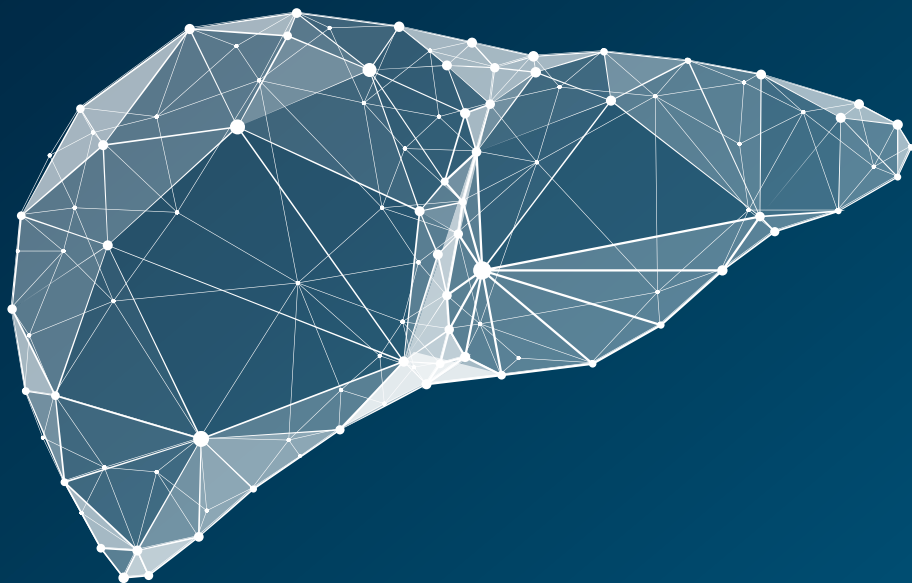


HEPATOLOGY

A clinical textbook

Wedemeyer, Mauss, Berg, Keitel, Rockstroh, Sarrazin

11th Edition **2024–2025**



17. Complications of liver cirrhosis

Benjamin Maasoumy, Jonel Trebicka

Summary

This chapter deals with the development of complications in patients with end stage liver disease. Liver cirrhosis is the common in stage of any chronic liver injury. After a rather long period of compensated stage with increasing fibrosis and liver insufficiency, portal hypertension develops also progressively and drive complications. Especially development of collaterals including varices, as well as development of kidney dysfunction with the ascites are the most common complications of portal hypertension. Alongside with portal hypertension, a complex process of augmenting inflammatory state takes place, first limited to the liver and later taking over the organism in the form of systemic inflammation. Both portal hypertension and systemic inflammation drive decompensation, with this maximal form acute on chronic liver failure (ACLF), characterised by development of organ failures and very high short-term mortality. Despite substantial research work treatment options are limited to nonselective beta blockers, non-absorbable antibiotics, albumin, TIPS and liver transplantation.

Clinical stages and pathophysiology of liver cirrhosis

Liver cirrhosis is widely regarded as the final stage in the natural history of liver disease. However, complications and prognosis vary widely among the affected patients (D'Amico 2006, D'Amico 2018). In the past, patients have only been stratified into compensated and decompensated cirrhosis. However, this does not adequately reflect the complex pathomechanism and the wide variety of clinical phenotypes (Figure 1) (D'Amico 2018, Engelmann 2021). Modern classifications distinguish up to seven distinct stages in the natural history of cirrhosis (D'Amico 2018, Schulz 2024). In patients with compensated cirrhosis or compensated advanced chronic liver disease (cACLD), the development of portal hypertension plays a key role in disease progression and the development of clinical complications. Portal

