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Review article: post-TIPSS hepatic encephalopathy—current knowledge and future perspectives

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Summary

Background: In light of the global rise in the burden of chronic liver diseases and liver cirrhosis, the number of patients suffering from decompensation events is expected to increase. Transjugular intrahepatic portosystemic shunts (TIPSS) provide effective long-term symptom control and may prolong transplant-free survival in portal hypertension-driven recurrent ascites and variceal bleeding. New-onset or recurrent hepatic encephalopathy (HE) after TIPSS insertion (post-TIPSS HE) represents the most severe post-interventional complication.

Aims: To provide insight into the epidemiology and risk factors for post-TIPSS HE and scrutinize the current state of the art in treatment and drug therapy options.

Methods: We conducted a literature search on post-TIPSS HE in patients with liver cirrhosis.

Results: Post-TIPSS HE occurs in up to 54.5% of cases and particularly early recurrent HE is associated with a dismal prognosis. In recent years, several risk factors for the development of post-TIPSS HE have been identified. These include not only parameters reflecting liver function (model for end-stage liver disease score/Child-Pugh score) as well as cognitive dysfunction caused by minimal HE but also extrahepatic factors such as sarcopenia and common medications such as proton pump inhibitors. In addition, new data on the benefit of rifaximin and of smaller stent grafts emerged and may improve the prevention of post-TIPSS HE.

Conclusions: Careful selection of TIPSS candidates is of utmost importance to reduce the risk of post-TIPSS HE. In this narrative review, we provide a concise overview of the current epidemiology and risk factors of the treatment options for post-TIPSS HE.

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1 | INTRODUCTION

Transjugular intrahepatic portosystemic shunts (TIPSS) provide effective and durable control of portal hypertension-driven symptoms. Additionally, TIPSS insertion may extend transplant-free survival (TFS) in patients with liver cirrhosis and recurrent ascites, although further studies are needed to warrant this finding.[1,2] In addition to treatment-refractory ascites, indications include refractory acute variceal haemorrhage (if first-line therapy has failed), secondary prophylaxis after variceal haemorrhage, if first-line therapy (endoscopic band ligature plus non-selective beta-blockers) has failed, Budd–Chiari Syndrome and portal vein thrombosis.[3] In 2010, a randomised controlled trial established the use of an "early TIPSS" (placement within 72 hours after admission) in high-risk patients after acute variceal haemorrhage.[4] Other indications, such as hepatorenal syndrome, require further research for a general recommendation.

The occurrence of new-onset, progressive or recurrent hepatic encephalopathy (HE) after TIPSS insertion (post-TIPSS HE) represents the most important complication of this therapeutic approach. HE is defined as a potentially reversible brain dysfunction that manifests with a wide spectrum of neuropsychiatric abnormalities caused by liver insufficiency and portosystemic shunting.[5,6] Clinically, it includes neurological and psychiatric abnormalities ranging from subclinical alterations to life-threatening coma. HE can roughly be divided into two groups: overt HE (OHE) and covert HE (CHE). While OHE comprises grades 2–4 according to the West Haven criteria, CHE combines the two lowest grades of HE—minimal HE (MHE) and HE grade 1 (HE1).[5] Patients with OHE present episodically or continuously with obvious, clinically detectable symptoms. In contrast, MHE is below the obvious clinical detection level and can only be diagnosed with the help of specialised neuropsychometric and neurophysiological tests.

HE is a very frequent complication in patients with liver cirrhosis, and MHE can be detected in about 30%-50% of all cirrhotic patients.[7,8] Although the consequences are serious, MHE, in particular, is often overlooked or diagnostics are even neglected in routine clinical practice.[9] This is concerning because MHE also impairs health-related quality of life (HRQoL), can lead to falls with subsequent bone fractures, and motor vehicle crashes and is associated with a higher risk for OHE.[7,10-12]

In this narrative review, we provide insight into the epidemiology and risk factors for post-TIPSS HE and scrutinise the current state of the art in treatment and drug therapy options.

2 | POST-TIPSS HE

2.1 | Epidemiology

HE is the most frequent TIPSS-associated complication in patients with liver cirrhosis. The overall incidence of post-TIPSS HE ranges from 23% to 54.5% during the first year after insertion (Table 1).[13-18] The severity of HE after TIPSS insertion also varies widely across different studies: In an Italian cohort of 78 cirrhotic patients treated with polytetrafluoroethylene-covered (PTFE-covered) stents, 44.8% of the patients experienced at least one episode of post-TIPSS HE, with 55% having an HE ≥ grade 3.[15] In contrast, in an American cohort including 376 patients, 52% developed a post-TIPSS HE, among whom only 9% had HE ≥ grade 3.[13] In patients with rescue or early TIPSS for variceal bleeding, the incidence rates of post-TIPSS HE do not seem to be increased compared to patients treated with drugs plus endoscopy.[19] A detailed overview of the post-TIPSS HE rate in several studies is given in Table 1.

