopic therapy) is effective in controlling bleeding from EV, GOV1 and 2 in patients at high risk of treatment failure defined as:
a) Child–Pugh class C (<14 points)
b) Child–Pugh class B with active bleeding at index endoscopy (1b, A).

**GVO**1 and 2: gastro-oesophageal varices type 1 and 2.

Votation 2.3 Votes in Favour 100%.
Comment: Available RCTs support the role of TIPS in patients with a high risk of treatment failure. Patients with HVPG levels >20 mmHg recorded within 24 h from bleeding [100] or in a Child–Pugh class C (<14 points) or actively bleeding at index endoscopy and in Child–Pugh class B [101] have been suggested to have a poor outcome. In such high-risk subjects [101] receiving TIPS within 72 h from bleeding, failure to control bleeding or to prevent rebleeding and mortality were significantly lower (3% vs. 45% and 13% vs. 39% at 1 year, respectively) without an increased risk of HE [102–104]. However, in recent surveillance studies, a survival benefit was not observed [102,105], although it approached statistical significance in one [101].

2.4. Which is the role of TIPS in failure of secondary prophylaxis of variceal bleeding?

**Statement 2.4**

In patients rebleeding despite an appropriate combined therapy (pharmacological* + endoscopic treatment**):

2.4a. Covered TIPS is the treatment of choice to prevent EV rebleeding (2b, B).

2.4b. TIPS may be used as a bridge treatment in patients eligible/listed for liver transplantation (4,C).

2.4c. TIPS is effective in the prevention of bleeding recurrence from GV and should be considered in this setting (2b,B).

2.4d. Balloon-Occluded Retrograde Trans venous Obliteration (BROTO) may be employed for uncontrolled bleeding or rebleeding from gastric varices (GV), in the presence of contraindication(s) to TIPS, and/or more compromised liver function (5,D).

2.4e. TIPS can be considered in patients with transfusion-dependent Portal Hypertensive Gastropathy (PHG), when NSBBs and/or endoscopic treatments fail (4,C).

2.4f. TIPS with or without embolization of the feeding vessel(s) may be employed for uncontrolled bleeding or rebleeding from ectopic varices (4,C).

*NBBs with or without 5-ISMN.

**Desophageal varices: endoscopic variceal ligation (EVL); Gastric varices: glue injection**

Votation 2.4 Votes in Favour 95%.
Comment: Patients surviving a first variceal bleeding episode have a two-year rebleeding risk of over 60% [100,106]. First-line therapy (FLT) is based on both NSBBs and EVL. RCT comparing TIPS to FLT, even if inhomogeneous, agreed that TIPS is highly effective in preventing rebleeding, although with a significantly burden of HE, but it did not improve overall mortality [107–109].

The lack of survival benefit following TIPS may be dependent on clinical deterioration in patients with recurrent bleeding and sequential treatments. Hemodynamic non-responders to secondary FLT should be considered earlier for TIPS. Preliminary, albeit uncontrolled, data indicate that allocation of these patients to TIPS reduces rebleeding rate and bleeding-associated mortality [5,97,106,110–113].

Bleeding episodes from GV occur at lower HVPG levels and tend to be worse in respect to those occurring from EV and require significantly more transfusions [114]. Although the available literature on GV bleeding is not as robust as the one for EV, all studies comparing TIPS vs. cyanoacrylate in bleeding GV demonstrated a significantly higher success rate in the TIPS group, with a greater burden of HE in derived subjects [14,115–123]. In patients with large gastro renal shunts and contraindications to TIPS (e.g. elderly patients or patients with refractory encephalopathy or more compromised liver function) BROTO may be considered for the treatment of GV bleeding [124–128].

**PHG** is mainly detected in patients with more advanced liver disease and in those previously receiving endoscopic haemostatic treatment for EV and GV (prevalence 11–80%) [129,130]. Incidence of acute bleeding and related mortality are quite low (3% and 12.5% at three years, respectively) [131–133]. Therefore, TIPS is unlikely to be proposed to these subjects. Nonetheless, patients in whom PHG causes both chronic and significant blood losses (requiring repeated transfusions), could be considered for TIPS [134,135].

**GAVE** is a rare finding in patients with PH (2%–3% incidence), which is not the leading pathogenic mechanism. Accordingly, GAVE is unresponsive to derivative treatment [135–137].

