Diploma Thesis

Endotipsitis in transjugular intrahepatic portosystemic shunt
A retrospective analysis

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Declaration

I hereby declare that I have written the submitted thesis independently and without any inadmissible help from third parties. I confirm that I have used no other than the declared sources. All utilized sources have been indicated as such and acknowledged by means of complete references in the text. Furthermore, I hereby declare that, insofar as artificial intelligence (AI) tools were used to generate and/or correct certain passages of text in the creation of this work, this use was carried out in compliance with ethical principles, academic integrity, and the guidelines of my university, and that this has been made transparent and appropriately marked.

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Kurzfassung

Hintergrund: Lebererkrankungen sind weltweit häufig und tragen erheblich zu Morbidität und Mortalität bei. Der transjuguläre intrahepatische portosystemische Shunt (TIPS) stellt eine wesentliche therapeutische Option im fortgeschrittenen Krankheitsstadium dar. Endotipsitis ist eine seltene, aber potenziell schwerwiegende Komplikation, welche definiert wird als Vegetationen innerhalb des TIPS Stents zusammen mit anhaltender Bakteriämie unter Ausschluss eines anderen infektiösen Fokus. Bis heute bleibt Endotipsitis schlecht verstanden und es liegen bislang nur wenig Fallberichte und kleinere Serien vor. **Methoden:** Es erfolgte eine restrospektive Analyse vom 230 Patient*innen, die zwischen Januar 2004 und Januar 2024 am Universitätsklinikum Graz einen TIPS erhielten. Untersucht wurden infektiöse Komplikationen nach dem Eingriff, um mögliche Fälle von Endotipsitis zu identifizieren sowie die Inzidenz von Infektionen, Bakteriämien und damit verbundene Outcomes zu erfassen. **Ergebnisse:** Nach TIPS traten Infektionen bei 14% der Patient*innen (n=30) auf, darunter fünf Fälle von Bakteriämie. Kein gesicherter Fall von Endotipsitis konnte identifiziert werden. Die 90-Tage-Mortalität lag bei 22%, die 6-Monats-Mortalität bei 33%. Patient*innen mit Infektionen innerhalb von 30 Tagen nach TIPS zeigten eine signifikant erhöhte kurz- und mittelfristige Mortalität im Vergleich zu späteren Infektionen ($p<0.01$) sowie als Patienten ohne Infektion nach TIPS ($p<0.01$). Ein Preemptiver-TIPS wurde signifikant häufiger bei Patient*innen durchgeführt, welche eine Frühinfektion hatten verglichen mit den Patient*innen ohne Infektion (57% vs. 20%, $p<0.01$). Konsistente Risikofaktoren für Bakteriämie konnten nicht identifiziert werden. **Schlussfolgerungen:** Die Ergebnisse bestätigen die extreme Seltenheit der Endotipsitis, zeigen jedoch, dass infektiöse Komplikationen nach TIPS relativ häufig und klinisch relevant sind. Die beobachteten Mortalitätsraten sind mit den Ergebnissen früherer Studien vergleichbar. Insbesondere frühe Infektion nach TIPS waren mit schlechteren Outcomes assoziiert, was die Notwendigkeit zukünftiger Studien zur Rolle einer antibiotischen Prophylaxe, zur Risikostratifizierung und zu verbesserten diagnostischen Strategien unterstreicht.

Abstract

Background: Liver disease is highly prevalent worldwide and contributes significantly to morbidity and mortality. Transjugular intrahepatic portosystemic shunt (TIPS) has become an essential therapeutic option in advanced disease. Endotipsitis, a rare but potentially severe complication of TIPS, is defined as vegetations within the TIPS stent and persistent bacteremia with exclusion of another infectious focus. To this day it remains poorly understood, with only a few case reports and series published to date. **Methods:** We retrospectively analyzed 230 patients at the University Hospital of Graz receiving TIPS between January of 2004 and January of 2024. We assessed infectious complications following the procedure to identify cases of endotipsitis and to evaluate the incidence of infection, bacteremia and related outcomes. **Results:** Infections after TIPS occurred in 14% of patients (n=30), including five cases of bacteremia. No definite case of endotipsitis was identified. Ninety-day and six-months mortality rates were 22% and 33%, respectively. Patients who developed infection within 30 days of TIPS had significantly higher short- and mid-term mortality compared to those with later infections ($p<0.01$) and patients without infection ($p<0.01$). Patients with early infection significantly more often received an early TIPS compared to patients without infection (57% vs. 20%, $p<0.01$). No consistent risk factors for bacteremia could be identified. **Conclusion:** Our findings confirm that endotipsitis is an extremely rare condition, whereas infectious complications after TIPS are relatively frequent and clinically relevant. Mortality rates and rates of infections in our cohort were comparable to previous reports. Particularly early infections after TIPS were associated with worse outcomes, highlighting the need for future studies addressing antimicrobial prophylaxis, risk stratification and improved diagnostic strategies.

Content

Abbreviations and Acronyms

18F-FDG	18F-fluorodeoxyglucose
ACLF	acute on chronic liver failure
ALT	alanine amino transferase
BBB	blood brain barrier
BCS	Budd Chiari Syndrome
BRTO	balloon occluded retrograde transvenous obliteration
CKF	chronic kidney failure
CSPH	clinically significant portal hypertension
CT	computer tomography
EASL	European Association of the Study of the Liver
eNOS	endothelial nitric oxide synthase
EVL	endoscopic variceal ligation
HE	hepatic encephalopathy
HH	hepatic hydrothorax
HRS	hepatorenal syndrome
HRS-AKI	hepatorenal syndrome - acute kidney injury
HRS-non-AKI	hepatorenal syndrome - non - acute kidney injury
HVPG	hepatic venous pressure gradient
IAC	internation ascites club
INR	international normalized ratio
LKH	Landeskrankenhaus
LOLA	L-ornithine L-aspartate
LVP	large volume paracentesis
MASLD	metabolic dysfunction associated steatotic liver disease
MELD	model of end stage liver disease
MRI	magnetic resonance imaging
NO	nitric oxide
NSBB	non selective beta blockers
PET	positron emission tomography
PH	portal hypertension
PHG	portal hypertensive gastropathy
PlGF	placental growth factor
PTFE	polytetrafluorethylene
PTHE	post TIPS hepatic encephalopathy
PTLF	post TIPS liver failure
PVT	portal vein thrombosis
RAAS	renin angiotensin aldosterone system
SBP	spontaneous bacterial peritonitis
SEC	sinusoidal endothelial cell
SEMS	self-expandable metal stents
TIPS	transjugular intrahepatic portosystemic shunt
TXA2	thromboxane A2
VEGF	vascular endothelial growth factor

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Introduction

Endotipsitis is a rare complication of transjugular intrahepatic portosystemic shunt (TIPS) placement, which is commonly used to treat portal hypertension in chronic liver disease. Since the term "endotipsitis" was first used by Sanyal et al. (1) in 1998, only about 40 cases have been documented and endotipsitis remains poorly understood. The initial aim of this investigation of approximately 250 patients who received a transjugular intrahepatic portosystemic shunt between 2004 and 2024 at the LKH Universitätsklinikum Graz was to identify potential individuals with endotipsitis and to compare these individuals to the rest of the patient group. This project represents a small contribution to bridging the current gap in research.

The portal venous system

Anatomy

The liver occupies a special place in the circulatory system because part of its function is to remove toxic and potentially harmful substances from the blood. Blood from the veins of the spleen, large and small intestine, pancreas, stomach and gallbladder is collected in the portal vein and, together with oxygenated blood from the hepatic artery, enters a complex system of vessels within the liver parenchyma - the sinusoids (2). The sinusoids have pores in their endothelial cell lining and are surrounded by hepatocytes. Between the hepatocytes and the sinusoids is a small space called the space of Dissé, containing specialized immune cells of the liver. Through the pores, the lumen of the sinusoid communicates with the space of Dissé, the hepatocyte and immune cells. After passing through the sinusoids, the blood is drained into the branches of the hepatic veins, which then lead to the inferior vena cava and from there to the heart and back into the systemic circulation (3).

Physiology

The portal venous system is a critical component of human circulatory physiology and plays a pivotal role in liver function and metabolic health. Blood from the gastrointestinal organs is rich in nutrients and toxins and is processed by the liver before it reaches systemic circulation. The hepatocytes are amongst the most richly perfused cells of the body with a unique blood supply. About ¼ of its supply is oxygenated blood from the hepatic artery and ¾ nutrient and toxin rich blood from splanchnic veins. After arterial and splanchnic blood mix in the sinusoids it is processed by the hepatocytes with their broad spectrum of detoxifying enzymes enabling harmful substances to be excreted. After blood is cleared it is collected in the hepatic vein and released back into the systemic circulation. Next to its role in drug and toxin metabolism the liver is crucial for lipoprotein synthesis, endocrine homeostasis and plasma protein production (2,4).

Portal hypertension (PH)

Portal hypertension is a condition characterized by an increase in pressure within the portal venous circulation, which subsequently gives rise to a series of associated symptoms. The term is defined as the difference in pressure between the inferior vena cava and the portal vein. The gold standard for diagnosis is the approximation of the hepatic venous pressure gradient (HVPG) through a jugular catheter, which measures both free hepatic venous pressure and wedged hepatic venous pressure (5). Values exceeding 5 mmHg are regarded as indicative of portal hypertension, while values exceeding 10 mmHg are considered clinically significant portal hypertension (CSPH), given that once this threshold is reached, the incidence of serious complications markedly increases (6). The etiology of portal hypertension varies geographically, with cirrhosis being the most frequent cause overall, followed by schistosomiasis and prehepatic portal vein occlusion, the latter two being particularly common reasons for PH in north Africa and Asia (7).

Hemodynamic changes and splanchnic vasodilation in PH

Given that systemic circulation is a dynamic system, whereby the blood flow to and from different organs can be adjusted according to a variety of factors to meet current needs, a change in resistance in the hepatic vascular system will have a systemic effect on the circulation (8). This effect results in a state of hyperdynamic circulation in portal hypertension, which can be described as a syndrome characterized by splanchnic and peripheral vasodilation, increased plasma volume and increased cardiac output (9). Initially, a sustained inflammatory response disrupts the complex auto- and paracrine relationships between the endothelial cells of the sinusoids, localized immune cells, pericytes surrounding the sinusoids and the hepatocytes (10). These changes result in the constriction of the sinusoid by release of vasoconstrictive mediators like thromboxane A2 (TXA2), impaired production of the potent vasodilator nitric oxide (NO) by the sinusoidal endothelial cells (SEC) and the transition of stellate cells surrounding the sinusoid into a contractile phenotype (8,10–12). The reduction of intrahepatic blood flow results in ischemic damage to the liver parenchyma, which ultimately leads to the replacement of healthy liver tissue with scar tissue and regenerative nodules. Conversely, the preceding splanchnic circulation undergoes a process of vasodilation. Endogenous nitric oxide synthase (eNOS) is activated in the splanchnic vascular bed and angiogenesis is promoted through the release of vascular endothelial growth factor (VEGF), which increases splanchnic blood flow and thus portal pressure (13). Hyperdynamic circulation leads to relative renal hypoperfusion which activates renin-angiotensin-aldosterone system (RAAS), resulting in an increase in plasma volume through dampened natriuresis and thus systemic blood pressure (14). Furthermore, rodent models showed that atrophy of sympathetic nervous fibers around the mesenteric tree may attribute to hypocontractability of the mesenteric arteries, further incrementing portal blood flow (15). This ultimately results in the formation of a vicious cycle, characterized by increased intrahepatic resistance, splanchnic vasodilation and parenchymal damage, which perpetuates the disease progress.

Collateral vessel formation

In an attempt to compensate for the heightened portal pressure, preexisting vessels are recruited and opened to relieve pressure from the portal venous system (8,10). Blood from the portal vein escapes into the collaterals, circumvent the liver altogether and blood flows directly into the systemic circulation. The development of collaterals largely depends on angiogenic factors, foremost VEGF and placental growth factor (PlGF), which are upregulated by the intestinal microvascular bed as a response to increased portal pressure (16,17). This is supported by studies showing that anti-VEGF therapy significantly reduces collateral vessel formation in cirrhosis in animal models (18). Although collaterals reduce portal pressure, collaterals alone do not alleviate the elevated pressure because splanchnic circulation is dilated and portal flow is increased, so both collaterals and splanchnic vasodilation must be addressed for successful therapy of PH (8). Collateral vessels are fragile and can bleed extensively, with esophageal and gastric variceal bleeding the major contributor to mortality because of portal hypertension (19). Additionally because blood now effectively bypasses the sinusoids, the liver cannot properly clear the blood of gut derived potentially harmful substances like ammonia, which now reach the systemic circulation, causing hepatic encephalopathy (20). Therapy of collateral vessels consists of pharmacotherapy with non-selective beta blockers (NSBB) like carvedilol and endoscopic variceal ligation (EVL).