2.2 | Pathophysiology

The underlying pathophysiology of HE is complex and consists of a complex interplay of hyperammonemia and systemic inflammation. Simply put, HE is driven by hyperammonemia-related neurotoxicity. However, the exact pathophysiology that triggers HE is still not sufficiently understood and not within the scope of this review.[20] In the context of post-TIPSS HE, two TIPSS-related factors must be considered: First and foremost, TIPSS insertion leads to a "steal" phenomenon: ammonia-enriched blood from the intestine bypasses the liver parenchyma, thus is not included in the urea cycle.[21] This results in further impaired ammonia degradation. Second, rat models demonstrated that portocaval shunting (e.g. caused by TIPSS) leads to increased activity of phosphate-activated glutaminase in the intestine, which results in an increase in gut-derived ammonia.[21,22] A comprehensive review of HE pathophysiology can be found elsewhere.[20]

2.3 | Risk factors for the development of post-TIPSS HE and patient selection

The occurrence of HE represents one of the major post-TIPSS complications and is associated with a dismal prognosis.[23] In particular, early recurrent OHE is linked with poor outcomes.[24] In general, careful pre-interventional patient selection is crucial to reduce the risk of post-TIPSS HE. Therefore, it is essential to know predictors for the development of HE after TIPSS insertion. A pre-TIPSS diagnostic workup proposed by the authors to evaluate the individual risk for post-TIPSS HE is displayed in Figure 1.

Overall, the best-studied risk factors include a history of OHE and impaired liver function. This is validated by a systematic review including 30 studies, which found that advanced age, history of HE and higher Child-Pugh scores showed the strongest association in predicting post-TIPSS HE.[25] Other important risk factors are higher Model of End-Stage Liver Disease (MELD) scores, arterial hypotension, hyponatremia, elevated serum creatinine, low levels of serum albumin and a portosystemic pressure gradient (PSG) lower than 5 mm Hg.[15,26] Another retrospective study of 376 patients found that in addition to advanced age, VIATORR stents without controlled expansion were significantly associated with the occurrence of HE

TABLE 1 Epidemiology and factors influencing the occurrence of post-TIPSS HE

Study	No. of patients	Trial design	Main TIPSS indication[d]	Overall HE incidence	HE incidence depending on TIPSS indication	HE grade ≥3	Necessity of a TIPSS diameter reduction	Factors influencing the occurrence of post-TIPSS HE in multivariate analysis
Riggio et al[48]	75	Single centre RCT, not blinded	Ascites: 25 (33.3%) VH: 50 (66.7%) Ascites + VH: n/a	25 (33%) within 1 month after TIPSS insertion	No significant differences (ascites vs haemorrhage)	13 (52%)[a]	1 (4%)[a]	Previous HE episodes (RH 3.79, 95% CI: 1.27-11.31) TMT-A Z-score >1.5 (RH: 3.55; 95% CI: 1.24-10.2)
Nardelli et al[43]	46	Prospective, single centre	Ascites: 23 (50%) VH: 23 (50%)	21 (46%) within 7 ± 9 months after TIPSS insertion	No significant differences (haemorrhage vs ascites)	n/a	n/a	MELD score (sHR: 1.16, 95% CI: 1.01-1.34) Sarcopenia (sHR: 31.3, 95% CI: 4.5-218.07)
Nardelli et al[29]	82		Ascites: 45 (54.9%) VH: 37 (45.1%)	35 (43%); follow-up period n/a	No significant differences (haemorrhage vs ascites)	n/a	3 (8.6%)[a]	Age (sHR 1.05, 95% CI 1.02-1.08) Child-Pugh score (sHR 1.29, 95% CI 1.06-1.56) covert HE (sHR 3.16, 95% CI: 1.43-6.99)
Berlioux et al[30]	54		Ascites: 33 (61%) VH: 19 (35%) Ascites + VH: n/a	19 (35%) during a median follow-up of 365 days (2-392)	OHE significantly more frequent in patients w/ refractory ascites	n/a	n/a	TIPSS due to refractory ascites (OR n/a) Low haemoglobin level (OR n/a) MHE diagnosed by CFF (OR n/a)[g] Renal failure (OR n/a)[g] History of OHE (OR n/a)[g]
Riggio et al[15]	78		Ascites: 29 (37.2%) VH: 49 (62.8%)	35 (44.8%) during a mean follow-up of 19.9 (±20.6) months	n/a	55% of the cumulative 89 HE episodes in 35 patients	6 (17.1%)[a]	Age (HR: 1.086, 95% CI: 1.05-1.13) serum creatinine (HR: 1.516, 95% CI: 1.02-2.26) serum sodium (HR: 0.926, 95% CI: 0.87-0.98) serum albumin (HR: 0.352, 95% CI: 0.19-0.67)
Seifert et al[17]	233	Retrospective, single centre	Ascites: 115 (49.4%) VH: 77 (33.0%) Ascites + VH: 41 (17.6%)	127 (54.5%) within 12 months after TIPSS insertion	No significant differences	25 (19.7%)[a]	9 (7.1%)[a]	Age (HR: 1.039, 95% CI: 1.013–1.066) Pre-TIPSS HE (HR: 3.695, 95% CI: 1.531-8.917)
Coronado et al[13]	376 (patients w/ history of HE were excluded)		Ascites: 138 (37%) VH: 139 (37%) Ascites + VH: 28 (7%)	194 (52%); follow-up period n/a	No significant differences	17 (9%)[a]	n/a	Age (OR: 1.04)[c] VCX endoprothesis (OR: 0.55)[c]
Yin et al[16]	373 (training cohort: 264, validation cohort: 109)		n/a	117 (31.4%) during a median follow-up of 37 (1–60) months103 (27.6%) within 12 months	n/a	n/a	n/a	Age (HR: 1.027, 95% CI: 1.002–1.052) Diabetes mellitus (HR: 1.844, 95% CI: 1.059–3.211) Child-Pugh stage C (HR: 6.678, 95% CI:1.679–8.889) Serum creatinine (HR: 1.013, 95% CI: 1.002–1.025) Serum sodium (HR: 0.935, 95% CI: 0.883-0.989)