Ectopic varices account for only 2–5% of variceal bleeding in cirrhosis. They bear a 4-fold increased bleeding risk compared to EV with a mortality rate as high as 40% [138]. In case of uncommon bleeding sites (such as ectopic varices and stomas), local endoscopic treatment is often either impossible or ineffective. Several uncontrolled studies have indicated that TIPS placement is effective in preventing rebleeding from ectopic varices [127,139–142]; it should be considered that ectopic varices are known to rebleed despite a reduction of PCG below 12 mmHg following TIPS [127,139,141–143]. Therefore, TIPS also allows embolization of the feeding vessel(s) and facilitates re-interventions in case of rebleeding. In this setting derivative surgery could still play a crucial role if TIPS is not technically feasible (Supplementary materials—Appendix 4).

**SESSION 3: TIPS for portal hypertension complications**

3.1. Is TIPS more effective than conservative/medical treatment (large volume paracentesis plus albumin infusion + diuretics) to treat refractory ascites (defined according the International Club of Ascites criteria) or recidivant ascites (3 episodes of tense ascites in 1 year)?

**Statement 3.1**

3.1a. TIPS is more effective than conservative/medical treatment to resolve refractory/recidivant ascites, greatly reducing the need of paracentesis (1a, A).

3.1b. TIPS should be considered in all patients with refractory/recidivant ascites (1a, A).

3.1c. In selected patients with refractory/recidivant ascites and without general contraindications (*) TIPS improves transplant-free survival (1a, A).

3.1d. In patients who are eligible for liver transplant, TIPS should be planned in agreement with a Transplant Centre (5,D).

3.1e. At present, in patients with ascites “early TIPS” is not indicated. The concept of “early TIPS” needs further definition (5,D)

See statement 1.12.

Votation 3.1. Votes in Favour 100%.
Comment: Efficacy: To date 6 RCTs performed with bare stents and including 390 patients and a meta-analysis have been conducted to compare TIPS and large volume paracentesis in patients with refractory/recurrent ascites [75,86,87,131,144–150]. In 2007 a meta-analysis of individual patient data has clearly demonstrated that the recurrence of tense ascites and the average number of paracentesis were significantly lower in patients receiving bare-metal TIPS than in those receiving paracentesis [83]. Survival: 6 RCTs provided different results on survival. While the unfavourable outcome showed by the first study published in 1996 can be explained by technical disability [146], the discrepancies among the other studies is likely due to patient selection and data analysis biases. Transplant-free survival was indeed significantly improved in 3 RCTs [131,145,147] but not in other two RCTs [75,146]. When the individual data of included patients were analysed, improvement of both actuarial probability of transplant-free survival and 12-months survival was shown in TIPS patients [83,131,145,147]. These RCTs excluded patients with advanced liver disease (as defined by serum bilirubin >5–6 mg/dl, INR >2, current or chronic HE >2 by West-Heaven scale), and renal failure (as defined by serum creatinine >3 mg/dl) [86]. Moreover, they included patients with recidiant non-refractory ascites [86].

Pre-OLT and early preventive TIPS. No study has assessed the possible role of TIPS in reducing the pre-transplant mortality risk of OLT candidates in patients with non-recidivant/non refractory ascites.
3.2. Which is the role of TIPS in type-II hepatorenal syndrome (HRS)?

Statement 3.2
3.2a TIPS is effective to treat type-II HRS associated to refractory/recidivant ascites (1b) [151].
3.2b TIPS cannot be recommended in unselected patients with type-I HRS (2b, B) [152-154].

Votation 3.2. Votes in Favour 100%.
Comment: A total of 61 patients with HRS receiving TIPS have been included in small studies [26,151-154]. Most of them have shown an improvement of renal function, with survival rates ranging from 20% for Type I and 70% in type II, while liver failure was the most frequent cause of death following TIPS.