Etiology

According to the equation $\Delta P=Q*R$, portal pressure increases when portal blood flow Q, resistance R or both increase. Depending on the site of increased flow or resistance, causes of portal hypertension can be classified as prehepatic, hepatic and posthepatic. An increase in intrahepatic resistance in cirrhosis is by far the most common cause of PH, followed by schistosomiasis and portal vein thrombosis as prehepatic causes. A detailed review of each etiology is beyond the scope of this study, so a brief overview is given in the relevant chapters. (7)

Prehepatic causes

Prehepatic portal hypertension is most commonly attributed to portal vein thrombosis (PVT), where a blood clot narrows the lumen of the portal vein, therefore increasing resistance. Inherited or acquired prothrombotic states can lead to PVT, but a slowed blood flow also plays an important role in the development of PVT in cirrhosis. Other causes include intra-abdominal tumors compressing the portal vein system from outside and, less commonly, congenital vascular anomalies or arteriovenous fistula. (21)

Intrahepatic causes

Cirrhosis

Cirrhosis is characterized by the ongoing replacement of healthy liver tissue with scar tissue. This process is called fibrosis and is the result of chronic liver injury and inflammation (22). It is a leading cause of morbidity and mortality worldwide with more than 120 million affected people (23). While hepatitis B and C have decreased as an etiology of cirrhosis due to better vaccination coverage and improved medication, there has been an increase in alcohol-associated liver disease and metabolically associated steatotic liver disease (MASLD) (24). The initial liver injury leads to a chronic inflammatory response, activating macrophages and myofibroblasts. Activated myofibroblasts begin depositing a fibrogenous matrix and collagen, impairing the relationship of hepatocytes and the sinusoids. Fibrosis forms regenerative nodules, impeding intrahepatic blood flow and causing elevated portal pressure (25). Inflammation causes a disruption in the complex signaling between cells, resulting in decreased production of vasodilators, mainly NO and increased vasoconstrictive mediators such as endothelin-1, leading to further intrahepatic resistance to blood flow (26). The replacement of healthy liver tissue with scar tissue is a slow and steady process that initially preserves liver function, known as the compensated state, in which there are few symptoms. Decompensation is defined as a rapid loss of liver function and occurrence of complications such as jaundice, ascites, gastrointestinal bleeding and hepatic encephalopathy (27). Although preventing decompensation is a major goal of modern medicine, 11% of patients with compensated cirrhosis are expected to experience decompensation each year (23). Apart from TIPS, which is mainly used to treat severe complications of portal hypertension in cirrhosis, the compensated state is managed by symptom control, lifestyle changes to remove triggering factors such as alcohol, unhealthy diet or control of viral hepatitis. Prognosis of cirrhosis varies depending on extrahepatic comorbidities and disease stage, with compensated cirrhosis showing a median survival of 12 years (27). Prognosis is significantly worse after decompensation but depends on the distinct decompensating event. To estimate prognosis scores like the Child Pugh Score and the Model of end stage liver disease Score (MELD) can be used to determine long term prognosis (25). Ultimately, liver transplantation should be considered in advanced stages of the disease.

Schistosomiasis

Schistosomiasis is a parasitic infection caused by trematodes that is prevalent in tropical and subtropical regions, particularly sub-Saharan Africa, South America and Asia. Although not common in the western world, in endemic areas it is a major cause of portal hypertension. During infection, the parasitic worm deposits its eggs in the prehepatic portal venules, which trigger a strong immune response leading to granuloma formation, fibrosis and increased presinusoidal resistance. Due to the presinusoidal intrahepatic site of increased resistance, the sinusoidal pressure is normal, which is why the HPVG, the most commonly used diagnostic tool for PH, is often normal in schistosomiasis. (28)

Posthepatic causes

Posthepatic causes arise from conditions that impede blood flow between the liver and the heart, leading to increased pressure within the preceding vascular system. Most clinically relevant of these conditions is Budd-Chiari-Syndrome (BCS), characterized by obstruction of the hepatic outflow or inferior vena cava. Other causes include congenital malformation and heart conditions like constrictive pericarditis and right heart failure, where blood is backed up before the right atrium and increases pressure in the portal venous system, ultimately leading to portal hypertension. (29,30)

Transjugular intrahepatic portosystemic shunt (TIPS)

Background

In chronic liver disease portal hypertension represents an early feature in the natural history and progression of liver injury and is the major contributor to the development of serious complications like variceal hemorrhage and ascites (8). Blood flows from the portal vein into the sinusoids and then into the hepatic vein. Increased portal pressure occurs when either blood flow or resistance along its path rises. The origin of increased resistance can lie in the portal vein itself, the sinusoids or the hepatic vein, therefore nomenclature distinguishes the causes of portal hypertension in prehepatic, intrahepatic and posthepatic (3,8). TIPS is an effective measure to reduce portal pressure, therefore preventing undesirable complications and outcome of portal hypertension (31). Nowadays TIPS can be used to treat patients who were deemed untreatable a few decades ago and represents a major achievement of modern medicine (32).

Concept of TIPS

TIPS is a minimally invasive medical procedure used in the management of portal hypertension, a serious condition emerging in chronic liver disease responsible for considerable mortality, morbidity and health care cost (33). A small channel is created through the liver parenchyma to allow blood to bypass the liver sinusoids and flow directly from the portal vein into the hepatic vein, effectively circumventing the liver. TIPS effectively relieves pressure off the portal venous system thus preventing and controlling the complications following portal hypertension, primarily variceal bleeding and recurrent ascites, showing a technical success rate of over 90% (31,34). Since TIPS was first implemented in the therapeutic regimen technical advances have improved the procedure steadily and optimal intervention techniques, patient selection and prevention of its complications are subject of ongoing research (35).

History and development

Since TIPS was first described by Rösch et al. in 1969 (36), much has changed, and technology has improved significantly. Colapitno et al. 1982 were the first to use TIPS in a series of 20 patients, but the long-term results seemed discouraging at the time due to frequent re-bleeding, with 9 patients dying within the first month (37). After the introduction of metallic expandable stents in 1985 by Palmaz et al. (38) in a series of canine experiments, the first Palmaz-stent was implanted in a human in Freiburg in 1988, starting the Freiburg TIPS project. At that time, the average duration of the TIPS procedure was about 8 hours. When Jean Marc Perarnau joined the project in 1990 and established sonographic targeting of the portal vein, the average procedure time dropped to 1-2 hours with significantly lower complication rates (35). By 1995, 500 patients had been treated in the project and the first results were published in 1993 (39). With the invention of polytetrafluoroethylene (PTFE) – covered self-expandable stent grafts in the early 2000´s shunt patency and survival were significantly improved compared to bare metal stents (40). Over the past decades, advances in technology, interventional techniques and consensus on optimal patient selection have improved the TIPS procedure astronomically.

TIPS today

Periinterventional measures

Before performing TIPS, preoperative measures are taken to facilitate the procedure and to prevent intra- and postoperative complications. Duplex sonography is used to identify anatomical abnormalities, and computer tomography (CT) or magnetic resonance imaging (MRI) may help with anatomical orientation, but are not routinely required (35). Echocardiography should be performed in patients with suspected cardiac impairment, as heart failure is a major contraindication to TIPS (6,41). In patients with hepatic hydrothorax and/or refractory ascites, paracentesis should be performed to improve respiratory function and to move the liver to a more anterior plane to ease puncture of the portal vein branch (35). A baseline laboratory assessment including liver function tests, renal function and coagulation status is routinely obtained. The MELD score is calculated as it is used as a predictor of mortality after TIPS. A MELD score >18 predicts significantly higher mortality within the first 3 months after TIPS (39). Finally, all risks and benefits of TIPS should be discussed with the patient and their family, and informed consent must be obtained. After successful intervention patients should be closely monitored for 6 hours and laboratory assessment of coagulation panel, blood count, liver and kidney function are done. Shunt patency is controlled the day after TIPS by doppler sonography and may be repeated within the first week. In further course, shunt patency should be monitored in regular intervals (42).

TIPS intervention – state of the art

Prior to intervention either general anesthesia is implemented or conscious sedation with midazolam and propofol can be used, depending on preference of practitioners. The right jugular vein is punctured and is the point of access to the inferior vena cava. Conventional technique involves puncture of the right portal vein branch via the right hepatic vein, however in cases where the hepatic vein is partially or completely occluded, e.g. in Budd-Chiari-Syndrome, direct puncture of the portal vein through the inferior vena cava can be done, termed the direct TIPS (43). A guidewire followed by an angled catheter is advanced into the hepatic vein under X-Ray or ultrasound guidance (42). For the puncture itself, two puncture sets are used, the closed coaxial system, where a stylette is advanced through a cannula, and the open Ross-Colapinto needle. An open needle allows for quick puncture and is inexpensive, while the closed coaxial system is more expensive but has been described as less invasive, although comparative studies are still missing (35). After puncture of a portal vein branch visual confirmation is gained using balloon occlusion hepatic venography with carbon dioxide. Correct access into the portal venous system is also indicated through a flush of blood after aspiration with a syringe on the TIPS needle. A contrasting agent is then introduced to confirm portal vein access. Once this transportal access is secured pressure measurement is performed. At this point in the procedure visible collaterals may be embolized with coils or an occluding agent, which has been shown to significantly reduce the risk of re-bleeding in patients with history of variceal bleeding in comparison to TIPS alone (42). An angioplasty balloon is used to expand the parenchymal channel, and the stent is placed and dilated to the appropriate diameter. After stent placement venography and pressure measurements are repeated and the pressure gradient between the right atrium and the portal vein is calculated. Austrian consensus guidelines recommend a post-interventional pressure gradient of <12 mmHg or at least a 50% reduction (41). Smaller 8mm diameter stents should be preferred to 10mm diameter stents, as they have been shown to be associated with better overall survival and a lower risk of post-TIPS hepatic encephalopathy and smaller impairment of liver function (44,45). PTFE-covered self-expanding stent grafts have become the standard of care, as they have shown improved overall survival compared with bare metal stents (46). The use of prophylactic antibiotics is controversial, although cephalosporins have been shown to reduce the incidence of bacterial infection after TIPS (47).

TIPS indications

TIPS is primarily indicated for the management of complications arising from portal hypertension, the most important indications being secondary prophylaxis of variceal bleeding and treatment of refractory ascites. These significantly contribute to morbidity and mortality in advanced liver disease, with variceal bleeding accounting for up to 30% of deaths in cirrhosis and refractory ascites affecting approximately 5%-10% of patients. An overview of all indications is given in table number 1. (48)

Variceal bleeding

Variceal hemorrhage is a serious complication of portal hypertension and cirrhosis that is best managed in an intensive care unit. At diagnosis, 30% of cirrhotic patients have varices, increasing to 90% after 10 years, 15% of patients with large varices will experience bleeding within one year, and up to 50% of patients with esophageal varices will experience bleeding at some point in their lives (49). To date, the mortality from acute variceal bleeding remains high at approximately 15% and the risk of recurrent bleeding after an acute episode is approximately 70% (50,51). Prophylaxis of variceal bleeding is managed with pharmacotherapy consisting of non-selective beta blockers (NSBB), endoscopic variceal ligation (EVL) or sclerotherapy. TIPS is indicated for prophylaxis of rebleeding, termed secondary prophylaxis, when EVL and NSBB fail to prevent rebleeding or are not feasible

(6,41). Acute variceal hemorrhage requires rapid extensive medical care and is associated with a considerable mortality ranging from 15%-20% (52). Aside from TIPS variceal bleeding is primarily treated with vasoactive drugs, addressing vasodilation of the splanchnic system, antibiotic prophylaxis and blood replacement and transfusion. Terlipressin, octreotide and somatostatin are effective vasoactive drugs to reduce HVPG and variceal pressure (53–55) and should be started as soon as possible, blood transfusion is implemented to a target hemoglobin level of 7-8 mg/dl and antibiotic prophylaxis with intravenous ceftriaxone 1g/24h must be administered upon admission (6,41). In acute variceal hemorrhage TIPS can be performed early within the first 72h upon admission, or as a rescue therapy when pharmacological treatment and EVL fail to gain bleeding control. Self-expandable metal stents (SEMS) or balloon tamponade can be used to temporarily achieve hemostasis until TIPS is available (6).