hypertension is defined by a portosystemic pressure gradient (PPG) of ≥ 6 mmHg (de Franchis 2022). However, the risk of associated complications, i.e. hepatic decompensation, remains negligible until a threshold of 10 mmHg is reached. This threshold indicates a so called clinical significant portal hypertension (CSPH) (de Franchis 2022, Jachs 2024a, Jachs 2024b). In the absence of CSPH and if the underlying liver disease has been adequately treated, patients do not necessarily require any specialised follow-up other than surveillance for hepatocellular carcinoma (HCC) due to the overall excellent prognosis (de Franchis 2022, Jachs 2024b, Semmler 2022). In contrast, those cACLD patients with CSPH should usually be followed by hepatologists for hepatic decompensation and may benefit from early treatment with non-selective beta-blockers (NSBB) even in the absence of large varices (Semmler 2021, Villanueva 2019). The gold standard for the diagnosis of CSPH in cACLD patients is the invasive transjugular assessment of the hepatic venous pressure gradient (HVPG). However, in the recent years several non-invasive alternatives have been established based on either elastography, blood tests (e.g. VITRO (Jachs 2023, Semmler 2024), 3P/5P model (Reiniš 2023, Sandmann 2023)) or a combination of different clinical and laboratory data (e.g. ANTICIPATE model (Abralde 2016, Pons 2021)). BAVENO VII proposed criteria based on liver stiffness and platelets, which have been best validated for chronic hepatitis C and are able to diagnose or rule-out CSPH in about 50% of the patients (Abralde 2016, Semmler 2022). Sequential application or combination of different non-invasive tests as well as the introduction of new techniques (e.g. spleen elastography) may reduce the grey zone in the future (Dajti 2022, Jachs 2023, Odriozola 2023) (Table 1). Validation will be required for different etiologies (including rare diseases) and different clinical situations (cured vs. ongoing liver disease) (Jachs 2024b, Sandmann 2023).

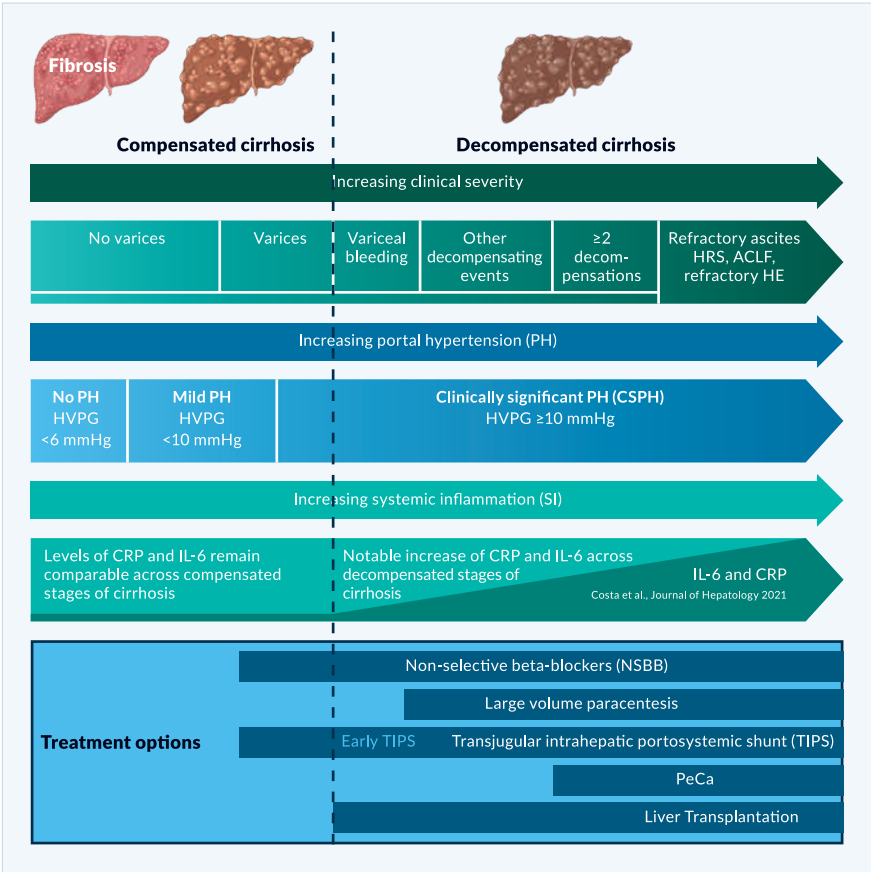


Figure 1. Modified after D'Amico et al., Journal of Hepatology 2018.