(Continues)

TABLE 1 Continued

Study	No. of patients	Trial design	Main TIPSS indication[d]	Overall HE incidence	HE incidence depending on TIPSS indication	HE grade ≥3	Necessity of a TIPSS diameter reduction	Factors influencing the occurrence of post-TIPSS HE in multivariate analysis
Lewis et al[39]	284		Ascites: 170 (60%) VH: 66 (23%) Ascites + VH: 23 (8%)	176 (62%) during a median follow-up of 479 days	No significant differences (ascites vs haemorrhage)	n/a	n/a	Age (IRR 1.05, 95% CI 1.03-1.07) Male sex (IRR 1.58, 95% CI 1.07-2.36) MELD score (IRR 1.06, 95% CI 1.01.-1.11) History of HE or HE-preventive drug intake (IRR 1.51 95% CI 1.04-2.20) PPI use (IRR 3.19, 95% CI 2.19-4.66)
Routhu et al[14]	678		Ascites: 198 (29.2%)VH: 367 (54.1%) Ascites + VH: 44 (6.5%)	257 (37.9%) during a mean follow-up of 35 months	No significant differences	n/a	14 (5.4%)[a]	Age (OR: 1.047, 95% CI: 1.026–1.068) Pre-TIPSS portal venous pressure (OR: 1.048; 95% CI: 1.015-1.081) serum creatinine (OR: 1.005; 95% CI: 1.002-1.009) diabetes mellitus with insulin treatment (OR: 1.863, 95% CI: 1.070-3.244) aetiology of portal hypertension (OR: 0.074; 95% CI: 0.013-0.437)
Fonio et al[67]	75 (patients w/ pre-TIPSS HE were excluded)		Ascites: 31 (41%) VH[f]: 26 (34.7%) Ascites + VH: n/a	27 (36%) within 6 months after TIPSS insertion	n/a	4 (14.8)[a]	n/a	Age (OR n/a)
Bettinger et al[23]	389		Ascites: 196 (50.4%)VH: 86 (22.1%)Ascites + VH: 58 (14.9%)	113 (29%) within 12 months after TIPSS insertion	No significant differences between ascites vs VH	11 (2.8%)[b]	10 (2.6%)[b]	Age (OR 1.03; 95% CI: 1.00–1.05)Pre-TIPSS HE (OR 32.3; 95% CI: 13.6–79.7)
Casadaban et al[68]	191		Ascites[e]: 92 (48%) VH: 94 (49%) Ascites + VH: n/a	81 (42%) within 30 days after TIPSS insertion	No significant differences (haemorrhage vs other)	27 (33,33%)[a]	3 (4%)[a]	Age > 65 years (OR n/a) MELD score > 18 (OR n/a)
Yao et al[69]	279 (all patients had primary HCC and portal hypertension)		Ascites[e]: 36 (12.9%) VH: 226 (81.0%) Ascites[e] + VH: 17 (6.1%)	114 (41%) within 3 months after TIPSS insertion	No significant differences	n/a	n/a	>3 TACEs/TAEs (OR: 4.078, 95% CI: 1.748-9.515) Hepatopetal main portal vein flow pre-TIPSS (OR: 2.362, 95% CI: 1.032–5.404). Reduction in post-TIPSS PSG (per 1 mm Hg; OR: 1.198, 95% CI: 1.073-1.336), MELD score (OR: 1.693, 95% CI: 1.390–2.062)

Abbreviations: CFF, critical flicker frequency; CTP, Child–Turcotte–Pugh; HCC, hepatocellular carcinoma; IRR, incidence rate ratio; MELD, Model for End-Stage Liver Disease; PSG, portosystemic pressure gradient; RH, relative hazard; RR, relative risk; sHR, sub-distribution hazard ratio; TMT, trail-making test; VCX, Viatorr TIPSS endoprosthesis with controlled expansion; VH, variceal haemorrhage.