3.3. Which is the role of TIPS in refractory hydrothorax* (RH)?

Statement 3.3
3.3a TIPS can be considered in refractory hydrothorax aiming at resolution of hydrothorax and reduction in number of thoracentesis (2b,B).
3.3b The effect of TIPS on survival and the risk factors for poor outcome are still not clearly defined in RH. Thus, the final decision to insert a TIPS should be reached on an individual patient basis after a multidisciplinary clinical evaluation (5,D).
*Defined as: symptomatic hydrothorax not responsive to standard medical treatment (sodium restriction and maximal tolerable doses of diuretics) requiring repeated thoracentesis

Votation 3.3. Votes in Favour 100%.
Comment: Refractory hydrothorax occurs in approximately 5-10% of patients with advanced cirrhosis. TIPS has been investigated as a treatment option in 8 uncontrolled retrospective studies [145,148,155-159] and several case reports. Overall 227 patients were included. The reported complete and partial responses were 58.3–71.0% and 11.0–20.8% respectively. An overall clinically relevant response (resolution of hydrothorax and reduction in thoracentesis) was shown in about 70% of patients. The average 30-days mortality rate is 22%. A high creatinine level is the strongest prognostic factor for early mortality. The 1-year survival ranges from 48 to 64%. Survival was correlated with response to TIPS, age <60 years and MELD score <15.

4.3. Is there a role for TIPS in Hepatopulmonary syndrome?

Statement 3.4
At present, there is no sufficient evidence to support the use of TIPS for the treatment of hepatopulmonary syndrome [5].

Votation 3.4. Votes in Favour 95%.
Comment: Few case reports described the successful treatment of HPS with TIPS placement [160]. In larger study on this topic [161] TIPS neither improved nor worsened gas exchange in patients with HPS.

SESSION 4: TIPS in vascular disorders

Sinusoidal occlusion syndrome (SOS*)
Hepatic veno-occlusive syndrome (SOS) is characterized by hepatomegaly, ascites, weight gain and jaundice, due to the damage of small hepatic vessels affecting particularly the sinusoidal endothelium with a partial or complete occlusion of small hepatic veins. The most frequent causes are hematopoietic stem cell transplantation (SCT) and alkalioid ingestion, but it is also observed after solid organ transplantation [162]. (Supplementary material—Appendix 2).
*Defined as: damage to small hepatic vessels affecting particularly sinusoidal endothelium with a partial or complete occlusion of small hepatic veins.

4.1. Is there a role for TIPS in Sinusoidal Occlusion Syndrome (SOS)?

Statement 4.1
4.1. TIPS is not indicated in Sinusoidal Occlusion Syndrome in Bone Marrow Transplanted Patients (C4), but may be considered in individual basis in Solid Organ Transplant Recipient as stand-alone treatment or as bridge to liver transplantation in a setting of multidisciplinary evaluation (4,C) [163,164].

Votation 4.1 Votes in favour 100%.

Comment: The incidence of SOS after SCT can be as high as 70%, depending on the specific diagnostic criteria, sample size and risk factors, which are highly heterogeneous among different cohorts [162]. In liver transplant recipients the largest series reported an incidence of 1.5%, mainly related to the number and severity of rejection episodes and azathioprine use. A poor outcome of SOS after bone marrow transplantation is reported with 63% mortality, mainly related to liver failure and renal insufficiency secondary to portal hypertensive complications. After liver transplantation only 7 patients with severe SOS have been treated with TIPS placement. Overall survival in this small cohort was good [163,164].

Portal vein thrombosis

4.2. Is TIPS feasible in the presence of portal vein thrombosis (PVT)?

Statements 4.2
4.2a TIPS is feasible in patients with portal vein thrombosis with and without cirrhosis, but it bears higher failure and complication rates when portal cavernoma, fibrous transformation of the main portal vein or intrahepatic branches thrombosis, are present (4,C).
4.2b Extension of the TIPS stent into the portal or superior mesenteric vein should be considered when recanalization of P/SVM is incomplete and the patient is not a liver transplant candidate (5,D).

Votation 4.2: 100%.

4.3. Which are the indications to TIPS in portal vein thrombosis?

Statements 4.3
4.3a TIPS can be considered to treat PVT in both cirrhotic and non-cirrhotic patients with progression of thrombosis despite adequate anticoagulant treatment, or when there is an absolute contraindication to anticoagulation, or with no response after a maximum of 6 months of anticoagulation treatment (3a, B).