Table 1. Selection of non-invasive tests (NIT) for the detection of clinically significant portal hypertension (CSPH)

NIT model	Required Parameters	Output Categories	Cut-off values (if available)
ANTICIPATE ¹ ANTICIPATE NASH ²	LSM + PLT LSM + PLT + BMI	CSPH probability (%) CSPH probability (%) in obese MASLD/MetALD patients	
Baveno VII ³	LSM + PLT	CSPH ruled-out, Grey zone, CSPH ruled-in	CSPH Ruled out: LSM ≤15 kPa + PLT ≥150x10 ⁹ /L CSPH Ruled in: LSM ≥25 kPa particularly validated for patients with virus- and/or alcohol-related cACLD and non-obese (BMI <30 kg/m ²) NASH-related cACLD
+ VITRO ⁴	LSM + PLT + VWF/PLT ratio	CSPH ruled-out, Grey zone, CSPH ruled-in	Baveno VII + CSPH Ruled out: VITRO ≤1.5 CSPH Ruled in: VITRO ≥2.5
+ Spleen stiffness measurement (SSM) ⁵	LSM + PLT + SSM	CSPH ruled-out, Grey zone, CSPH ruled-in	CSPH Ruled out if at least two of the following present: LSM ≤15 kPa; PLT ≥150 x 10 ⁹ /L; SSM ≤ 40kPa CSPH Ruled in if at least two of the following present: LSM >25 kPa; PLT <150 x 10 ⁹ /L; SSM > 40kPa
3P Model ⁶	PLT + Bilirubin + INR	CSPH probability (%)	
5P Model ⁶	PLT + Bilirubin + APTT + CHE + Gamma GT	CSPH probability (%)	

NASH: non-alcoholic steatotic liver disease, LSM: liver stiffness measurement, PLT: platelets, BMI: body mass index, CSPH: clinical significant portal hypertension, MASLD: metabolic dysfunction associated steatotic liver disease, cALCD: compensated advanced chronic liver disease, VWF: von Willebrandt factor, SSM: spleen stiffness measurement, INR: international normalised ratio

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The progression of earlier stages of cirrhosis is directly correlated with the degree of portal hypertension (Costa 2021, Ripoll 2007). In the decompensated stage (dACLD), the absolute HVPg level becomes less important. Patients’ prognosis and morbidity are determined by hepatic impairment, the presence of extrahepatic complications of cirrhosis and systemic inflammation (Angeli 2018, Costa 2021, D’Amico 2018, Engelmann 2021, Trebicka 2020d).

Hepatic impairment may include inadequate liver detoxification as indicated by elevated bilirubin or ammonia levels. Both are associated with patient survival. Bilirubin is widely used and included in several prognostic scores (Table 2). The value of ammonia has been controversial in the past. Limitations include interlaboratory variation. Recently, promising results have been published when local upper limits of normal are considered for interpretation (Ballester 2023, Tranah 2022). Hepatic synthetic capacity could be assessed by either INR or albumin. Serum cholinesterase may also be of value in certain situations (Stockhoff 2022).

Table 2. Scores for disease severity assessment in liver cirrhosis

Score	Included parameters	Interpretation	Comment
MELD Score ¹	Creatinine + Bilirubin + INR	Scores range from 6-40.	Predicts three-month survival in patients with liver cirrhosis. OPTN Score from 2002-2016.
MELD Na ²	Creatinine + Bilirubin + INR + Sodium (Na)	Scores range from 6-40.	Predicts three-month survival in patients with liver cirrhosis. OPTN score from 2016-2022.
MELD 3.0 ³	Creatinine + Bilirubin + INR + Sodium (Na) + Albumin + Sex	Scores range from 6-40.	Predicts three-month survival in patients with liver cirrhosis. Current recommendation from the OPTN since 2022.
Child-Pugh ⁴	Bilirubin + Albumin + Quick + Ascites + Hepatic encephalopathy	Scores range from 5-15. Child-Pugh class A (5-6 pts.), Child-Pugh class B (7-9 pts.), Child-Pugh class C (10-15 pts.)	Child-Pugh class correlate with one- and two-year patient survival. OPTN Score pre-2002.
CLIF-C AD ⁵	Age + WBC + Creatinine + INR + Sodium (Na)	Scores range from 0-100. CLIF-C AD ≥60: high risk (3-month mortality >30%) CLIF-C AD ≤45: low risk (3-month mortality <2%)	CLIF-C acute decompensation (AD) score predicts survival of patients with acute decompensation of cirrhosis who do not have acute-on-chronic liver failure (ACLF)

It is generally preferable to use a validated online calculator to calculate each score as there are several caveats relating to minimum and maximum values assigned in the respective scores and subcategories, which make manual calculations prone to error.