[a] Percentage refers to patients with HE.

[b] Percentage refers to all patients of the cohort.

[c] Data from single-predictor regression models.

[d] Missing percentages to 100% include rarer indications.

[e] Patients with hepatic hydrothorax are included.

[f] Acute and recurrent variceal haemorrhage.

[g] No independent predictors in multiple Cox regression analysis.

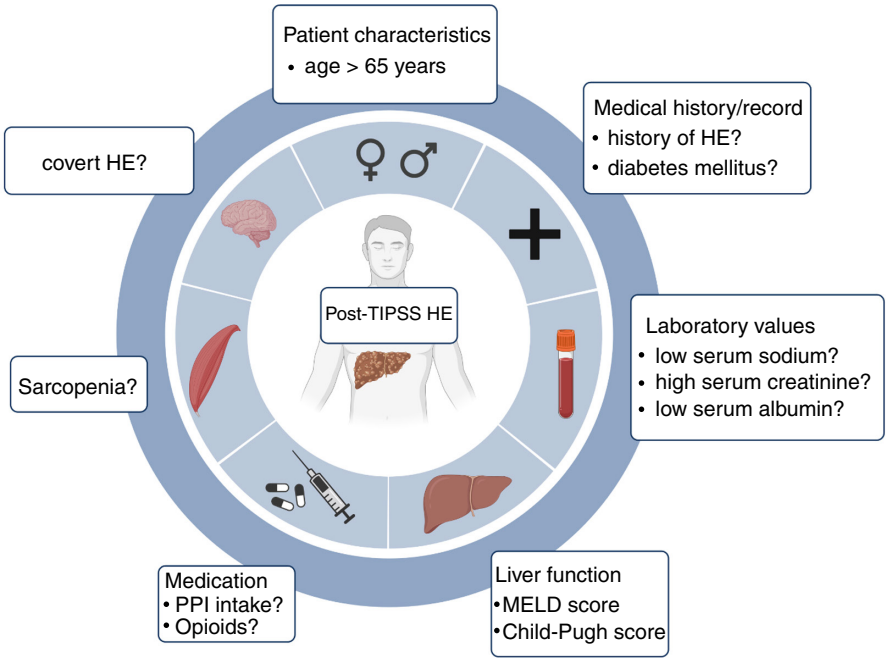

FIGURE 1 Proposed pre-TIPSS diagnostic workup to evaluate the individual risk for post-TIPSS HE

TABLE 2 Overview of established tests for detecting MHE and their ability to predict post-TIPSS HE

Test modality	Validated for predicting post-TIPSS HE	Advantages	Disadvantages
PHES	Yes (however, there are conflicting findings)[29,30]	• Guideline recommended gold standard for detection of MHE • Validated in several countries • Inexpensive	• Requires trained personnel • Time-consuming
CFF	Yes[30]	• Independent of education and without learning effect	• Requires expensive special equipment • Not studied in the United States
EEG[70]	No	• Independent of education and without learning effect	• No cut-offs available for the prediction of post-TIPSS HE • Requires trained personnel • Time-consuming
CRT[71]	No	• Testing time about 10 min	• No cut-offs available for the prediction of post-TIPSS HE • Mainly studied in Denmark • Requires a computer
ICT[72]	No	• Testing time about 14 min	• No cut-offs available for the prediction of post-TIPSS HE • Requires a computer
Scan test[73]	No	• Testing time: depending on how many difficulty levels the patient manages, usually a few minutes	• No cut-offs available for the prediction of post-TIPSS HE • Requires a computer
Stroop test (EncephalApp)[35]	No	• Testing time about 10 min • Point-of-care test	• No cut-offs available for the prediction of post-TIPSS HE • Requires smartphone or tablet
QuickStroop[74]	No	• Testing time about 1 min • Point-of-care test	• No cut-offs available for the prediction of post-TIPSS HE • Requires smartphone or tablet • Not studied outside of the United States
S-ANT1[33]	No	• Testing time only 1 min • Free of costs	• No cut-offs available for the prediction of post-TIPSS HE • Requires validation in different countries and languages

Abbreviations: CFF, Critical Flicker Frequency; CRT, Continuous Reaction Time; EEG, electroencephalography; HE, hepatic encephalopathy; ICT, Inhibitory Control Test; MHE, minimal hepatic encephalopathy; PHES, Psychometric Hepatic Encephalopathy Score; S-ANT1, simplified Animal Naming Test.

after TIPSS placement.[13] However, it has to be mentioned that especially a history of OHE may not be a contraindication for TIPSS in well-selected patients when a clear and remediable trigger can be identified. This is supported by studies reporting on early and rescue TIPSS placement in patients with variceal bleeding—a well-known trigger for HE.[19,27]