Votation 4.3 Votes in favour 100%.
Comment: The spontaneous recanalization rate of acute PVT in non-cirrhotic patients is rare and response to anticoagulation therapy has been described in about 50%. Therefore development of chronic portal vein thrombosis (20% portal cavernoma) and appearance of portal hypertensive complications eventually occur in about 50% of patients [165-167]. Moreover these patients bear an increased risk of splanchenic venous system thrombosis and biliary complications. According to multivariate analysis of clinical studies, prophylaxis of variceal bleeding is similar between cirrhotics and non cirrhotics [165–167], and, in selected patients, low mortality and re-bleeding rates have been observed after surgical porto systemic shunting [168]. However, the proportion of patients in which these shunts are feasible remains unclear.

In cirrhotic patients, PVT is the most common thrombotic event, with an annual incidence up to 12% in absence of HCC [169,170]. Despite a spontaneous recanalization has been described in up to 40% of cases (mainly in partial PVT), progression of thrombosis has also been reported in 48% up to 70% of patients at 2 years [171–173]. Data on the efficacy of medical anticoagulation to treat PVT come from cohort studies which included 163 anticoagulated patients with different regimens (LMWH or VKA). Reremission rate ranged from 55% to 75% with mean interval time of about 6 months [173-180]. In patients with extension of the thrombus into the superior mesenteric vein the risk of intestinal infarction and associated mortality is higher [181]. TIPS have been performed in patients with PVT at different severity, mostly non cirrhotic and even in presence of cavernomatous transformation of the portal vein [9,11,20,173] (Supplementary material—Appendix 3). The patency of intra-hepatic portal veins branches and partial thrombosis of the main trunk are positive prognostic factors for technical success [182]. The thrombotic occlusion of the intrahepatic portal vein branches compels the use of transcatheter approach which bears an increased risk of complications [183,184]. In most cases, the indication for TIPS was not PVT “per se” but rather the complications of portal hypertension. In liver transplant candidates with progressive portal
ven thrombosis, early TIPS placement could be considered aiming at ensuring a patent portal vein during the transplant procedure.

Budd chiari syndrome (BCS)

BCS results from blockage of exit of the blood from the liver either due to hepatic vein thrombosis or obstruction of the inferior vena cava [185,186].

4.4. Is TIPS indicated in hyper acute and chronic BCS?

**Statements 4.4**

4.4a In BCS patients, a stepwise approach, TIPS with covered stent is indicated in case of failure of anticoagulation (and angioplasty when feasible), represented by persistent ascites, renal failure or elevated transaminases [5,182].

4.4b Listing for liver transplantation should be considered in case of a prognostic index score greater than 7 in patients candidate to TIPS for BCS (2b, B) [183].

4.4c. When TIPS is attempted to treat hyper acute BCS with acute liver failure presentation, the listing process for transplantation should not be delayed (4.C).

Votation 4.4: Votes in favour 100%.

Comment: In BCS, liver injury results from hepatic congestion, and side-to-side portacaval shunts were previously used for the management of this disorder. At present, a wide array of options are available for patients with BCS, ranging from no intervention to liver transplantation. A validated model (based on encephalopathy, ascites, prothrombin time and bilirubin) has been developed which allows for the prediction of survival of patients with BCS: only in patients with an intermediate prognosis, a side-to-side portacaval shunt showed a positive impact on survival [187]. There have been a number of case reports and small series on the outcome of patients with BCS who have received a TIPS showing worse results in patients with underlying more advanced liver disease [19,188,189] and acute hepatic failure [190,191]. Patients with chronic disease did much better with relief of symptoms, improvement in liver function and a good intermediate (2–4 years) survival [190,191]. In a retrospective report from Europe on 221 patients with BCS, a lower than expected success rate (92%) and a higher than expected complication rate (18%) was observed, highlighting the technical difficulties in positioning a TIPS in patients with hepatic vein thrombosis [5]. One and ten year transplant free survival were 88% and 69% respectively which are better than predicted by a risk scoring system developed for BCS patients. TIPS dysfunction was observed significantly more often in those who received a bare as compared to a covered stent [5]. Positioning a TIPS in patient with BCS can be difficult when the hepatic veins are completely occluded: in this case a transcaval approach for TIPS may be performed but this procedure should be reserved to highly experienced centres [192].

4.5. Is TIPS indicated for non-cirrhotic idiopathic portal hypertension (INCPH)?

**Statements 4.5**

4.5. TIPS can be considered in NCIPH, applying the same indications utilized for the management of portal hypertensive complications (3b, B). Caution is needed in patients with refractory ascites, kidney failure and comorbidities (3b, B) [193].