Early TIPS

Pre-emptive or early TIPS describes the use of TIPS in a selected group of patients who are at high risk of failure of conventional treatment and early re-bleeding and is placed within the first 72 hours, ideally within the first 24 hours after admission. This patient group is defined by the current consensus on the therapy of portal hypertension (6,41) as having liver disease with Child-Pugh class C <14 points, Child-Pugh class B with active bleeding and patients with HVPG >20mmHG. A cohort study of 63 patients showed a significantly higher survival rate, fewer days spent in intensive care and a lower incidence of rebleeding in the early TIPS group compared with pharmacotherapy and EVL (56). In patients fulfilling the criteria for early TIPS, acute on chronic liver failure (ACLF), hepatic encephalopathy and hyperbilirubinemia should not be considered as a contraindication to TIPS (6). In patients with a Child-Pugh score >14 points, lactic acidosis and an updated MELD score ≥30 points, TIPS should be considered individually but may be futile (41).

Rescue TIPS

Rescue or salvage TIPS is performed in patients unresponsive to conventional pharmacologic and endoscopic treatment. It is an effective measure in achieving hemostasis, with studies reporting success rates of over 90% (34). Despite its efficacy salvage TIPS is associated with considerable mortality, with studies reporting an overall mortality of 37%

(57). Although this mortality rate seems to be quite high, it is important to consider the patient population receiving salvage TIPS procedure being of high risk and having failed prior conventional therapy. To find predictors to confidently identify patients with a high risk of dying of salvage TIPS is subject of ongoing research. In a study including 58 patients by Azoulay et al. presence of sepsis, the need of catecholamines and the use of balloon tamponade were independent predictors of early mortality after salvage TIPS, however this cannot be transferred onto general population (58). Whether all patients with failure to control bleeding with conventional therapy should receive salvage TIPS is an ongoing debate but is still the current recommendation (6).

Ascites

Ascites is the accumulation of fluid inside the peritoneal cavity. It is the most common complication of cirrhosis, with more than 50% of patients developing ascites within 10 years and represents a major contributor to liver-related hospital admission (59). In addition, ascites is a sign of poor prognosis with transplant free mortality rate of 15-20% at one year (27). Although the pathophysiology of its formation is incompletely understood certain factors contribute to its development. Hyperdynamic circulation in portal hypertension leads to a relative decrease in arterial pressure, activating counteracting mechanisms like the sympathetic nervous system and the RAAS (60). Also, the intestinal capillaries show a weakened secretory and mechanical barrier function, which allows bacterial products and viable bacteria to enter the mesenteric lymphatic network. This process is called bacterial translocation and plays a vital role in the development of infection, in particular spontaneous bacterial peritonitis (SBP) and alters capillary permeability (61). Altered membrane permeability combined with the increased oncostatic pressure because of hyperdynamic circulation leads to the location of fluid inside the peritoneal cavity (62).

Ascites is diagnosed in clinical examination and ultrasound imaging and graded according to the European association of the study of the liver (EASL) into three grades, with grade 1 termed mild ascites requiring no specific therapy, grade 2 labeled moderate ascites and grade 3 describing large ascites with marked abdominal distension (63). Uncomplicated ascites is distinguished from complicated ascites by the absence of complications like hepatorenal syndrome (HRS), hyponatremia and SBP. Grade 2 is managed by natriuretic medication, namely spironolactone and furosemide, while in grade 3 large volume paracentesis (LVP) seems to be the safer and faster option (63,64).

Role of TIPS in ascites

As defined by Arroyo et al. in the international ascites club (IAC) refractory ascites is ascites, that cannot be mobilized or the early recurrence of which cannot be satisfactorily prevented by medical therapy (65). First line of treatment is repeated LVP with the administration of albumin (8g/ L of ascites removed). Diuretic therapy should be discontinued in those patients who do not excrete >30mmol of sodium per day under diuretic treatment (63). TIPS however offers a causal treatment option in refractory ascites, as it interrupts the hyperdynamic circulation by effectively lowering HVPG. The efficacy of TIPS in the management of refractory ascites has been shown in several studies (66). Generally, TIPS indicated in refractory ascites is performed electively and patient selection is crucial to avoid poor outcomes. The goal of TIPS in this scenario is to find a balance between adequate ascites control, risk of hepatic encephalopathy and reduction of liver function (60). A study of 171 patients with refractory ascites comparing 10 mm to 8 mm stent grafts reported improved ascites control with no increased risk of hepatic encephalopathy in the group receiving 10 mm stent grafts (67).

Hepatorenal syndrome

Hepatorenal syndrome is a critical complication of advanced liver disease characterized by a functional kidney failure with the absence of structural kidney damage. It is commonly assumed that it results from the complex circulatory changes in portal hypertension, but newer literature suggests that systemic inflammation and oxidative stress play a role in the development of HRS (68). The most important risk factor for HRS is SBP with approximately 30% of patients with SBP developing HRS, so screening and immediate treatment of patients with SBP is important in prevention and treatment (69). HRS is classified into two types, HRS-1 and HRS-2, where in HRS-1 the kidney failure is acute and develops rapidly and in HRS-2 the kidney failure progresses slowly over time. Recent discussions have led to a newer nomenclature classifying HRS-1 as HRS with acute kidney injury (HRS-AKI) and HRS-2 as either a type of chronic kidney failure (CKF) or as HRS without AKI (HRS-non-AKI) (65). TIPS has emerged as a potential treatment for HRS, in particular in cases refractory to standard therapy with terlipressin and albumin. The rationale for TIPS in HRS is based on its ability to reduce portal pressure, the key driver in pathophysiology of hyperdynamic circulation and HRS (70). Studies showed that TIPS in

HRS-AKI and HRS-non-AKI led to significant improvement of clinical-laboratory parameters and promising data suggested a potential benefit for transplant free survival of patients (71,72). Although a clear benefit is emerging in current data, more research is needed for confident criteria on patient selection, considering the risks of TIPS procedure. However, in HRS it is considered an excellent bridge therapy in patients waiting for liver transplantation, considering the high mortality rate of HRS-AKI of about 90% (73).

Hepatic hydrothorax

Hepatic Hydrothorax (HH) is a critical complication of portal hypertension associated with considerable morbidity and mortality. It occurs in about 5% of patients with advanced cirrhosis and shows a clear right sided dominance (85%) (70). The mainstay of treatment is dietary salt restriction, diuretic therapy and pleural intervention. Thoracentesis and pleural catheter carry significant morbidity (74). Large pleural effusion can present with shortness of breath, hypoxemia or respiratory failure, but patients with smaller effusion may be asymptomatic. It is diagnosed by exclusion of primary pulmonary, cardiac or pleural pathology and imaging with X-ray, computer tomography or ultrasound (75). Because of its rarity, evidence on the use of TIPS in HH is limited to several case reports and non-controlled studies. However, compared to other treatment options like pleurodesis and repeated thoracentesis TIPS was reported with high response rates and rather good long term survival (70), which is why TIPS is indicated in HH in current guidelines (6,41).

Portal vein thrombosis

Portal vein thrombosis is the narrowing or occlusion of the portal vein due to a blood clot. It represents the most common vascular disorder of the liver and the most common thrombotic event in cirrhosis, with an overall incidence of about 1%, in some risk groups as high as 26%, and carries significant morbidity and mortality (76–78). The blood clot develops according to the triad of Virchow due to slowed blood flow, endothelial injury or a hypercoagulability of the blood. Most cases of PVT are associated with advanced cirrhosis, but risk factors include malignancy, myeloproliferative disorders and inherited hypercoagulable states like protein-C- and protein S-deficiency or factor V-Leiden-mutation (78). PVT can be classified into a partial and total form and a chronic or acute course, with chronic and partial PVT mostly being an accidental find in imaging and presenting asymptomatic. Acute and total PVT however can present with gastrointestinal bleeding and abdominal pain due to intestinal infraction (77). Usually, management of PVT consists of removing the blood clot via anticoagulation, thrombolysis or thrombectomy but TIPS has emerged as a potential treatment, in particular in patients with underlying cirrhosis. TIPS in PVT is technically difficult, because the thrombus can be hard to puncture, especially once thrombus undergoes cavernous transformation, but technical advancement and improved image guiding has led to high success rates of TIPS in PVT (79). Nowadays TIPS is considered a safe and feasible alternative therapy in selected patients with PVT (79,80).

Budd Chiari syndrome

Budd-Chiari-syndrome is a heterogenous group disorders characterized by the congestion of the hepatic venous outflow. Obstruction can develop at any level of hepatic outflow from small hepatic veins to the inferior vena cava and even the right atrium (81). Blood stasis and infraction lead to hypoxic damage, fibrosis and ultimately cause cirrhosis if not treated. Its incidence in the general population is estimated with about 1 in 100 000 with primary myeloproliferative disorders being the leading cause for BCS (29). Clinical presentation may vary depending on the level and extent of the obstruction and can be classified into a fulminant, acute, subacute and chronic presentation (82). Therapy is aimed at controlling development of ascites, further formation and extension of venous thrombi and managing the underlying disease (83). In patients uncontrollable by conventional therapy TIPS can offer an effective way treatment by means of decompressing the congested liver. Traditional TIPS intervention can be difficult in BCS due to the conventional transjugular route being obstructed, but newer techniques termed “direct TIPS”, involving a ultrasound guided percutaneous insertion of a needle into a portal venous branch and directly puncturing the inferior vena cava, facilitate the insertion of TIPS (84). Due to the rarity of BCS prospective cohort studies investigating the correct timing of TIPS in BCS and patient selection are difficult, but existing literature support the efficacy and safety of TIPS in treatment of BCS (85).

TIPS in portal hypertensive gastropathy

Portal hypertensive gastropathy (PHG) is a common complication of cirrhotic and non-cirrhotic PH and is characterized by specific endoscopic findings of the gastric mucosa, dilation of venules without presence of inflammation. Prevalence seems to be significantly higher among patients with cirrhosis but varies widely from 20%-98% (86). Pathophysiology of PHG remains incompletely understood but hyperdynamic circulation seems to play a vital role as it increases flow through gastric vessels and decreases gastric mucosal perfusion, which could be demonstrated by improvement of PHG after TIPS (87,88). Most prevalent problem in PHG is chronic gastrointestinal bleed with subsequent anemia and iron insufficiency, occurring in 3%-60% of patients, but severe forms can lead to acute bleeding as well (89). Management depends on specific symptoms of PHG and ranges of NSBB and iron replacement in chronic bleed to vasoactive medication, antibiotics and transfusion in acute bleeding. TIPS is indicated if bleeding is refractory and does not respond to medical therapy and was shown to be an effective treatment of uncontrollable PHG (86–88).

Overview of TIPS indications

An overview of the indications for TIPS procedure according to the Austrian consensus on the diagnosis and management of portal hypertension in advanced liver disease (Billroth IV) (41) and the renewing consensus in portal hypertension (Baveno VII) (6) is given in the Table below (Table 1).