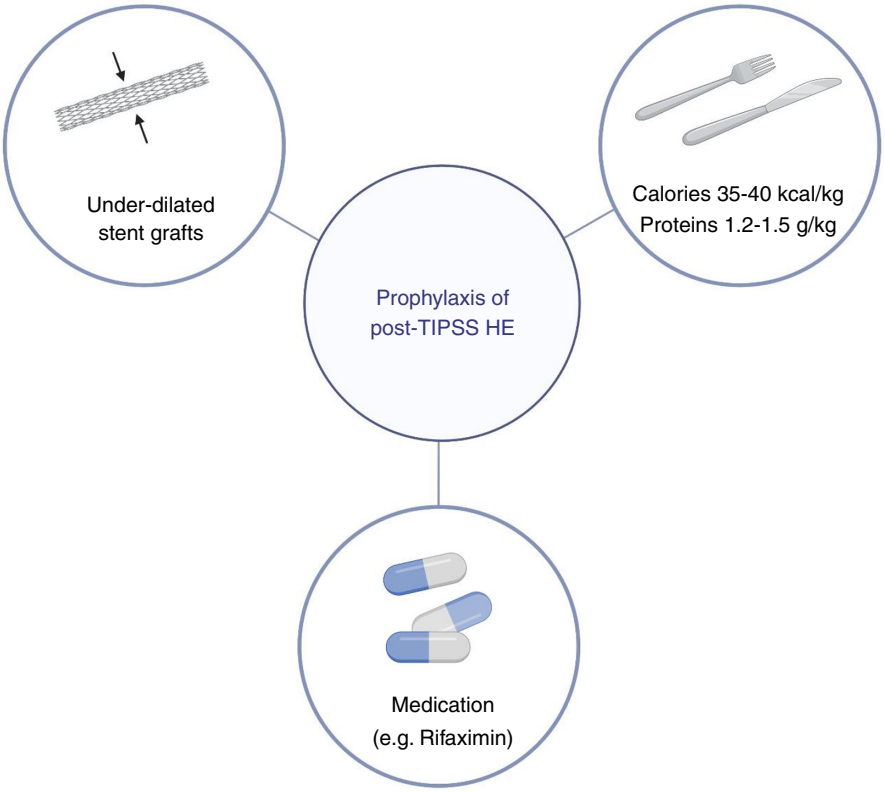

FIGURE 2 Recommended prophylaxis of post-TIPSS HE

2.4 | CHE as a risk factor for post-TIPSS HE

CHE comprises the two lowest grades of HE—MHE and HE1.[5] Several studies in patients with liver cirrhosis have demonstrated that patients with CHE have a remarkably higher risk for the development of OHE.[7,28] Consequently, neuropsychometric and neurophysiological tests used for the detection of CHE are highly valuable tools to predict post-TIPSS OHE. In this context, Nardelli et al were able to demonstrate in a cohort of 82 patients that pathological results in the portosystemic hepatic encephalopathy score (PHES) were associated with a higher OHE risk after TIPSS insertion (sHR 3.16, 95% CI 1.43-6.99).[29] Especially in patients referred for TIPSS implantation because of refractory ascites, PHES had an excellent negative predictive value of 88% to exclude future OHE episodes.

A study by Berlioux et al including 54 patients found that ruling out MHE by evaluation of the Critical Flicker Frequency prior to TIPSS implantation yielded a negative predictive value of 91% for the occurrence of recurrent OHE (defined as the occurrence of three or more episodes) or one episode longer than 15 days.[30] Thus, comprehensive pre-TIPSS evaluation of HE including diagnostic tools for detecting MHE seems to be useful and mandatory.[31] Table 2 provides an overview of established tests for detecting MHE and their ability to predict post-TIPSS HE as well as potential disadvantages. In general, the lack of standardisation complicates the comparability of these tests.

Ammonia plays a central role in the development of CHE as well as post-TIPSS HE. Recently, the determination of ammonia and its time course after an amino acid challenge has been studied as a predictive factor for post-TIPSS HE.[32] Here, a higher increase in blood ammonia and increased responses in sleepiness and psychometric tests after amino acid challenge were associated with the development of post-TIPSS HE. However, these findings have to be confirmed in future studies before clinical implementation.

Future studies in this field should also aim at evaluating additional CHE testing strategies such as the simplified Animal Naming Test or the EncephalApp Stroop, which have also been shown to be reliable predictors for the development of OHE in patients without TIPSS.[7,33-35]

2.5 | Common medications as risk factors for post-TIPSS HE

In recent years, proton pump inhibitors (PPIs) have been identified as potential risk factors for a wide variety of complications of liver cirrhosis such as spontaneous bacterial peritonitis (SBP) or HE.[36,37] Results of studies with a focus on HE risk under PPI treatment are partly conflicting. There is only one prospective study available, which found an association between PPI use and the development of MHE and OHE.[37] In contrast, a recently published large study neither found an association between PPI use and the presence of CHE nor OHE-related readmission.[8] In patients with TIPSS, there seems to be an association between PPI use and post-TIPSS HE. A recently published study by Sturm et al identified PPI use as an additional, dose-dependent risk factor for the development of post-TIPSS HE.[38] However, it has to be mentioned that the overall quality of evidence is low. Nevertheless, given the fact that up to 60% of the patients receive PPIs without a valid indication,

PPI treatment should be discontinued if no longer needed prior to TIPSS placement.[39]

Other medications that are known risk factors for the development of HE include opioids, benzodiazepines, or even diuretics potentially leading to volume depletion.[40,41] Although these have not been well studied in the context of post-TIPSS HE, a critical re-evaluation of the indication before TIPSS insertion seems inevitable.