*Defined as: an increased portal venous pressure gradient in the absence of a known cause of liver disease and portal vein thrombosis.*

Votation 4.5: votes in favour 100%.

Comment: In contrast to the high prevalence of this disorder in India, INCPH is a rare disease in the Western world. Associated risk factors for INCPH are chronic infections, exposure to medication or toxins, thrombophilia, immunological disorders, and genetic disorders. Multifactorial aetiology can also be encountered. Chronic abdominal infection the most important etiological factor among Eastern patients, whether thrombophilia is relevant for Western patients. The majority of patients with INCPH initially present with signs or complications of portal hypertension (mainly variceal bleeding and splenomegaly). These patients usually have preserved liver function. Liver function impairment occurs mainly in the context of intermittent conditions [194]. In 69 biopsy proven cases of INCPH with a mean follow-up of 6.7 ± 4.6 years, all had evidence of portal hypertension at diagnosis, and 42% were symptomatic [195]. Amongst 41 patients with NCIPH treated with TIPS for portal hypertensive complications 11 died: serum creatinine, ascites as indication for TIPS and the presence of significant comorbidities at the time of the procedure emerged as death-related risk factors [193].

**SESSION 5: TIPS in liver transplant setting**

Patients on the waiting list for liver transplantation (LT) often require treatment of complications related to portal hypertension such as gastrointestinal bleeding, refractory ascites or vascular thrombosis. Besides medical or endoscopic treatments, reduction of portal hypertension by trans jugular intrahepatic Porto systemic shunt (TIPS) may be required if other measures fail, in order to preserve their candidacy for LT [196].

5.1. Which are the indications and contraindications to TIPS placement in patients listed for LT?

**Statement 5.1**

5.1a. The indications and contraindications to TIPS in patients listed for LT are identical to those recommended for non waitlisted patients (2b, B) [123].

5.1b. A specific indication to TIPS in patients listed for LT is to maintain patency of portal vein if at risk of occlusion (2b, B) [11,196].

5.1c. In the absence of priority for liver transplantation, TIPS should be considered for patients with low MELD scores or MELD exceptions (2b, B) [123].

Votation 5.1: Votes in Favour: 95%.

Comment: TIPS has been shown to be effective in managing complications of portal hypertension also in patients listed for LT [25,196,197,201]. However, TIPS placement in patients on the waiting list for LT may influence several clinical aspects not only related to the outcome of primary complication of liver disease (i.e. gastrointestinal bleeding or refractory ascites), but also related to the patient’s priority in the waiting list due to MELD score modifications [10,11,196,197,199,201–203].

5.2. Can TIPS placement have an impact on transplant surgery and/or intra-operative management?

**Statements 5.2**

5.2a. The choice of adequate stent length, positioning, and extension from the portal to the hepatic vein, is paramount to avoid hampering vascular cross-clamping at the time of surgery (4.C) [115,196,199,202,203,207].

Votation 5.2 Votes in Favour 100%.

Comment: The presence of TIPS on the one hand may reduce the intraoperative blood loss following portal decompression but on the other it may enhance the difficulty of the transplant procedure. In about 28% of LT patients TIPS had migrated, increasing the time spent on by pass and complexity of transplant operation. The presence of TIPS however does not have any influence on intra-operative blood requirements, length of hospital stay or early survival after LT [115,196,199,202,203,207]. No significant advantage in performing TIPS before living donor liver transplantation has been observed [125].

5.3. Which is the role of TIPS in post-LT patients?

**Statement 5.3**

5.3a. TIPS after LT is indicated to treat portal hypertension-related complications secondary to recurrent liver disease* (2b,B) and venous complications** (2b,C) [192,163,164].

*Refractory ascites, gastrointestinal bleeding

** Portal vein thrombosis (PVT), Sinusoidal obstruction syndrome (SOS).

Hepatic venous outflow obstruction (HVVO), Small for size syndrome (SSS)

Votation 5.3. Votes in Favour: 100%.