	Indication	Patient selection	Level of recommendation
Variceal hemorrhage	Pre-emptive / former termed early-TIPS (<72h after bleeding)	I. Patients with Child Pugh Score class C <14 II. Patients with Child B8-B9 + active bleeding under vasoactive treatment III. Patients with HPVG >20 mmHG	A1[1]/B1[2]

	Rescue/Salvage-TIPS in acute Variceal Bleeding	I. Patients with failure to control bleeding with SX-Ella Danis Stent II. Patients with failure to control bleeding with pharmacologic treatment	B1[1]
	Elective TIPS in secondary prophylaxis	I. Secondary prophylaxis after failure of NSBBs + EVL II. Patients who cannot tolerate EVL or NSBBs for secondary prophylaxis	B1[2]
Ascites	Recurrent Ascites (requiring ≥3 LVP within one year)	Patients who have recurrent ascites despite maximum dose pharmacotherapy	A1[1]/B1[2]
	Refractory Ascites	Ascites in Patients that lack the response of diuretic treatment/ maximum dose cannot be administered due to side effects	B1[2]
Other	Hepatic Hydrothorax	Patients with recurrent hepatic hydrothorax unresponsive to diuretic therapy	B1[2]
	Hepatorenal Syndrome	Patients with HRS-non-AKI (previously termed HRS-Type 2)	B1[2]
	Budd-Chiari-Syndrome	When other endovascular treatment is not feasible and patient does not improve under pharmacotherapy	B1[1]
	Portalhypertensive Gastropathy (PHG)	Patients with recurrent bleeding from PHG despite	C1[1]

		NSBB and endoscopic treatment	
	Portal vein thrombosis	Patients with thrombosis of the portal vein trunk without recanalization on anticoagulation	C2[1]/C1[2]

Table 1: Overview of TIPS indications - Level of recommendation graded according to Baveno VII Consensus labeled with [1] and according to the Billroth IV Criteria labeled with [2]

Alternatives to TIPS placement in treatment of PH

TIPS is highly effective in managing complications of portal hypertension but requires extensive resources and expertise, which is why it is performed in specialized centers. Pharmacotherapy with NSBB remains first line therapy for primary prophylaxis of variceal hemorrhage and vasoactive medication like terlipressin, octreotide and somatostatin being used for acute episodes (6,41). Endoscopic intervention can be a powerful tool, with variceal ligation being as effective as pharmacotherapy in primary prophylaxis (90). Next to ligation sclerotherapy can be performed, obliterating varices with a sclerosant agent, which can offer success in controlling varices but requires surveillance afterwards (91). Balloon-occluded retrograde transvenous obliteration (BRTO) has shown lower risks of rebleeding and postoperative hepatic encephalopathy compared to TIPS in gastric varices (92). Surgical creation of a portosystemic shunt can be an option in managing PH, but since most patients with PH pose a significant risk in surgery its role is limited to patients with good liver function (Child-Pugh-Class A and B) whose primary and only problem is recurrent bleeding (93). Ultimately the only causal treatment of advanced liver disease and portal hypertension remains to be liver transplantation, offering the highest survival rate and a chance of complete rehabilitation in suitable candidates, but to achieve good outcome careful evaluation is needed (94).

TIPS contraindications

Prior to TIPS several preexisting conditions can dramatically favor an undesirable outcome and should therefore be carefully considered. The current Austrian consensus on the diagnosis and management of portal hypertension in advanced chronic liver disease (Billorth IV) (41) defines the absolute and relative contraindications as follows:

Absolute contraindications for TIPS placement:

- Severe liver failure (Child Pugh Score ≥C14) for elective TIPS placement
- Severe and uncontrolled (porto)pulmonary hypertension
- Symptomatic heat failure (in particular right heart failure and tricuspid regurgitation)

As TIPS requires the cooperation of gastroenterologists, radiologists as well as anesthesiologists, TIPS always is a team-based decision. Relative contraindications as listed below can severely aggravate preexisting problems, greatly enhance the risk of operation or make technical implementation difficult or not feasible.

Relative contraindications for TIPS placement:

- Asymptomatic heart failure
- Asymptomatic (porto)pulmonary hypertension
- Recurrent episodes of hepatic encephalopathy not related to acute bleeding, diuretics, electrolyte disturbance or infection
- Extensive hepatic malignancy or unrelieved biliary obstruction
- Bilirubin of >3-5mg/dL for elective procedures
- PVT or splanchnic vein thrombosis (TIPS requiring recanalization of thrombosis should be referred to expert centers)
- Any severe extrahepatic disease associated with a limited life expectancy

Efficacy

Although TIPS is a complex procedure, it has gained popularity over the last decades and its role in the therapy of advanced chronic liver disease is constantly evolving. TIPS can be a successful treatment of patients with severe cirrhosis who were otherwise untreatable a few decades years ago (31). TIPS seems to be a successful method of portal decompression in more than 80% of cases (31,32). In selected patients it offers significant beneficial effects on morbidity, mortality and transplant free survival with the most robust data on patients with refractory ascites (66,95–97). However, TIPS still carries the risk of complications such as post TIPS hepatic encephalopathy (HE), post TIPS liver failure and technical complications.

Complications

The complex anatomy of the portal venous system and difficulty of puncture makes TIPS procedure a highly sophisticated technique requiring extensive experience of practitioners. Due to its complexity the procedure itself may bring along complications like failure of finding adequate puncture, puncture of the liver capsule, bleeding or infection.
A large cohort study including 948 patients reported major complication in 30 patients or 3,2% with a procedural mortality rate of 0,84% or death in 8 patients, most deaths being attributed to accelerated liver failure (98). Generally, TIPS is considered a safe procedure with a relatively low procedural complication rate, but next to technical complications TIPS can cause adverse effects on metabolism and organ function, which is why TIPS must be considered carefully.

Technical complications

Due to the complex anatomy and difficulty of puncture technique TIPS is a highly sophisticated procedure requiring extensive experience from practitioners. Due to the challenging technical aspect, complications have been described with an incidence as high as 20%, but most of these complications are minor and do not influence survival or morbidity (99). Major complications include perforation of the liver capsule, bile duct injury, continuous organ failure and infection. Injury of the hepatic artery or its branches is uncommon with about 6% only being of clinical significance in less than 2% (100). In the era of PTFE-covered self-expandable stents, stent migration and displacement have become a rarity (42). Generally, TIPS is considered a safe procedure with a low complication rate compared to treatment alternatives. Technical advances of the past decades have significantly improved TIPS procedure leading to safer and faster interventions (35).

Post TIPS hepatic encephalopathy (PTHE)

In advanced liver disease and after TIPS the development of hepatic encephalopathy remains a significant concern. Hepatic encephalopathy is a reversible impairment of brain function due to an increased gut derived toxin load on systemic circulation. Although complete pathogenesis remains the subject of research, ammonia as a primary driver of HE is clearly indicated in a large body of research (101). Ammonia, normally metabolized in the hepatocytes, can cross the blood brain barrier (BBB) when its blood concentration rises, leading to increased glutamine synthesis inside the astrocytes, causing them to swell up and impair regular function. Newer insight found that low grade systemic inflammation in advanced liver disease also contribute to HE by damaging the integrity of the blood brain barrier, thus facilitating ammonia going across (102). This manifests, depending on the severity in a variety of cognitive symptoms. According to the West-Haven-Criteria HE is graded into covert HE (grade I) and overt HE (grad II, III and IV), with grade I only being detectable in neuropsychological exams, grade II appearing with lethargy and disorientation for time, grade III with confusion and gross disorientation and ultimately stupor and coma termed as grade IV (20). Development of HE after TIPS is no different than in advanced liver disease, but the relieved portal pressure after TIPS comes at the cost of further compromising liver function and metabolism as TIPS shunts large volume of blood with high ammonia concentration around the liver into the systemic circulation (103). Treatment includes medical prophylaxis with lactulose and rifaximin. Lactulose targets ammonia production and uptake from the gut while rifaximin, a poorly soluble broad-spectrum antibiotic, targets systemic inflammation. Rifaximin has been reported to have additional effects that are not clearly understood yet, but its synergistic effect with lactulose to treat HE is used in practice (104). L-Ornithine-L-Aspartate (LOLA) can be added to further decrease serum ammonia levels by increasing endogenous glutamine synthesis from ammonia (105). In severe cases a reduction of TIPS diameter, reducing the shunt volume can be necessary, which has been described not to increase the risk of new variceal bleeding but is associated with partial reoccurrence of ascites. Risk for PTHE differs significantly from patient to patient with age above 70, poor liver function, large stent diameters and history of prior HE being precipitating factors for PTHE (102). Also, procedural factors impact the risk of PTHE with HE being more common after TIPS in acute uncontrollable bleeding and in cases where the HVPG was decreased beyond 60% (106). Incidence of PTHE varies widely with a review of about 50 studies of the past decade reporting an incidence of 7%-61% regardless of follow up time (102). After all PTHE is a major reason for readmission after TIPS placement and is a huge burden on patients and health care as it impairs quality of life and affects caregivers alike (107).

Post TIPS Liver Failure (PTLF)

Acute liver decompensation is defined as an acute deterioration of liver function following a precipitating event, in this case the TIPS placement. It is marked by a sudden increase of liver function tests including alanine-aminotransferase (ALT), international normalized ratio (INR) and bilirubin. After TIPS portal venous perfusion pressure is reduced significantly and portal flow can in fact reverse and result in some degree of ischemia (108). Additionally, the placed stent can compress or occlude hepatic arteries or portal vein branches, causing potential infraction and ischemia (109). Without the possibility of timely transplantation TIPS reduction or occlusion plays an important role in treatment of PTLF. Overall PLTF is a rare but disastrous complication of TIPS intervention. (110)

Endotipsitis

Tipsitis or endotipsitis is the localized infection of the stent shunt placed in the liver parenchyma leading to subsequent symptoms of infection and bacteremia. To date, there are only case reports and series, so Endotipsitis remains incompletely understood. A detailed review of the status quo of current data is provided in the respective chapter.

Endotipsitis

History and current data

Endotipsitis is a rare but potentially life-threatening complication of TIPS. The first description of infection following TIPS insertion was in April 1997 by Schiano et al. reporting fatal fungemia resulting from an infected TIPS (111). One year later Sanyal and Reddy coined the term endotipsitis and provided initial diagnostic criteria conducted from a total of 8 cases of endotipsitis over three years (1). In their analysis a definite infection was defined as clinically significant bacteremia, consisting of fever and multiple positive blood cultures, with vegetations or thrombi inside of the TIPS stent, and a probable infection as sustained bacteremia and unremitting fever with apparently patent TIPS under exclusion of other sources of infection. Since the initial report, over 40 cases have been described in literature, and the initial diagnostic criteria have been subject of discussion. Incidence of fever and bacteremia have been reported to vary from 2%-25% of patients following TIPS, yet concrete incidence of endotipsitis remains unknown due to lack of uniform definition and paucity of data (112). Recent reviews analyzing the relevant records between 1965 and 2009 estimated incidence to be at around 1,5% with a predominance of male patients and alcoholic liver disease (112,113). After Sanyal and Reddy proposed the first diagnostic criteria more suggestions of stricter and more specific criteria have been brought forward. DeSimone et al. defined sustained bacteremia as two blood cultures drawn >12 hours apart, that are positive for the same organism, without another identifiable source of infection (114). Later, Armstrong and Macleod proposed an even more specific criteria with two or more blood cultures being positive for the same organism, the first and the last at least being 7 days apart (115). Although significant effort has been made to find a strong definition and robust diagnostic criteria the lack of histopathologic studies for diagnosis of endotipsitis has been critiqued (116).

Diagnosis

The problem with definite diagnosis and reason for controversy is the feasibility of analyzing thrombotic material of the TIPS stent to clearly identify it as the source of infection. Stent removal is generally impractical and is only possible during autopsy or after liver transplantation. Therefore, diagnostic criteria in a similar fashion to other intravascular infections have been proposed to diagnose endotipsitis. Diagnosis, however, requires a high level of suspicion and an extensive workup to exclude any other source of infection. A comprehensive imaging workup includes doppler sonography to assess shunt patency, computer tomography to evaluate collections or abscesses and echocardiography to rule out endocarditis. The use of 18 F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET)/CT has been described to potentially identify TIPS correctly as source of infection in a recent case study (117). Emphasis is put on to the relevance of blood cultures before implementation of antibiotic therapy to have proof of unremitting bacteremia.

Endothelial biopsy to obtain tissue for cultures and histopathologic analysis has been described in diagnosis of endovascular infections, but the procedure is not widely available and in the diagnostic criteria proposed over the years biopsy is not required for definite diagnosis (118). Reviews suggested a distinction of early and late infection with early infection within 120 days of TIPS and late infection after this timespan (112). A temporal relationship of TIPS manipulation and infection has been suspected in late infections, but data is too scarce to draw any conclusions, however in isolated cases this may add to the level of suspicion. Ultimately a case-based approach is recommended, with index suspicion being the driving factor in unexplained bacteremia. (112–114)

Management

The management of endotipsitis remains challenging due to the lack of standardized treatment options, with recommendations footing on reviews and experience of individual case reports. Primarily a prolonged course of antibiotics is used as removal of TIPS stent is often impractical and complications of PH would recur (112). Specific choice of antimicrobial substance should be guided by results of cultures and susceptibility testing. Patients may also require more than one course of antimicrobial medication for successful treatment. In suspected fungemia amphotericin B and fluconazole seem to be the drugs of choice, while in bacteremia an empirical treatment with broad spectrum antibiotics is used (112). The length of treatment is not yet well defined, but a six-week course of intravenously administered antibiotic therapy has been recommended, however there have been reports of courses over 1000 days or even indefinitely (119). Mizrahi et al. could not find a correlation of duration of treatment and success rate in their analysis of 36 patients with endotipsitis (112). When no resolution of infection can be achieved, liver transplantation seems to be the only option although there has been a report of successful surgical removal of TIPS (120). Antibiotic prophylaxis before the initial TIPS procedure to prevent early infection through procedural microbial seeding has been suggested, but a study following up on 64 patients undergoing TIPS procedure concluded no use of antibiotic prophylaxis in prevention of early infection (121). Mortality of endotipsitis is reported to be as high as 32% in a recent study of 56 cases, but ultimately more data is needed for robust conclusions (119). (112,119–121)

Future perspective

There is an urgent need to establish uniform definitions, prophylaxis, and treatment protocols in endotipsitis (119). Large scale multicenter studies are needed to provide adequate data for robust conclusions, which are however difficult due to the rarity of the disease. Innovative approaches are emerging in detecting early infection in TIPS procedure with procalcitonin being explored as a potential biomarker (122). Furthermore, the application of novel imaging techniques, such as intravascular optical coherence tomography, may improve our ability to detect early biofilm formation within TIPS stents (123). As our understanding of the microbiome's role in liver disease advances, future studies may also explore the potential role of gut microbiome in development of endotipsitis (124).