Abbreviations

CLIF-C AD: Chronic Liver Failure Consortium Acute Decompensation; INR: International Normalised Ratio; MELD: Model for End-Stage Liver Disease; MELD Na: MELD score incorporating serum sodium; MELD 3.0: Updated MELD score incorporating sodium, albumin, and sex; Na: Sodium; OPTN: Organ Procurement and Transplantation Network; WBC: White blood cell count.

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Various forms of hepatic decompensation (distinct cirrhosis-associated complications) can occur. However, the clinical and prognostic relevance differs between complications and also depends on the number of events, e.g. patients with a single event of variceal bleeding without ascites have a better outcome than those with ascites but without portal hypertensive bleeding (D'Amico 2014, D'Amico 2006). The current BAVENO VII criteria propose a distinction between first and subsequent hepatic decompensation. First hepatic decompensation could be either overt ascites, overt hepatic encephalopathy and/or variceal bleeding. Further decompensation is associated with higher mortality and is defined by the development of either a second decompensation event (ascites, encephalopathy or bleeding), jaundice, refractory ascites or hepatorenal syndrome (de Franchis 2022).

In the final stage of cirrhosis, systemic inflammation becomes an important part of the pathophysiology. CSPH is one of the key factors involved in this process. CSPH contributes to an impairment of the intestinal barrier ("leaky gut"). This leads to translocation of bacteria and bacterial compounds (pathogen-associated molecular patterns, PAMPs) (Trebicka 2021b). Hepatic and extrahepatic cell and tissue damage, such as that caused by underlying liver disease, leads to a systemic increase in damage-associated molecular patterns (DAMPs). PAMPs and DAMPs trigger the secretion of proinflammatory cytokines following systemic arterial vasodilation. This has the potential to further worsen portal pressure by increasing splanchnic and hepatic arterial inflow. However, this is limited by the cardiac capacity to compensate for the required hyperdynamic circulation (cirrhotic cardiomyopathy) (D'Amico 2018, Engelmann 2021) (Figure 2).