2.6 | Sarcopenia as a risk factor for post-TIPSS HE

Muscle alterations like sarcopenia are frequent in patients with decompensated liver cirrhosis and, due to the importance of muscle in ammonia metabolism, sarcopenia may be linked to HE.

Although several studies have found sarcopenia to be a relevant risk factor for the development of post-TIPSS HE, there are also studies reporting negative results. Nardelli et al were able to demonstrate that not only sarcopenia but also muscle quality as defined by myosteatosis were significantly associated with the presence of MHE and the development of OHE in patients with liver cirrhosis.[42] The same findings were validated in patients undergoing TIPSS insertion. Here, impaired liver function as reflected by higher MELD scores and sarcopenia were independently associated with the occurrence of post-TIPSS HE.[43] Remarkably, in this study, only patients with sarcopenia developed post-TIPSS HE within the first months after insertion. However, a recent retrospective study of 107 patients undergoing TIPSS insertion for refractory ascites showed that sarcopenia was neither associated with the occurrence of de novo HE nor with higher mortality.[44] In addition, TIPSS itself has positive effects on body composition in the long term: TIPSS implantation leads to both weight and muscle gain as well as overall better body composition in malnourished patients with liver cirrhosis, which in turn may improve cognitive deficits.[45,46] In addition, several further risk factors of HE can be improved by TIPSS placement including lower rates of gastrointestinal haemorrhage, hypovolaemia or infections such as SBP.[47] Taken together, sarcopenia should be no exclusion criterion for TIPSS insertion. However, sarcopenic patients should be monitored closely for post-TIPSS HE and may be in the highest need of preventive measures.

2.7 | Prophylaxis of post-TIPSS HE

2.7.1 | Non-drug-based prophylaxis

Given that sarcopenia is independently associated with the development of post-TIPSS HE in cirrhotic patients, improving the nutritional status of TIPSS candidates may help to prevent post-TIPSS HE (Figure 2).[43] Currently, there are no specific guideline recommendations for nutritional advice in patients with TIPSS. However, recommendations should be given in accordance with guidelines for secondary prevention after a bout of OHE.[5] Patients should be advised to maintain a sufficient calorie intake of about 35–40 kcal/kg body weight/day. Additionally, protein intake should be about 1.2–1.5 g/kg body weight/day with a focus on plant-based proteins. Moreover, long catabolic periods should be avoided and the ingestion of a late-night snack is recommended.

2.7.2 | Drug-based prophylaxis

In patients with liver cirrhosis without TIPSS, the drug-based prophylaxis of the development of HE mainly focuses on disaccharides (e.g. lactulose), antibiotics like rifaximin and amino acids like L-Ornithine-L-Aspartate (LOLA). Guidelines currently do not recommend any primary HE prophylaxis after TIPSS placement.[5] Though studies are evolving and recent data may lead to changes in future guidelines recommendations. This is mostly explained by a study illustrating that neither rifaximin nor lactulose prevented post-TIPSS HE any better than placebo.[48] However, Bureau et al recently published a large randomised and placebo-controlled trial on the use of rifaximin in the prevention of OHE after TIPSS insertion. In total, 197 patients undergoing TIPSS for intractable ascites or prevention of variceal bleeding were included in the study. Patients in the verum arm were treated with 600 mg rifaximin twice daily beginning 14 days before TIPSS. During the follow-up of 168 days, rifaximin reduced the occurrence of OHE compared to placebo with an odds ratio (OR) of 0.48 (95% CI 0.27-0.87). However, rifaximin had no influence on TFS, which may be attributed to a lack of power for this endpoint. Additionally, it has to be mentioned that the effect of rifaximin on the prevention of post-TIPSS HE did not reach significance in the subgroup of patients without a history of OHE.[49] In addition, it is noteworthy that the prophylaxis of HE with lactulose was not allowed in this trial. Nevertheless, these findings will likely result in a guideline recommendation for rifaximin to prevent post-TIPSS HE (Figure 2). Though the use of rifaximin for this indication is currently off-label, another ongoing multicentre randomised, controlled, double-blind trial (PEARL trial, NCT04073290) is comparing rifaximin plus lactulose to placebo plus lactulose administered 3 days prior to TIPSS insertion to 3 months post-TIPSS.[50]

A recent single centre, retrospective study including 233 patients reported that rifaximin plus lactulose is effective in preventing recurrent HE in patients with pre-TIPSS HE at 1, 3 and 12 months post-TIPSS.[17] However, in this study, patients without pre-TIPSS HE did not benefit from this combination. Remarkably, LOLA had no additional benefit when added to lactulose and rifaximin.[17] Routine administration of albumin after TIPSS insertion did not reduce the incidence of post-TIPSS HE.[51]

Trials investigating the drug- or stent-based prophylaxis of post-TIPSS HE are summarised in Table 3.