Patients and Methods

Data from all patients receiving TIPS at the LKH Universitätsklinikum Graz between January 2004 and January 2024 was retrospectively analyzed. One case with definite diagnosis of endotipsitis, which occurred outside of the study timespan, is described as an exemplary case report but is excluded from statistical analysis. Beforehand, approval from the Ethics Committee of the medical University Graz was given (39290ex2324). Data was collected through the medical information system "openMEDOCS", which was implemented in January of 2004, therefore setting the starting point of data collection. Cases with unsuccessful TIPS placement and patients under the age of 18 years were excluded from the statistical analysis. Patients with insufficient data, e.g. complete lack of records prior to TIPS, were also excluded. Patients with orthotopic liver transplantation after TIPS but before infection were excluded from statistical analysis of infectious complications. The following data was assessed during data collection:

- **Demographic data**: Sex, age, etiology of portal hypertension, reason and date of hospital admission, length of hospital stay, weight, height, BMI
- **Technical data concerning TIPS**: Nominal Diameter of TIPS, length of TIPS, HVPG before and after TIPS placement, TIPS dilation and pressure of the portal vein and right atrium before and after TIPS placement
- **Medical history prior to TIPS**: Episodes of bleeding and last bleeding date, ascites, diagnosis of hepatocellular carcinoma, PVT, SBP, HE, Ascites and large volume

paracentesis, main indication of TIPS, the use of early TIPS, systolic and diastolic blood pressure and heart rate

- **Laboratory parameters within 48 hours before TIPS**: Electrolytes, creatinine, GFR, Urea, bilirubin, albumin, PTT, INR, Ammonia levels, C-reactive protein, AST, ALT, GGT, hemoglobin, platelet count, white blood cell count, fibrinogen, D-dimer and HbA1c. Severity of disease were assessed using Child Pugh Score, MELD and MELD-Na-Score, MOTS and FIPS-Score
- **Medication intake**: Doses of Furosemide, Spironolactone, Propranolol, Carvedilol and proton pump inhibitors, use of rifaximin, other antibiotics than rifaximin, lactulose, LOLA, antiplatelet therapy, anticoagulants, statins or metformin
- **Data regarding history of infection**: Infection up to three months prior to TIPS, type of infection if present, infection upon admission, infection in follow-up (regardless of set follow up timespan), type of infection in follow-up, blood cultures, antibiotic regimen, foreign installations, type and name of pathogen, length of therapy, course and outcome
- **Post TIPS medical history**: Orthotopic liver transplantation, newly diagnosed hepatocellular carcinoma, PVT, HE, Occlusion of TIPS, intervention of TIPS and regarding type of intervention, recurrence of bleeding, necessity of LVP or pleural paracentesis, death and if so reason of death
- **Six-month follow-up data (on average six months, minimum three, maximum nine months:** Laboratory parameters and medication intake (as defined above)

Statistical Analysis

All statistical analysis was performed using SPSS (version 29, IBM Corp.). Data was recorded and managed using Microsoft Excel (version 2502 Build 16.0.18526.20168). Categorial variables were expressed as absolute values and relative values (percentages), continuous variables as median (interquartile range, IQR) or mean value. For all statistical tests *p* values less than 0,05 were deemed significant. Test for normal distribution was done using Shapiro Wilk Test. In inferential statistics for normally distributed metric variables paired and unpaired T-Test was used and Wilcoxon-Log-Rank-Test for non-normally distributed values. For categorial variables chi square test was used for comparison and when more than 20% of expected frequencies were below 5, fishers exacter test was used instead.

Results

Patient characteristics and demographics

Between January 2004 and January of 2024 254 patients underwent TIPS procedure at the medical University Hospital of Graz. 24 Patients were excluded from statistical analysis due to failure of TIPS implantation (n= 7). Patients were also excluded in case of insufficient data (n=17). The remaining 230 patients were included in the analysis.

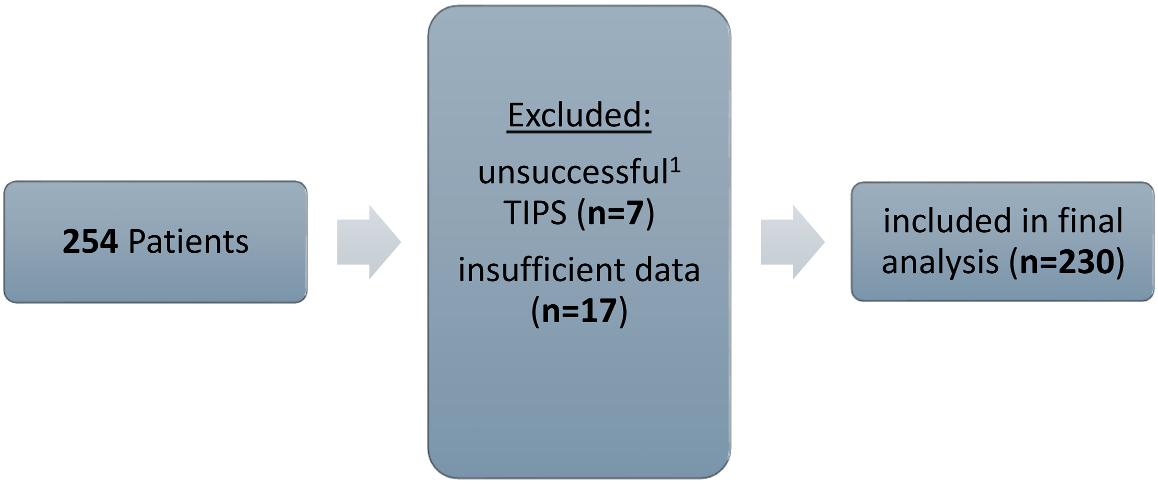

Figure 1: Flowchart of patient selection - [1] TIPS unsuccessful due to cavernous transformation, partial or total PVT or anatomic feasibility

The majority of patients were male (n=166; 72%). Patient age ranged from 23 to 90 with a median of 58 years (IQR 15.5). HVPG prior to TIPS ranged from 2 mmHG to 54 mmHG with a median of 17 mmHG (IQR 8.5). After TIPS HVPG dropped to a median of 7 mmHG, ranging from 1 mmHG to 46 mmHG (IQR 5). Median HVPG difference before and after TIPS was 9 mmHG, ranging from 0 to 38 mmHG of pressure reduction (IQR 8). Main indication for TIPS was refractory ascites in 109 cases (47%) followed by portal hypertensive bleeding in 90 cases (37%). In patients receiving TIPS due to bleeding, salvage- or rescue-TIPS was performed in 52 patients (23%). The most common etiology for portal hypertension was alcohol associated liver disease (ALD) in 174 cases (76%) followed by viral hepatitis in 12 cases (5%) and Budd-Chiari Syndrome in 6 cases (3%). In

10 (4%) cases the origin of portal hypertension was unknown. Severity of liver disease was assessed using MELD-Score, MELD-Na-Score and Child-Pugh-Score. Child Pugh Score ranged from 5 to 14 with a mean value of 11 (IQR 5). MELD-Score ranged from 6 to 42 with a median of 12 (IQR 7) and MELD-Na ranged from 6 to 40 with a mean value of 15 (IQR 10). The complete distribution of etiological categories and demographic data is presented in figure 2.

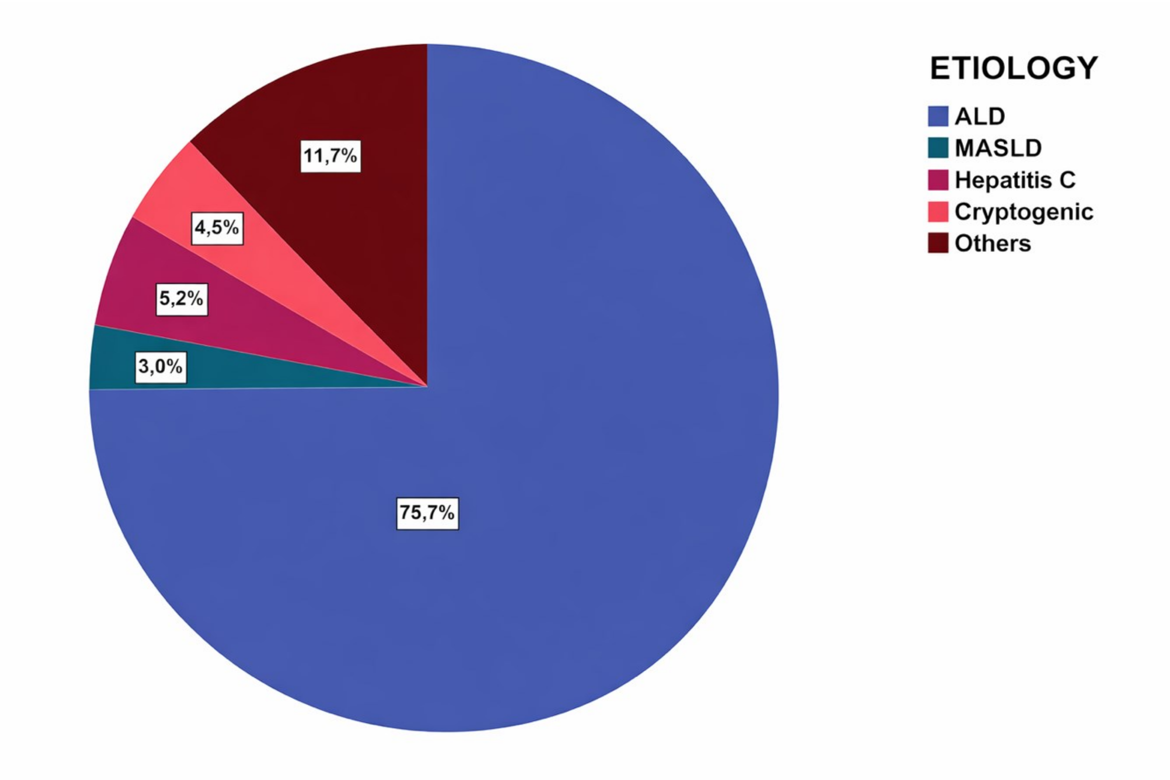

Figure 2: Etiologies of portal hypertension - ALD = alcoholic liver disease; MASLD = metabolic dysfunction-associated steatotic liver disease; Others consisting of autoimmune hepatitis (0.9%), hemochromatosis (0.9%), ALD + hemochromatosis (0.9%),PBC = primary biliary cholangitis (2.2%), BCS = Budd-Chiari-Syndrome (2.6%), ALD + hepatitis C (1.3%), drug induced liver injury (DILI) (0.9%), chronic right heart failure (0.4%), idiopathic (0.9%), hepatitis B (0.9%) and chronic graft versus host disease (cGcHD)(0.4%)

Pre-TIPS medical history and infections prior to TIPS

Records regarding the history of liver disease prior to TIPS were reviewed. Before TIPS placement, 145 (63%) patients had ascites of any grade, 114 (49%) either had a first or a recurrent episode of gastrointestinal hemorrhage, 27 (12%) were hospitalized for hepatic encephalopathy (HE) of any grade, 7 (3%) had hepatocellular carcinoma prior to TIPS, 25 (11%) had at least a partial portal vein thrombosis (PVT), and 18 (8%) patients had a history of at least one episode of spontaneous bacterial peritonitis (SBP). An infection within three months before TIPS placement was recorded in 24 (10%) patients, of which 7 (29%) had pneumonia, 6 (25%) had SBP and 3 (13%) had uncomplicated urinary tract infection. Another 7 patients (29%) were found to have an otherwise specified infection and in 1 (4%) patient, the focus of infection remained unclear. The median duration of hospital stay was 10 days (IQR 15) and ranged from 0 to 141 days. 10 patients (4%) were found to already have an infection upon admission or developed an infection during the same hospital stay of the TIPS placement, but before the TIPS procedure. Out of these 10 patients with infection upon admission, 5 (50%) had pneumonia, 2 (20%) an SBP and 3 (30%) upper respiratory infection, termed otherwise specified infection. The table below summarizes patient characteristics regarding infections prior to TIPS placement (Table 2).