Comment: After LT portal hypertension and related complications may evolve because of allograft dysfunction/rejection, biliary complications, and recurrent disease [163,164,198,200,204–210]. Peculiar indications to TIPS in liver transplanted patients refer to treatment of
several vascular complications. These complications accounted for PVT, SOS, and HVOO [163,164]. The use of TIPS in treatment of PVT after LT has been associated with a reduced risk of bleeding and technical complications in comparison with trans hepatic puncture for portal vein interventional procedures [204,205]. Although no randomized trials evaluated the efficacy and safety of TIPS in treating SOS, some Authors have suggested that TIPS placement can be tried in carefully selected patients with SOS after LT, particularly if retransplantation is not an option [164,192]. Despite HVOO after LT is uncommon, it is a life-threatening complication if untreated. Because of the small sample size behind the current data on TIPS in patients with HVOO [204], TIPS placement for treating HVOO cannot be routinely recommended, but considered in a individual patient basis, potentially as a bridge to retransplantation [205]. SSS, which develops in a graft with a suboptimal parenchymal mass, is more frequent in LT performed with partial grafts. Until now, the treatment options for SSS focused to reduce the portal flow via the embolization of a portion of spleen. Some reports showed the efficacy in treating SSS with TIPS placement. Because the number of treated patients is still very limited, TIPS placement for SSS should be considered in selected cases, when no other treatment options are available [163,164].

5.4. Are there specific technical issues and feasibility of TIPS placement after LT?

**Statement 5.4**

5.4a. Knowledge of portal and hepatic venous anatomy and surgical anastomoses is paramount to appropriate TIPS positioning after LT (conventional technique vs. latero-posterior or termino-lateral piggyback anastomoses and partial grafts) [2c, B] [198,204,210].

5.4b. TIPS feasibility in whole-size LT does not differ from what reported in non-transplant patients (2B) [200,204–206,208,210].

A 5.4c. TIPS feasibility rates in partial graft and in kinked piggyback anastomoses are lower (4) [206].

**Votation 5.4. Votes in Favour: 100%.
Comment: TIPS placement can be difficult after LT [198,204–206,208,210] particularly in split grafts, particularly for those derived from left liver lobe. This is related to the fact that almost all interventional radiologists are accustomed to performing the TIPS from a right or middle hepatic vein approach while targeting the right portal vein. Real time ultrasound guidance or gun-site technique may be useful to place the TIPS in the left hepatic vein [210].**

5.5. Which are the complication rates of TIPS placement after LT?

**Statement 5.5**

the incidence of TIPS obstruction, infections and development of hepatic encephalopathy are similar between LT and non-LT patients (2b, B) [198,204,210].

**Votation 5.5 Votes in Favour 100%.
Comment: It must be noted that more recent data concerning the rates of TIPS obstruction, infection and the development of hepatic encephalopathy after LT compared to native liver, derived from studies involving the use of covered stents [204]. This observation may explain why in the past, when bare stents were used, rates of complications after TIPS placement in LT patients were evaluated more frequently than in native livers [198,204,208,210].**

5.6. Which are the clinical response rates and the outcome of TIPS placement after LT?

**Statement 5.6**

5.6a. The overall clinical response rates to TIPS in LT patients is lower than in pre-transplant patients, mainly in the case of refractory ascites (2b) [209,210].

5.6b. In LT recipients with a MELD score >15 and in those with refractory ascites secondary to HCV recurrence with a MELD score >12, TIPS has been associated with greater failure rates in the pre-direct antiviral agents (DAA) era: thus, it should be considered with caution if no DAA option is available (2b, B).

**Votation 5.9 Votes in Favour: 100% and 85%.
Comment: Most recent studies report that TIPS appears to be less clinically effective in LT compared with native liver transplant patients [205,208–210]. Moreover, TIPS for treating ascites after LT is likely to have a poor clinical response [209]. Although this difference in**

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**Box 1 Tips indications in marginal clinical settings to control bleeding or to prevent rebleeding.**

Some clinical scenarios may pose concerns about the appropriateness of TIPS procedure, mainly due to the potential higher incidence of procedure-related complications and/or a worst outcome. Notably, the outcome of portal hypertension complications could be negatively affected by underlying comorbidity. The following box is an attempt to clarify the feasibility of TIPS in patients affected by chronic kidney diseases (CKD), haemophilia, myeloid metaplasia and in pregnancy. Please note that these lines of information are mainly based on few case reports or small series of patients. Therefore, indication to TIPS must be evaluated on an individual patient basis.