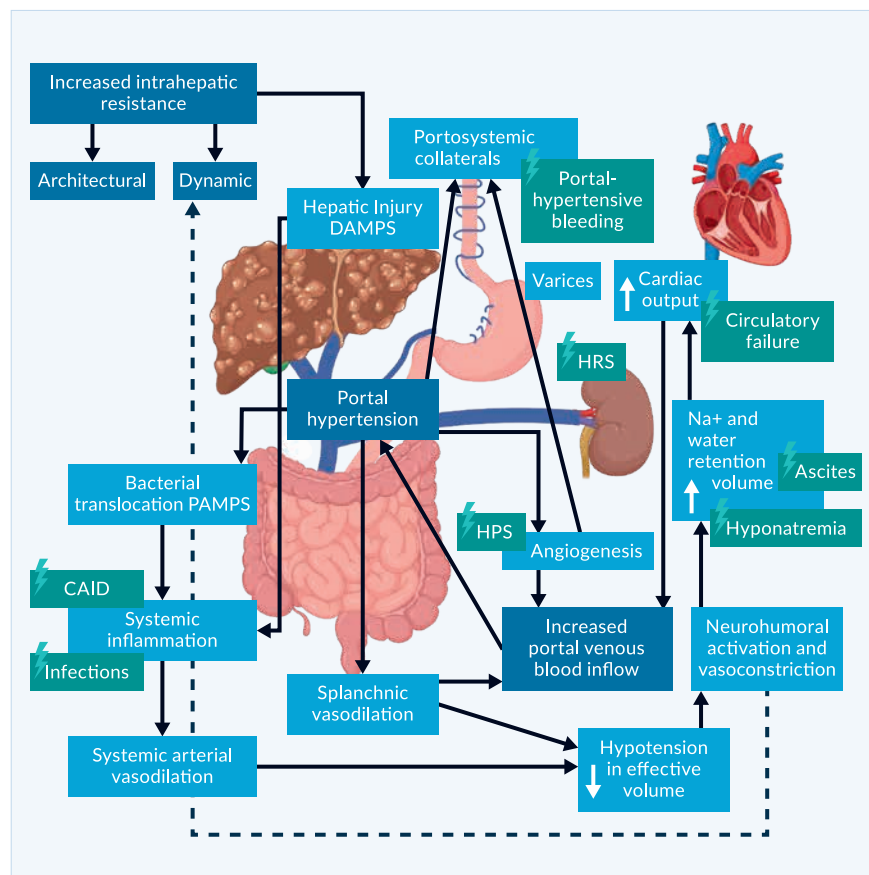


Figure 2. Adapted from Rodrigues et al., JHEP Reports 2020.

Pathophysiology and management of specific complications

Ascites

Clinical manifestation and relevance

Ascites is the most common event of first hepatic decompensation (18–48% of cases) (D'Amico 2018, Jepsen 2010, Planas 2004). The annual incidence in cACLD patients has been estimated to be 5–10% (Angeli 2018, Ginés 1987). It indicates a significant change in the natural history of liver cirrhosis with a dramatic increase in mortality (D'Amico 2006). Ascites is graded as mild (only detectable by ultrasound, grade 1), moderate (moderate abdominal distention, grade 2) and large (marked abdominal distention, grade 3) (Angeli 2018). While mild amounts of ascites are usually not associated with clinical

symptoms, large amounts lead to significant morbidity. Clinical symptoms may include abdominal tightness, weight gain, loss of appetite, abdominal hernias and immobility. Ultimately, this leads to frailty, sarcopenia and a reduced health-related quality of life (HRQOL) (Hui 2024, Merli 2019). Small defects in the diaphragm can also accumulate in the pleural space as so-called hepatic hydrothorax, which can result in shortness of breath (Hui 2024).

Recurrent ascites is defined as ascites that occurs at least three times within 12 months. Refractory ascites is defined as ascites that cannot be mobilised despite adequate sodium restriction and diuretic treatment, either because of non-response (diuretic-resistant) or intolerance of treatment (diuretic-intractable) (Angeli 2018, Arroyo 1996a). Refractory ascites indicates the final stage of liver cirrhosis and is linked to particularly poor survival (Salerno 1993, Tergast 2023, Tergast 2022). Therefore, patients with refractory ascites should be considered for liver transplantation (Angeli 2018).

Pathogenesis

Ascites is considered to be the consequence of CSPH, sodium and water retention as well as decreased oncotic pressure (Figure 3). CSPH and impaired venous drainage in portal system may increase capillary leakage and lead to drainage fluid into the abdominal cavity. Moreover, CSPH and inflammation results also leads to arterial vasodilation resulting in a decreased effective arterial blood volume. The physiological neurohumoral response to this is an activation of the renin-angiotensin-aldosterone system (RAAS) that mediates sodium and water retention in kidney. In the cirrhotic patient it will ultimately lead to sodium and water overload and is considered as the main driver of hydropic decompensation. Finally, impaired hepatic protein synthesis may contribute to ascites manifestation as the liver is the source of the majority of serum protein, in particular albumin.