Characteristics of patients with infections within 3 Months prior TIPS placement (n=24)

Feature	***Amount, n (%)***
Female sex	***7 (29%)***
Diabetes mellitus	***4 (17%)***
Type of infection:	
Pneumonia	***7 (29%)***
Urinary tract infection	***3 (13%)***
Spontaneous bacterial peritonitis (SBP)	***6 (25%)***
Other specified infection	***7 (29%)[1]***
Infection of unclear focus	***1 (5%)***

Child-Pugh-Class:	
A	***1 (5%)***
B	***6 (25%)***
C	***12 (50%)***

Table 2: Characteristics of patients with infections within 3 months prior to TIPS (n=24) [1]Other specified infections included upper respiratory infections (e.g. sinusitis), soft tissue and skin infections or gastrointestinal infections

Baseline laboratory parameter

Laboratory parameters from three months prior to TIPS placement were considered valid. The full range of parameters is shown in Table 3 below.

Laboratory parameter (unit)	*Valid*	*Minimum*	*Maximum*	*Median*	*IQR*
Sodium (mmol/L)	*228*	*120.0*	*149.0*	*139.0*	*6.0*
Potassium (mmol/L)	*226*	*1.9*	*6.5*	*4.1*	*0.8*
Creatinine (mg/dL)	*225*	*0.3*	*8.7*	*1.0*	*0.6*
GFR (ml/min/BSA)	*210*	*6.7*	*311.0*	*81.1*	*46.5*
BUN (mg/dL)	*212*	*4.0*	*289.0*	*41.0*	*46.5*
Bilirubin (mg/dL)	*203*	*0.2*	*32.0*	*1.40*	*1.8*
Albumin (g/L)	*174*	*1.0*	*58.0*	*3.3*	*0.8*
PT (%)	*226*	*24*	*114.0*	*61.0*	*24.0*
INR	*220*	*0.9*	*2.7*	*1.3*	*0.3*
ALT (U/L)	*216*	*4.0*	*2017.0*	*22.0*	*20.0*
AST (U/L)	*204*	*11.0*	*2703.0*	*40.0*	*30.0*
GGT (U/L)	*210*	*4.6*	*3056.0*	*97.5*	*121.0*
Hb (g/dL)	*227*	*5.9*	*16.7*	*10.1*	*2.8*
WBC (G/L)	*227*	*1.2*	*28.5*	*6.46*	*4.3*

CRP (mg/L)	*214*	*0.6*	*194.0*	*12.30*	*18.5*
PLT (G/L)	*227*	*17.1*	*466.0*	*115.0*	*101.0*

Table 3: Distribution of laboratory parameters within 3 months prior to TIPS placement; GFR = glomerular filtration rate, BUN =blood urea nitrogen, PT = prothrombin time, INR = international normalized ratio, ALT = Alanine Amino transferase, AST = aspartate amino transferase, GGT = gamma-glutaminyl transferase, Hb = hemoglobin, WBC = white blood cells, CRP = C-reactive protein, PLT = platelet count

Baseline medication intake

At the time of TIPS placement, medication intake and dosage was assessed for diuretics (furosemide and spironolactone), NSBB´s (propranolol and carvedilol) as well as proton pump inhibitors. The intake of L-ornithine L-aspartate (LOLA), lactulose, rifaximin and other antibiotics, statins, metformin, anticoagulants or anti-platelet drugs was also recorded. The table below provides an overview of medication and dosage amongst the patient population (Table 4).

Medication	***Cases (%)***	***Valid***	***Min. Dose (mg)***	***Max. Dose (mg)***	***Median Dose (mg)***	***IQR (mg)***
Furosemide	*145 (63%)*	*221 (96%)*	*20*	*250*	*40*	*20*
Spironolactone	*133 (58%)*	*221 (96%)*	*12.5*	*600*	*100*	*100*
Propranolol	*36 (16%)*	*221 (96%)*	*10*	*80*	*25*	*20*
Carvedilol	*82 (36%)*	*205 (89%)*	*0*	*50*	*12*	*6.3*
PPI	*144 (63%)*	*220 (96%)*	*0*	*120*	*40*	*40*
LOLA	*137 (60%)*	*214 (93%)*				
Lactulose	*112 (49%)*	*212 (92%)*				
Rifaximin	*168 (73%)*	*213 (93%)*				
Antibiotics[1]	*43 (19%)*	*226 (98%)*				
Statins	*2 (1%)*	*212 (92%)*				
Anticoagulants[2]	*20 (7%)*	*211 (92%)*				
Metformin	*3 (1%)*	*213 (93%)*				
Antiplatelet-therapy[3]	*9 (4%)*	*212 (92%)*				

Table 4: Overview of medication and dosage at point of admission to TIPS procedure; PPI = proton pump inhibitors (mainly Pantoprazole), LOLA = L-ornithine L-aspartate, [1]Antibiotics other than Rifaximin, [2]Vitamin K Antagonists or direct oral anticoagulants, [3]Aspirin or P2Y12- Antagonists

Post TIPS outcome and follow up data

After six months, 75 of 230 patients (33%) had died, 154 patients (67%) were still alive, and the fate of 1 patient (<1%) was unknown. By the end of the observation period, 104 patients (45%) had died, 121 (53%) were still alive and the outcome was unknown in 5 patients (2%) due to loss of follow-up. 23 patients (10%) had received liver transplantation (LTX) within 6 months after TIPS, thereof, 22 patients (97%) were still alive at 6 months follow-up. To focus on short-term outcome, 90-day survival was also assessed. After exclusion of already transplanted patients (n=12) 90-day survival was 78% (n=170), 22% (n=47) patients had died and <1% (n=1) were lost to follow up. The median number of days patients were observed was 522 days (IQR 1114) with a range between 0 to 5083 days. Of the 104 patients who had died at the end of our observation period, 23 (22%) had died of hemorrhage, 11 (11%) of acute hepatic decompensation, 13 (13%) due to infection, 9 (9%) because of HE, 2 (2%) due to right heart decompensation and 46 (44%) because of other unspecified causes. Following TIPS placement, 78 patients (34%) developed overt HE, 15 (7%) were diagnosed with hepatocellular carcinoma (HCC) and 34 patients (15%) had at least one (further) episode of hemorrhage. 36 patients (16%) required paracentesis of ascites at least two times after TIPS and 6 (3%) received drainage of pleural effusion. TIPS revision was necessary in 19 patients (8%), thereof, 5 (26%) required TIPS reduction, 2 (11%) needed dilation of TIPS, 4 (21%) required angioplasty or balloon dilation, 5 (26%) needed another TIPS with 3 of them who received parallel TIPS after failure of TIPS-recanalization and in the remaining 2 patients, angioplasty was performed and a “TIPS in TIPS” was placed. A total of 40 (19%) patients underwent liver transplantation within the observational period. None of the patients had undergone liver transplantation before TIPS. MELD-Score was calculable in 101 (61%) patients with a median value of 9 points (IQR 3), a maximum of 20 and a minimum of 6. Child-Pugh-Score could be calculated in 90 patients (54%) with a median score of 6 points (IQR 2), a maximum of 12 and a minimum score of 3. Six months after TIPS placement, laboratory parameters were reassessed (Table 5).

Laboratory parameters at six-month follow-up

Laboratory parameter (unit)	*Valid*	*Minimum*	*Maximum*	*Median*	*IQR*
Sodium (mmol/L)	*133*	*123.0*	*146.0*	*138.0*	*6.0*
Potassium (mmol/L)	*134*	*3.0*	*5.8*	*4.0*	*0.7*
Creatinine (mg/dL)	*134*	*0.4*	*8.7*	*0.9*	*0.4*
GFR (ml/min/BSA)	*119*	*6.6*	*145.5*	*85.9*	*36.4*
BUN (mg/dL)	*93*	*3.5*	*127.0*	*34.0*	*27.0*
Bilirubin (mg/dL)	*124*	*0.2*	*16.1*	*1.3*	*1.5*
Albumin (g/L)	*102*	*1.4*	*4.8*	*3.6*	*0.8*
PT (%)	*128*	*22.0*	*117.0*	*66.0*	*30.0*
INR	*123*	*0.9*	*2.9*	*1.2*	*0.4*
ALT (U/L)	*129*	*5.0*	*797.0*	*26.0*	*22.0*
AST (U/L)	*128*	*12.0*	*1751.0*	*43.0*	*35.5*
GGT (U/L)	*129*	*11.0*	*2142.0*	*99.0*	*185.0*
Hb (g/dL)	*133*	*3.2*	*15.5*	*11.4*	*3.0*
WBC (G/L)	*131*	*1.6*	*16.8*	*5.2*	*2.8*
CRP (mg/L)	*129*	*0.3*	*185.0*	*4.6*	*9.9*
PLT (G/L)	*134*	*8.0*	*705.0*	*120.0*	*85.0*

Table 5: Distribution of laboratory parameters 6 months after TIPS placement; GFR = glomerular filtration rate, BUN =blood urea nitrogen, PT = prothrombin time, INR = international normalized ratio, ALT = Alanine Amino transferase, AST = aspartate amino transferase, GGT = gamma-glutaminyl transferase, Hb = hemoglobin, WBC = white blood cells, CRP = C-reactive protein, PLT = platelet count

After six months 154 patients (67%) were still alive. At six-months follow-up (defined as 12-36 weeks after TIPS), it was re-assessed whether certain drug groups were prescribed. Drug records were available in 105 patients (73%). Table 5 provides an overview of drug-intake and dosage at 6 months after TIPS. When comparing follow-up medication with baseline data before TIPS, we detected a significant reduction in the prescribed doses of furosemide *(50.4 [44.8-56.0] vs 29.4 [20.9-37.9], p <0.01)*, spironolactone *(148.0 [131.7-164.4] vs 66.5 [51.0-81.9], p <0.01)* and proton pump inhibitors *(51.2 [47.1-55.2] vs 27.4 [22.4-32.4], p <0.01)*. A significant increase of serum potassium levels *(135.3 [134.2-136.3] vs 137.6 [136.6-138.6], p <0.01)* and hemoglobin *(10.3 [9.8-10.7] vs 11.5 [11.0-12.0], p <0.05)* as well as a significant reduction of serum albumin *(4.0 [2.6-5.6] vs 3.6 [3.5-3.7], p <0.05)* and CRP *(17.4 [14.0-20.9] vs 14.6 [7.8-21.4], p <0.01)* could be identified by comparing laboratory parameters before and six months after TIPS. Lastly MELD Score decreased significantly comparing patients who provided measurement before and after TIPS *(12.0 vs 9.9 [0.8-3.4], p <0.01)*.