**CKD**

The available data suggest considering TIPS placement to prevent rebleeding or control bleeding in patients affected by CKD, even in end-stage renal disease requiring renal replacement therapy [223,224]. Patients can be “rebalanced” to a new euvoletic state by rapid dialysis after TIPS creation, to avoid the development of fluid overload, pulmonary oedema and TIPS dysfunction due to elevated right atrial pressure afterload. However, the risk of marked encephalopathy in subjects with haemodialysis-dependent end-stage renal disease is high. Therefore it appears reasonable to reserve TIPS to patients suitable for combined liver/kidney transplantation.

**Haemophilia**

The available data suggest considering TIPS placement in haemophilic patients who bleed or rebleed despite an optimal pharmacological and endoscopic treatment. With peri-procedure factor VIII supplementation, TIPS have been placed without complications and the outcomes appear to be comparable to those in patients without haemophilia [225–228].

**Pregnancy**

Treatment of bleeding EV occurring during pregnancy is a rare but relevant clinical dilemma. Complications of portal hypertension are associated with significant increases in both mortality and complications during pregnancy or in the post-partum period. Increase in portal hypertension occurs during the last stages of the second trimester of pregnancy and is associated with increased risk of portal hypertension related bleeding in the later stages of pregnancy [229–231]. The available literature suggest considering TIPS placement in pregnant patients who bleed or rebleed despite an optimal pharmacological and endoscopic treatment. If caesarean section is mandatory, TIPS could prophylactically decompress abdominal wall varices if they provide high operative risk [232–234].

**Hepatic myeloid metaplasia in IM**

Extra medullary haematopoiesis in the liver can lead to portal hypertension and related complications even in the absence of thrombosis of the hepatic or splenoportal veins. Hepatic myeloid metaplasia may cause both sinusoidal and presinusoidal portal hypertension. Treatment of the complications of PHT might not differ from that of patients with cirrhosis. Indeed, available data support TIPS as a rescue treatment to control portal hypertension complications (variceal bleeding and ascites) [235–237].

*CKD, chronic kidney disease; IM, idiopathic myelofibrosis.*
the outcomes seem to be consistent among the studies it should be pointed out that they differ from each other in the definition of clinical success for ascites response and in the retransplant thresholds. Only few studies evaluated the clinical response to TIPS after LT in relationship to the combination of MELD score and the indication to TIPS [200,201,204,209]. Most Authors agree that transplant free survival is poorer and MELD threshold predicting poor survival is lower those of patients with native livers [201,209,210]. The availability of the new DAAs is expected to modify the outcome of post-LT TIPS in HCV positive recipients. At present, there are no data to differentiate post-TIPS PPG target between LT and non-LT patients.

SESSION 6: unusual indications to tips placement

Please note that these lines of information are mainly based on few case reports or small series of patients. Therefore, indication to TIPS must be evaluated on an individual patient basis. Non-cirrhotic portal hypertension (NCPH) in HIV. Non-cirrhotic portal hypertension (NCPH) has been reported as a liver disease in Human Immunodeficiency Virus (HIV)-infected patients under antiretroviral therapy (ART) [211] Combination of non-exclusive mechanisms has been described: primary endothelial damage of terminal portal veins induced by HIV or immunologic disorders, mitochondrial toxicity by didanosine and thymidine analogues [212]. It is characterized by heterogeneous liver histological findings, frequently identified as nodular regenerative hyperplasia and clinical manifestations of portal hypertension with well-preserved liver function [213,214]. The key issues in the management of patients with idiopathic noncirrhotic portal hypertension are related mainly to treatment and prevention of variceal hemorrhage. While data are limited in this population regarding the best approach, patients are typically managed in the same manner as those with portal hypertension due to cirrhosis (2.C).