2.7.3 | Stent-based prophylaxis

To reduce the risk of neointimal hyperplasia after TIPSS placement and thus minimise the probability of TIPSS occlusion, the use of

TABLE 3 Prophylaxis of post-TIPSS HE

Trial		No. of patients	Trial design	Intervention	Primary endpoint	Results
Bureau et al[49]	Drug-based prophylaxis	197	Randomised, double-blind, multicentre, placebo-controlled	Rifaximin (600 mg twice daily) vs placebo 14 days pre-TIPSS to 168 days post-TIPSS	OHE within 168 days post-TIPSS	Incidence of OHE was 34% (rifaximin) vs 53% (placebo), OR: 0.48 (95% CI: 0.27-0.87). No differences in AEs or TFS
Riggio et al[48]		75	Single centre RCT, not blinded	Lacticol (60 g/day) vs rifaximin (1200 mg/day) vs placebo immediately post-TIPSS	OHE within 1 month post-TIPSS	No differences in each group regarding 1-month incidence and rate of severe HE episodes
Wit et al[50]		Recruting	Multicentre randomised, double-blind, placebo-controlled (PEARL trial, NCT04073290)	Rifaximin (550 mg twice daily) plus lactulose (25 ml twice daily) vs placebo plus lactulose (25 ml twice daily) 3 days pre-TIPSS to 3 months post-TIPSS	OHE within 3 mo post-TIPSS	Ongoing
Seifert et al[17]		233	Retrospective, single centre	Lactulose mono (LM) vs rifaximin mono (RM) vs lactulose + rifaximin (LR) (±l-ornithin-l-aspartate (LOLA)) vs no prophylaxis	OHE within 1, 3 and 12 mo post-TIPSS	LM: no differences. LR is effective in preventing recurrence of HE in pts with pre-TIPSS HE at 1, 3 and 12 mo post-TIPSS, but no differences were found in pts without pre-TIPSS HE. No additional benefit of LOLA to LR
Riggio et al[51]		23	A prospective, non-randomised clinical trial with controls from[58]	Albumin 1 g/kg body weight for the first 2 d after TIPSS insertion. Then 0,5 g/kg body weight at fourth and seventh days followed by albumin once a week for a total of 3 wk	OHE within 1 mo post-TIPSS	No differences in the OHE incidence
Wang et al[57]	Stent-based prophylaxis	127	Single centre RCT	8 mm vs 10 mm PTFE-covered stents	Shunt dysfunction	No differences regarding shunt dysfunction, recurrent bleeding, TFS and overall OHE within a median follow-up of 27 mo. Significant lower rate of spontaneous OHE in the 8 mm stent group (27% vs 43%, RR: 47%)
Schepis et al[61]		Training cohort: 42; Control cohort: 53, validation cohort: 47	Multicentre, prospective, non-randomised	Underdilated (6–7 mm) vs ≥8 mm PTFE-SGs (training vs control cohort). 6 mm in the validation cohort	OHE within 6 months post-TIPSS, shunt dysfunction, recurrent ascites or variceal bleeding, portocaval pressure gradient reduction	Significant decrease in HE incidence in the underdilated stent group (27% vs 54%), with no differences regarding recurrence of variceal bleeding or ascites. Results were confirmed in the validation cohort
Riggio et al[58]		45	Single centre RCT	8 mm vs 10 mm covered stents	OHE	8 mm stents reduced the efficacy of TIPSS-related symptom control. No differences regarding HE occurence between both groups
Praktinkjo et al[59]		114	Single center, prospective case–control study	VIATORR Controlled Expansion stent graft (VCX) vs underdilated VIATORR TIPSS stent graft (both underdilated 8 mm)	Survival	Significant decrease of post-TIPSS HE, uncontrolled ascites, heart failure and improved 1-y survival in the VCX group

Abbreviations: AEs, adverse events; OHE, overt hepatic encephalopathy; OR, odds ratio; PTFE, polytetrafluoroethylene; PTFE-SGs, polytetrafluoroethylene-covered stent grafts.; RCT, randomised controlled trial; RR, risk reduction; TFS, transplant-free survival; TIPSS, transjugular intrahepatic portosystemic shunt.