Medication intake and dosage at six-months follow-up

Medication	*Cases (%)*	*Min. Dose (mg)*	*Max. Dose (mg)*	*Median Dose (mg)*	*IQR (mg)*
Furosemide	*65 (39%)*	*20*	*375*	*40*	*40*
Spironolactone	*62 (37%)*	*20*	*400*	*100*	*63*
Propranolol	*11 (7%)*	*10*	*120*	*40*	*60*
Carvedilol	*40 (24%)*	*1*	*50*	*12.5*	*18.75*
PPI	*63 (38%)*	*20*	*120*	*40*	*0*
LOLA	*42 (25%)*				
Lactulose	*34 (20 %)*				
Rifaximin	*28 (17%)*				
Metformin	*0 (0%)*				
Statins	*0 (0%)*				
Antiplatelet therapy[1]	*15 (9%)*				
Anticoagulants[2]	*11 (7%)*				

Table 6: Overview of medication dosage at point of admission to TIPS procedure; PPI = proton pump inhibitors (mainly Pantoprazole), LOLA = L-ornithine L-aspartate,[1]Aspirin or P2Y12- Antagonists, [2]Vitamin K Antagonists or direct oral anticoagulants

Significant findings in comparison of pre and post TIPS parameters

	Pre TIPS	*Post TIPS*	*P-value*
Furosemide dosage (mg)	*50.4*	*29.4*	*<0.01[1]*
Spironolactone dosage (mg)	*148.1*	*66.5*	*<0.01[1]*
PPI´s (mg)	*51.2*	*27.4*	*<0.01[1]*
Serum potassium (mg/dl)	*135.3*	*137.6*	*<0.01[1]*
Hemoglobin (mg/dl)	*10.3*	*11.5*	*<0.01[1]*
Serum albumin (mg/dl)	*4.1*	*3.6*	*<0.05[1]*
C-reaktive Protein (mg/dl)	*17.5*	*14.6*	*<0.01[1]*
MELD Score	*12.0*	*9.9*	*<0.01[2]*

Table 7: Comparison of pre and post TIPS medication and laboratory parameters; [1]Wilcoxon signed rank test, [2]paried T test comparing n=90 patients providing both pre and post TIPS MELD Score values,

Post-TIPS infection

An infection following TIPS placement was reported in 39 (17%) patients. Nine patients (4%) had already undergone liver transplantation by the time of post-TIPS infection and were therefore excluded from the subsequent analysis. The median time interval between TIPS placement and the development of an infection was 47 days (IQR 272). 8 (27%) patients were female and 22 (73%) were male. Diabetes mellitus was present in 8 (27%) of patients who developed post-TIPS infection. Within patients with post-TIPS infection, 5 (17%) had bacteremia proven by positive blood cultures. The most common types of infection were pneumonia (n=6; 20%), urinary tract infection (n=5; 17%) and SBP (n=4; 13%). In 5 patients (17%) the focus of infection remained unclear and 10 (33%) had other specified infections, including infection of upper respiratory tract, gastrointestinal tract, skin and soft tissue. Of 30 patients with infection, infection was resolved in 23 cases (77%), 6 patients (20%) had died from infection, and 1 patient (3%) was lost to follow up. The choice of antibiotic substances was highly individual but most used agents were piperacillin/tazobactam (27%), fluoroquinolones (17%) and amoxicillin/clavulanic acid

(13%). Intensive care treatment due to infection was necessary for 17 patients (57%). No significant relation between development of infection and gender ($\chi^2(1, N=221) = 0.005$, $p = 0.9$), diabetes mellitus ($\chi^2(1, N=221) = 0.07$, $p = 0.8$) or Child Pugh Score ($\chi^2(3, N=221) = 4.9$, $p = 0.179$) was found. The characteristics of patients with an infection after TIPS are summarized in Table 8 below.

Characteristics of patients with post-TIPS Infection

Feature	***Amount n (%)***	***Median***	***IQR***
Age	--	*63.5*	*14*
Female sex	*8 (27%)*	--	--
MELD-Score	--	*12*	*6*
Child-Pugh-Score	--	*9.5*	*5*
Days between TIPS and onset of Symptoms	--	*47*	*272*
Type of infection			
Pneumonia	*6 (20%)*	--	--
Urinary tract infection	*5 (17%)*		
Spontaneous bacterial peritonitis	*4 (13%)*		
Focus unclear	*5 (17%)*		
Other specified infections	*10 (33%)*[1]		
Antibiotic treatment (first line)	*27 (90%)*	--	--
Regimen			
Piperacillin/Tazobactam	*8 (27%)*	--	--
Fluoroquinolones	*5 (17%)*		
Amoxicillin/clavulanic acid	*4 (13%)*		
Cephalosporines	*3 (10%)*		
Length of course	--	*14*	*18*

Positive blood cultures	*5 (17%)*	--	--
Admission to ICU	*17 (57%)*	--	--
Outcome death	*6 (20%)*	--	--
Diabetes mellitus	*8 (27%)*	--	--

Table 8: Characteristics of 40 patients with documented infection after TIPS; [1]Other specified infections included upper respiratory infections (e.g. sinusitis), soft tissue and skin infections or gastrointestinal infections

Comparison of patients with infection after TIPS vs without infection

It was assessed whether there were significant differences in certain characteristics between patients who developed an infection after TIPS and those who did not. No significant differences between the two groups could be found. A complete overview is provided in Table 9 below.

Parameter	***Post-TIPS infection (n=30)***	***No infection (n=169)***	***P-value***
Female sex	*8/30 (27.7%)*	*44/169 (26.0%)*	*0.942[1]*
Age (mean)	*58 (SD 11.9)*	*57 (SD 11.3)*	*0.667[3]*
Diabetes mellitus	*8/29 (27.6%)*	*40/159 (25.2%)*	*0.783[1]*
Pre-TIPS SBP	*1/30 (3.3%)*	*15/169 (8.9%)*	*0.304[1]*
TIPS_MELD (mean)	*14 (SD 6.1)*	*13 (SD 6.1)*	*0.292[3]*
TIPS_CPS (median)	*11 (IQR 5)*	*11 (IQR 4)*	*0.363[4]*
TIPS_MOTS[5] (median)	*1 (IQR 1)*	*1 (IQR 1)*	*0.749[4]*
3-month-mortailty	*5/27 (18.5%)*	*22/156 (14.1%)*	*0.672[2]*
6-month-mortality	*9/29 (31.0%)*	*44/161 (27.3%)*	*0.934[1]*

Table 9: Significant findings comparing patients with and without infection after TIPS ; [1]Chi-Square Test, [2]fishers exacter Test, [3]unpaired T-Test, [4]Mann-Whiney-U Test, [5] Score ranging from 0 to 3 to predict post TIPS mortality

Comparison of early and late infections after TIPS

To further investigate the group of post TIPS infections a comparison was drawn between patients developing an infection within 30 days after TIPS, in further termed early infections, and late infections after more than 30 days. Of 30 infections after TIPS, 14 (47%) patients had an early infection and 16 (53%) had a late infection. The early infection group consisted of 6 (43%) patients with pneumonia, 2 (14%) patients with SBP, 5 (36%) patients with other specified infections and 1 (7%) patient with infection of unknown focus. The late infection group consisted of 5 (17%) patients with urinary tract infections, 2 (7%) patients with SBP, 4 (13%) infections of unknown focus and 5 (17%) other specified infections. In the group of patients with early post-TIPS infections, a significantly higher three months mortality rate *(36% vs. 0%, p<0.01)* and six months mortality rate *(27% vs 0%, p<0.05)* could be found. A complete overview of comparison as given in the table below (Table 10).

Parameter	***Early infection (n=14)***	***Late infection (n=16)***	***P-value***
Female sex	*1/14 (7%)*	*9/16 (56%)*	*0.064[1]*
Age (mean)	*56 (SD 13.6)*	*60 (SD 10.3)*	*0.406[2]*
Diabetes mellitus	*4/13 (31%)*	*6/16 (38%)*	*0.526[3]*
Pre-TIPS SBP	*0/14 (0%)*	*1/16 (6%)*	*0.533[3]*
TIPS_MELD (mean)	*15 (SD 6.3)*	*13 (SD 5.9)*	*0.337[1]*
TIPS_CPS (median)	*11 (IQR 4)*	*8 (IQR 5)*	*0.173[4]*
TIPS_MOTS (median)	*1 (IQR 1)*	*0 (IQR 1)*	*0.416[4]*
3-month-mortailty	*5/14 (36%)*	*0/15 (0%)*	***<0.05[3]***
6-month-mortality	*9/14 (27.0%)*	*0/15 (0%)*	***<0.01[3]***

Table 10: Comparison of early and late TIPS infections; [1]chi-square test, [2]unpaired t-test, [3]fishers exacter test, [4]Mann-Whintey-U test

Comparison of early infection and the remaining cohort

Lastly, comparing the group of early TIPS infections (n=14) to all other patients (n=216) no significant difference of characteristics could be found. However, early infections were significantly more frequent in patients receiving early TIPS, meaning within 72h, ideally 24h upon hospital admission, compared to patients who had elective TIPS placement *(n=8/14; 57% vs. n=44/216; 20%, p<0.01).* Additionally, like in comparison of early vs. late TIPS infections, six months mortality *(64% vs. 28%, p<0.01)* as well as three months mortality *(42% vs. 16%, p<0.05)* were significantly higher in the patients developing early infection compared to the rest of the patients. Overview of this comparison is given below (Table 11).

Parameter	*Early infection (n=14)*	*Remaining Patients (n=216)*	*P-value*
Female sex	*1/14 (7%)*	*63/216 (29%)*	*0.061[1]*
Age (mean)	*56 (SD 13.6)*	*58 (SD 11)*	*0.576[2]*
Diabetes mellitus	*4/13 (31%)*	*52/206 (25%)*	*0.435[3]*
Pre-TIPS SBP	*0/14 (0%)*	*18/216 (8%)*	*0.309[3]*
TIPS_MELD (mean)	*15 (SD 5.5)*	*14 (SD 5.4)*	*0.286[1]*
TIPS_CPS (median)	*7 (IQR 0)*	*8 (IQR 2)*	*0.546[4]*
Early TIPS	*8/14 (57%)*	*44/216 (20%)*	***<0.01[3]***
3-month-mortailty	*5/12 (42%)*	*30/187 (16%)*	***<0.05[3]***
6-month-mortality	*9/14 (64%)*	*53/192 (28%)*	***<0.01[3]***

Table 11: Comparison of patients with early infection (n=14) to the remaining patient collective (n=216); [1]chi-square test, [2]unpaired t-test, [3]fishers exacter test, [4]Mann-Whintey-U test

Patients with Bacteremia

Of the 30 patients who showed signs of infection after TIPS, five (17%) with positive blood cultures could be identified. Most patients were male (80%). All patients had a fever and four out of five required intensive care. One of the patients' blood cultures was positive for fungi (20%) but no dominant organism could be identified overall. Eighty percent of patients with bacteremia had alcohol-related portal hypertension as the underlying condition for their TIPS procedure. No risk factors for the development of bacteremia after infection following TIPS could be identified. Table 12 below provides an overview and briefly summarizes each case.

Feature	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Sex	male	female	male	male	male
Etiology Of liver disease	alcohol related	cryptogenic	alcohol related	alcohol related	alcohol related
Diabetes mellitus[1]	no	no	no	yes	no
PVT	no	no	no	no	no
MELD-Score/CPS[2]	13/B7	18/8B	8/12C	21/11C	9/8B
Fever	yes	yes	yes	yes	yes
Admission to ICU	yes	yes	yes	yes	no
Organism in blood-culture	Staphylo-coccus epidermidis	Enterococcus faecalis, Stenotropho-nomas maltophlia	Pseudomo-nas aeroginosa, Klebsiella oxytoca	Klebsiella pneumoniae, Candida albicans	Staphylo-coccus aureus
Type of infection	Pneumonia	Pneumonia	Pneumonia	Pneumonia	specified other
Onset[3]	6	60	10	35	55
Regimen	Ciprofloxa-cin, Linezolid	Piperacillin/ tazobactam, Levofloxacin, Linezolid	Meropenem, Ciprofloxa-cin	Piperacillin/ tazobactam, Anidula-fungin	Cefalexim, Cefotaxim
Outcome	resolved	resolved	death	death	resolved
Ltx[4]	no	no	no	no	no

Table 12: Characteristics of 5 Patients with bacteremia after TIPS; [1]Either type I or Type II,[2]Child-Pugh-Score, [3]Number of days after TIPS when infection was first diagnosed, [4]Liver transplanted

Suspicion of endotipsitis

In total, 5 patients with proven bacteremia, as indicated by positive blood cultures, were identified between January 2004 and January of 2024. As none of the patients showed TIPS dysfunction or evidence of vegetations/thrombi inside TIPS, none of them fulfilled the current criteria for endotipsitis. Two patients with bacteremia died of sepsis and multiple organ failure, and three patients were lost to follow-up soon after discharge despite the infection being resolved. Therefore, no reported cases were identified within the set timeframe. However, a few months after the end of the observation period, we identified a definite case of endotipsitis in a 79-year-old male patient (case report below).