General surgery

The risk of surgery should be considered individually depending upon the clinical setting: the presence of cirrhosis and the type of procedure: cirrhotic patients who present for elective and emergent surgery pose a formidable challenge for the surgeon because of the high reported morbidity and mortality. The Child-Turcotte-Pugh (CTP) score has been used for decades to evaluate preoperative severity of liver dysfunction and to predict postoperative outcome. The MELD score has been shown to predict accurately the 3-month mortality for cirrhotic patients after TIPS placement. Surgery is generally well-tolerated by cirrhotic patients in Child-Turcotte-Pugh class A or with a MELD <10 [215]. Surgery is generally permissible in patients in Child-Turcotte-Pugh class B or with a MELD 10–15 (except those undergoing extensive hepatic resection or cardiac surgery) who have undergone thorough preoperative preparation [216]. Patients with portal hypertension bear an increased risk of bleeding during intra-abdominal surgery. Therefore, it has been suggested that preoperative TIPS placement may improve the prognosis of cirrhotic patients submitted to abdominal surgery [217]. Contraindications for TIPS placement are identical whether or not the patient is a potential candidate for abdominal surgery. Portal decompression with neoadjuvant TIPS placement might reduce the risk of intraoperative bleeding and perioperative complications in patients with cirrhosis undergoing surgery, but experience is limited, and a case-by-case multidisciplinary-based decision should be made (4.D).

Cardiac surgery

Cardiac surgery is associated with increased mortality in patients with cirrhosis compared to other surgical procedures. A number of risk factors for hepatic decompensation following cardiac surgery have been identified including the total duration of cardiopulmonary bypass, use of non-pulsatile as opposed to pulsatile cardiopulmonary bypass, and need for perioperative supportpressor support [218]. Cardiopulmonary bypass can exacerbate underlying coagulopathy by inducing platelet dysfunction, fibrinolysis, and hypocalcaemia. Thus, the least invasive options, such as angioplasty, valvuloplasty, or minimally invasive revascularization techniques, should be considered in patients with advanced cirrhosis who require invasive intervention for cardiac disease [219]. TIPS might be considered before cardiac surgery in selected patients with portal hypertension. However, the role of preoperative TIPS has not been well studied in this context, where TIPS placement is strongly affected by the heart conditions: a careful multidisciplinary evaluation is warranted before opting for TIPS (5.D) [218,219].

Paediatric patients

Portal hypertension (PH) in children differs from adults in two main aspects: (1) Cirrhotic disease has usually an early onset and a rapid progression, leading to transplantation in the first two years of life (i.e. biliary atresia). Consequently, the length of the follow-up of children with severe cirrhotic PH is short. (2) Non-cirrhotic causes of portal hypertension instead are very common and long-standing, representing the main group of patients in the follow up for PH [220]. These patients usually have extra hepatic portal vein obstruction (EHPVO) and conditions characterized by the wide spectrum of the liver ductal plate malformation. Very commonly they develop severe bleeding episodes unresponsive to medical and endoscopic treatment, as well as hypersplenism, but do not progress to end-stage liver disease, and therefore have no indication for liver transplantation. In this setting porto-systemic shunting has become an important tool in the armamentarium available to control severe PH, especially in non-cirrhotic conditions [168]. When covered stents were not yet available, TIPS in children has been used both in cirrhotic and non-cirrhotic patients with a moderate success [221]. A recent study showed that children with severe portal hypertension could be managed very successfully with covered TIPS, with no significant complications and a good control of bleeding in the mid-term [222]. In another study, TIPS was successfully placed in 11 of 13 (85%) children weighing more than 10 kg, including cirrhotic, non-cirrhotic and transplanted patients. Following TIPS, the Porto systemic gradient decreased to below 10 mmHg, portal hypertension complications resolved in 10 of 11, no clinically apparent encephalopathy developed; TIPS revision was necessary in 3 patients. Shunts were patent at follow-up (0.2–67 months) in 7 children without transplant and in 4 children (1.5–33 months) with transplant [220].

Feasibility and safety:

TIPS has been shown to be technically feasible and safe in children weighing more than 10kg of body weight (4.C).

Efficacy:

TIPS as been effective in children with cirrhotic and non-cirrhotic PH, as well in liver transplant complications. However, further studies are strongly advocated to support the routine use of TIPS out of expert centres, in children with PH unresponsive to medical and endoscopic treatment (4.D).

Areas requiring investigation in TIPS positioning and patient assessment

The possible future studies regarding the TIPS should include the management of most frequent side effects, which are strictly correlated with the diameter of the shunt. Indeed, a variable diameter of TIPS may change the volume of porto systemic shunting remotely controlled to tune for varying requirement.

Conflict of interest

None declared.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.dld.2016.10.011.

References


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