PTFE-covered stent grafts has become standard in the recent decade and is highly recommended.[52,53] While initially a higher risk of post-TIPSS HE for covered stent grafts in comparison to bare metal stents has been reported, these results could not be confirmed in external validation as the HE rate did not differ significantly.[54,55] Furthermore, a recent meta-analysis of the latest randomised controlled trials (RCTs) identified an even lower rate of HE in patients treated with covered stents.[56] From a pathophysiological point of view, this may be explained by the fact that TIPSS dysfunction/occlusion may expose patients to new decompensation events like variceal bleeding or ascites complicated by SBP, consequently triggering HE. Thus, covered stents should be favoured, in particular, to reduce the risk of TIPSS dysfunction/occlusion.[53] Nevertheless, investigations regarding the optimal diameter and the grade of dilation of PTFE-covered stent grafts are still ongoing.

In 2017, a RCT including 127 patients undergoing TIPSS placement for secondary prophylaxis of variceal bleeding showed that 8 mm covered stents were equally effective in preventing rebleeding within 2 years but were associated with a 47% reduction of the risk of spontaneous OHE compared to 10 mm stents.[57] Though, there was only a trend for a lower rate of overall HE in this trial ($P = 0.075$). In contrast, another smaller RCT including 45 patients reported a significant reduction in the efficacy of TIPSS-related symptom control (particularly ascites) in patients receiving 8 mm instead of 10 mm diameter endograft, while the risk of developing HE did not differ between both groups.[58] An additional option is the use of underdilation of nominal larger stent grafts. In particular, the underdilation of nominal 10 mm stent grafts to 8 mm. While the underdilation might be beneficial regarding the risk of post-TIPSS HE, it still offers the potential of full dilation in case of hemodynamic TIPSS failure or ineffective symptom control. A recently published study investigated the effects of a novel VIATORR Controlled Expansion stent graft (VCX), which can be specifically used underdilated on 8 mm. This novel VIATORR was compared in its underdilated form to a conventional VIATORR TIPSS stent graft in underdilated (8 mm) and nominal (10 mm) diameter regarding prognosis as well as post-TIPSS HE.[59] Here, the authors found that patients treated with VCX had significantly lower rates of post-TIPSS HE, uncontrolled ascites and heart failure during the follow-up as well as lower 1-year mortality. This effect could be attributed to the fact that conventional VIATORR stent grafts, in contrast to VCX, are passively expanded by haemodynamics already after 6 weeks.[60] Following these results, further underdilation has to be investigated in the future.

A prospective, multicentre (but non-randomised) trial including 95 cirrhotic patients reported a significant decrease in the occurrence of post-TIPSS HE after implantation of underdilated self-expandable PTFE-covered stent grafts with a diameter of 6–7 mm without loss of efficacy regarding recurrent variceal bleeding or ascites. These results were confirmed in an additional validation cohort of 47 patients cohort receiving PTFE stent grafts with a diameter of 6 mm.[61]

Taken together, additional prospective and randomised trials are needed to delineate the effect of e.g. underdilated stents in more detail.

2.8 | Management of post-TIPSS HE

In most cases, the treatment of acute HE after TIPSS does not differ from the treatment of OHE in patients without TIPSS.[5] Patients with higher grades of HE (HE grade 3–4 and Glasgow coma score less than 7) should be admitted to the intensive care unit as they are usually unable to protect their airways. Importantly, infections (e.g., SBP) as a common and reversible HE trigger, should be rapidly excluded or treated in both patients with and without TIPSS.

The treatment of choice for first-line therapy of HE remains lactulose, administered orally or by enemas.[5] There are also data indicating the usefulness of a combination therapy containing lactulose and rifaximin for the treatment of OHE.[62] However, it has to be mentioned that the administration of rifaximin for the treatment of OHE is off-label. In patients with a hard-to-treat bout of OHE, the initiation of intravenous LOLA should be considered. Two recent studies from India indicated that the addition of LOLA could decrease the time to reverse HE.[63,64] Besides drug-based therapy, catabolic states should be avoided and protein restriction should be omitted.[5] In patients with recurrent or therapy-refractory post-TIPSS HE, stent diameter reduction or complete TIPSS occlusion are potential interventional therapies.[65,26] However, TIPSS occlusion is associated with a high risk of severe (iatrogenic) complications.[66] Especially, in patients undergoing TIPSS insertion due to variceal bleeding, the management of rebleeding is challenging. Thus, liver transplantation should always be considered in the first instance for recurrent and refractory post-TIPSS HE.

3 | CONCLUSIONS AND FUTURE DIRECTIONS

Post-TIPSS HE remains a frequent and severe post-interventional complication for patients with liver cirrhosis. However, optimised patient selection based on cognitive performance, nutritional status and liver-related factors may reduce the incidence of post-TIPSS HE (Figure 1). Additionally, the widespread use of stent grafts with controlled expansion with the opportunity to precisely adjust the stent diameter may be an appealing approach to improve prognosis. Regarding drug prophylaxis, it is likely that the recently published high-quality data on rifaximin to reduce post-TIPSS HE could change guideline recommendations.[49] However, further high-quality studies, especially on the combination of lactulose and rifaximin, are urgently needed and eagerly awaited.[50]

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