Case report of severe and persistent endotipsitis in a 79-year-old patient

A 79-year-old Caucasian male patient was admitted to our clinic for elective TIPS-placement. The patient suffered from alcohol-related cirrhosis and had a history of severe acute-on-chronic pancreatitis with mechanical cholestasis which was treated with a bare metal stent in the common bile duct approximately six months before admission. At time of admission the patient’s liver disease was scored as MELD score 6 and a Child-Pugh score of B7 and paracentesis was necessary every six days due to refractory ascites. Prior history also included multiple episodes of SBP, the most recent two months prior to admission as well as diabetes mellitus, chronic partial portal vein thrombosis, sarcopenia and pleural effusion. Risks and benefits of elective TIPS placement were discussed extensively and ultimately decision in favor of TIPS placement was reached because of very poor quality of life due to massive ascites. TIPS was then placed in general anesthesia, due to scar tissue with stenosis of the extrahepatic portal vein, an extension from the portal vein towards the mesenteric vein was implemented. On the first post procedural day, the patient developed signs of sepsis. Blood cultures were drawn and empiric antibiotic therapy with piperacillin and tazobactam was started immediately. The patient went on to progress into septic shock but ultimately was not admitted to the ICU because of limited rehabilitation potential due to severe sarcopenia and cirrhosis. Blood cultures identified E. coli (3MRGN) and Enterococcus faecium. Three weeks after TIPS, fungemia with candida tropicalis occured. In further course blood cultures remained positive for E. coli and E. faecium with E. coli (4MRGN) being identified at day 25 after TIPS. After the initial blood cultures, therapy was adapted and linezolid was added and after the last cultures an antibiotic regimen of meropenem, vancomycin and anidulafungin was implemented. No clear focus could be found, and endocarditis was ruled out by transesophageal echocardiography. At day 50 after TIPS, a PET-CT-scan was performed, in which the TIPS could finally be identified as primary focus of infection. In response, antibacterial therapy was reevaluated and ceftazidime and avibactam were implemented for 28 days in total, which lead to the patient improving and sterile blood cultures in follow up. During hospitalization multiple problems were addressed. The bare metal stent of the common bile duct could be replaced 4 weeks after TIPS due to suspicion of relations between the biliary stent, the recurrent bacteremia and the endotipsitis. Due to PET-positive pleural effusion, pleural drainage was performed, which lead to rapid clinical improvement. After 70 days of hospitalization, the patient was discharged in stable general condition, but outpatient intravenous application of antibiotics is still necessary. Liver transplantation was not considered a viable option in this case due to the risk of sepsis with immunosuppression after LTX and ultimately the wish of the patient. An outpatient therapy concept was designed in cooperation with the Departments of Intensive Care and Infectiology, consisting of a PICC line through which amikacin is applicated in an outpatient facility three times a week. The risks of central line infection and recurring bacteremia were discussed with the patient in detail. At the last follow-up approximately 19 months after discharge from hospital, the patient was in good overall condition, follow-up PET CT showed a reduction in tracer uptake within the right lobe of the liver alongside the TIPS, amikacin therapy is tolerated well, kidney function tests are within normal range with an eGFR of 70 ml/min and ascites is resolved completely. The patient can live independently and reports a markedly better quality of life than before TIPS.

Discussion

Summary of results and interpretation

In our retrospective analysis we analyzed 230 patients receiving TIPs from January 2004 until January 2024 at the university hospital of Graz. Six-months-mortality after TIPS was 33% and 90-day mortality rate was 22%. Most common reason for death was hemorrhage with 10% (n=23) followed by hepatic decompensation in 5% (n= 11). Mainly patients with recurrent ascites received TIPS at our center with 109 cases (47%), followed by gastrointestinal bleeding as the second most frequent indication with 90 cases (39%). We found patients six months after TIPS to have significantly lower CRP ($p<0.01$) and serum potassium ($p<0.01$) along with reduced serum albumin ($p<0.05$), which possibly reflects the beneficial effect of TIPS on resolving ascites and thus preventing SBP and systemic inflammation (66,125). Additionally, patients needed significantly less diuretics and PPI after TIPS ($p<0.01$), which makes sense considering one primary indication for TIPS placement is ascites that is no longer responsive to diuretics, so patients would likely have received larger dosages to exhaust pharmacotherapy before TIPS (6,41). There were 39 (17%) patients with an infection after TIPS, but 9 (4%) patients had received a liver transplantation before they developed infection and were therefore excluded from further analysis. The remaining 30 patients (14%) had an onset of infection averaging 190 days after TIPS, ranging from 5 to 1472 days. Most common type of infection overall was pneumonia (n=6, 20%), followed by urinary tract infection (n=5, 17%) and SBP (n=4, 13%). We compared early infections after TIPS within 30 days to late infections after this period and found that 14/30 (47%) patients developed an infection early and 16/30 (53%) patients after 30 days. The most common early infection was pneumonia (n=6, 43%) followed by SBP (n=2, 14%). No significant difference in demographics and characteristics could be identified between patients developing an infection after TIPS and those who didn’t. Comparing patients with an early infection (<30 days) to those with late infections (>30 days) and to all patients without early infection, both 90-day and six-month mortality were significantly higher in the early infection group ($p<0.05$). These findings suggest that patients with advanced liver disease who develop an infection within 30 days after TIPS placement are at markedly increased risk of short- and mid-term mortality compared to those with later infections. This observation indicates that the timing of infection may reflect underlying vulnerability or reduced hepatic reserve. The impact of infection on mortality in severe liver disease has been demonstrated in previous studies (126,127). This interpretation is further supported by our finding that patients receiving rescue TIPS were significantly more likely to develop early infection ($p<0.01$). Rescue TIPS is typically performed in the setting of acute decompensation or life-threatening complications of portal hypertension, serving as a marker of advanced disease and heightened susceptibility to infection (57). Still, it remains possible that patients developing an early infection were in poorer clinical condition to begin with and thus have a higher mortality independent of infection. Studies with a larger cohort and prospective design are necessary to clarify these associations. Bacteremia could be found in 5 (17%) patients with an infection, but none of these patients developed PVT, so no patients fulfilled the criteria for endotipsitis at our facility between January of 2004 to January of 2024. However, a case of persistent endotipsitis from Mai 2024 is described as an exemplary case report, but is excluded from statistical analysis. Lacking a case within our timespan, no risk factors for the development of endotipsitis could be identified.

Comparison to existing literature

These findings demonstrate the rarity of the disease and the high index of suspicion required for diagnosis. All five patients who developed bacteremia after infection had a patent TIPS, ruling out diagnosis of endotipsitis. Although the timeframe was set to 20 years, our patient population was too small to draw conclusions about risk factors for developing bacteremia and potentially endotipsitis after TIPS. While studies report an estimated incidence of about 1%, we could not identify any cases of endotipsitis at our center (112–114). However, considering the case presented after the timeframe set for statistical analysis, the reported incidence at our center might be close to 1% after all. The incidence of bacteremia with one result of positive blood cultures at any time during observation period after TIPS at our center was 2.1%. In literature the incidence of bacteremia after TIPS varies widely depending on the observation period following TIPS and due to the heterogenic definition of bacteremia in context of TIPS. While a large retrospective single center study from 2016 recorded 9 out of 466 TIPS patients (1,9%) with transient bacteremia (positive blood cultures once at any point after TIPS within the observation period) (128) a smaller study of similar design recorded transient bacteremia in 39 out of 96 receiving TIPS (40%) and 7 patients (7%) with persistent bacteremia (at least two separate positive results). Looking at the infection rate after TIPS in general, our recorded 14% (n=30/221), after excluding patients with LTX before infection, is very comparable to what other studies found (121,129). Mainly patients with recurrent ascites received TIPS at our facility with 109 cases (47%), followed by gastrointestinal bleeding as the second most frequent indication with 90 (39%), which is expected looking at similar studies (32). Other retrospective analyses of the outcome after TIPS reported mortality rates within 90 days of 22-27% (130,131). We recorded a similar result with a 90-day mortality rate of 22%. Due to the scarcity of evidence regarding infections following TIPS procedures, it is rather difficult to interpret these figures in the context of the available literature.

Clinical implications

Drawing clinical implications out of our analysis is challenging. Endotipsitis was so rare at our center that drawing a clear guideline for procedure to avoid infection after TIPS is impossible. The role of prophylactic antibiotics to prevent early infection after TIPS is still subject of ongoing debate. The last randomized controlled study conducted investigating a single dose cephalosporin vs. placebo was done prior to the era of covered stents (47). What we can learn from our case report is that antibiotic prophylaxis can be useful in certain situations, for example, in cases involving patients with a common bile duct stent who require a TIPS procedure. This is supported by recent studies which suggest that patients who have undergone recent biliary surgery are at a higher risk of infection (132). Other studies suggested that in patients with a thrombosed TIPS antibiotic prophylaxis before any intervention related to bacteremia would be a wise choice, but this is merely an anecdotal recommendation (1). Ultimately, the latest EASL guidelines also recommend a case-by-case approach when it comes to antibiotic prophylaxis before TIPS (133). At our center no antibiotic prophylaxis is routinely implemented. Further research is necessary to develop a risk profile, identify individuals at high risk of developing endotipsitis and early infection, and establish uniform guidelines on antibiotic prophylaxis. The only reasonably stable conclusion for clinical duty is the awareness of endotipsitis as a viable diagnosis of patients with recurrent signs of bacteremia after TIPS.

Limitations

Limitations of the study are mainly rooted in the retrospective, single center design and the limited number of cases. Although the dataset covers a long timeframe with 20 years no definite case of endotipsitis and only 5 cases of bacteremia could be identified. Given the rarity of this complication, statistical analysis is restricted to descriptive comparison. With no case of endotipsitis and only five cases of bacteremia under 230 patients, the statistical power of inferential analysis is insufficient to draw reliable conclusions of significant differences between the two groups. Furthermore, the conclusions derived from this analysis can only relate to bacteremia after TIPS and not to endotipsitis, as it was ruled out in all five cases due to absence of vegetation inside the TIPS. Another limitation arises from incomplete follow up data. Many patients travelled considerable distance to our center for the intervention, so subsequent examinations and treatments may occur outside of our hospital and are not captured in our clinical information system. This likely results in an underreporting of infectious complication and bacteremia after TIPS. Finally, the single center design limits the generalizability of our findings. Nevertheless, the long observation period represents a strength, and the descriptive data obtained provides valuable insight into the frequency and clinical course of bacteremia after TIPS and thereby forms a basis for future multicenter and prospective investigations.

Outlook on future research

Infection after TIPS has been studied in recent literature, but many aspects remain unclear. One important gap is the topic of antibiotic prophylaxis: there is still no uniform guideline on the use of antibiotic prophylaxis in TIPS procedure. Existing studies were conducted in the era of uncovered stents, and technological advances since then may have altered infection risk. New randomized controlled studies are necessary to gather clear evidence of the efficacy of antibiotic prophylaxis and when it should be implemented (47,121,133). Furthermore, diagnosis of endotipsitis is challenging and requires a high level of suspicion. Most patients are examined exhaustively before definite diagnosis, so perhaps studies identifying high risk individuals for development of endotipsitis would help solve this issue. Current diagnostic practice leans on blood cultures, imaging evidence of vegetation within the TIPS stent and rigorous examination to exclude other sights of infection. The gold standard, however, remains microbial analysis of tissue samples from within the TIPS stent, for which removal of the TIPS is required. Removal of TIPS is only feasible during liver transplantation or autopsy– in both cases diagnosis seems to be more of retrospective explanation rather than a diagnosis followed by therapeutic consequence. Developing a method of intravascular salvage of tissue material for analysis could therefore greatly improve diagnostic feasibility, but a lot of research is still necessary which individuals might profit from such an examination. Recent advances in imaging technology such as intravascular optic coherence tomography could be used to detect early biofilm formation within TIPS Stents and therefore lead to a new approach to diagnosing endotipsitis , also the role of new biomarkers is being explored in the context TIPS occlusion (122,123). Future research could also focus on new antimicrobial substances, better understanding of biofilm formation and dynamic of endovascular infection, to improve therapeutic options in highly challenging conditions.

Conclusion

Our retrospective analysis over a 20-year period confirms the rarity of endotipsitis and highlights the diagnostic challenges associated with this elusive condition. While infections following TIPS were not uncommon in our cohort, no definite case of endotipsitis was identified within the defined observation period. However, a case shortly after the timeframe set for statistical analysis suggests that the incidence at our center may align with the estimated 1% reported in current literature (112–114). Due to the limited number of cases, no risk factors for post-TIPS bacteremia or endotipsitis could be determined. These findings underscore the importance of multicenter studies to better understand the risk profile and clinical course of endotipsitis. Future research should aim to improve diagnostic strategies, define guidelines on antibiotic prophylaxis and identify high-risk patients. Advances in imaging techniques and microbiological diagnostics may play a crucial role in facilitating earlier and more accurate diagnosis in the future. This study contributes to building the foundation for future multicenter analyses and reinforces the clinical relevance of monitoring infectious complications following endovascular interventions such as TIPS.

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