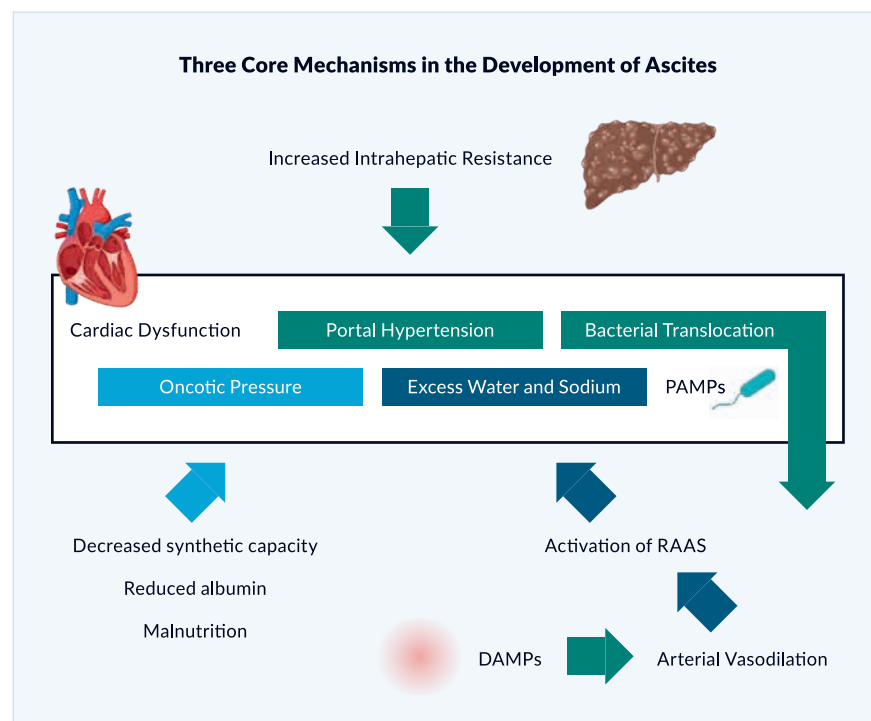


Figure 3. Adapted from Zakim and Boyers's Hepatology 6th edition; EASL „CPG decompensated cirrhosis”, J Hepatol 2018; Bhathal PS, et al. J Hepatol 1985; Rockey DC, et al. Gastroenterology 1998.

Diagnostic work-up

First ascites manifestation requires a structured diagnostic work-up, which usually includes a diagnostic paracentesis. While cirrhosis is certainly the most common cause of ascites, other differential diagnoses such as heart failure, intra-abdominal malignancy, portal vein thrombosis must be ruled out at this stage. The general appearance of the ascites can already lead to assumptions about its origin (e.g. if it is red or milky). In addition, total ascites protein and albumin should be determined. Albumin levels can be used to calculate the simple serum ascites albumin gradient (SAAG). Using a threshold of 1.1 g/dL, the SAAG is supposed to differentiate ascites due to portal hypertension from other causes in more than 95% of the cases (Runyon 1992). Low ascites protein levels support the suspicion of a classic transudate, e.g. due to CSPH, and levels below 1.5 g/dL indicate an increased risk for spontaneous bacterial peritonitis (SBP) (Guarner 1999, Llach 1992, Moreau 2018, Runyon 1986). Levels above 2.5 g/dL are suspicious for other causes of ascites (Runyon 1992). If malignancy is suspected, cytology should be performed on samples of at least 50-100 mL (Angeli 2018, Arroyo 1996b). Ascites level of cholesterol and carcinoembryonic antigen

levels may be useful in case repeated cytology remains inconclusive (Angeli 2018, Gulyás 2001). After ascites has been attributed to liver cirrhosis and CSPH, subsequent episodes do not always require the same level of work-up. However, any worsening or new onset of ascites should raise the question of a possible precipitating event of hepatic decompensation (e.g., infection) that requires specific treatment (de Franchis 2022, Jalan 2014b, Moreau 2013).

Treatment

Therapeutic strategies are directly derived from the pathomechanisms discussed above and include nutritional, pharmaceutical and interventional measures. In general, a stepwise approach should be followed. However, presentation with grade 3 ascites may also justify direct initiation of combination therapy.

Nutrition

Sodium restriction is considered to be the treatment of choice in patients with ascites targeting the RAAS-induced retention of sodium and free water. However, overall efficacy is limited and a certain degree of natriuresis is required. Current EASL guidelines recommend limiting salt intake to 4.6-6.9 g per day (Angeli 2018). While more restrictive regimens may result in faster resolution of ascites, they are associated with impaired caloric intake and increased risk of renal failure. Moreover, it remains almost impossible for patients to follow such recommendations in their daily routine, as it is not possible to calculate the exact amount of salt in all meals. A more practical approach is to advise them not to add extra salt to their regular meals.

Fluid restriction is often used to treat ascites. However, its role is widely overestimated. In particular, there are no data that convincingly support its widespread use. In addition, fluid restriction has the same disadvantages as sodium restriction in terms of reducing overall caloric intake. At present, it is only recommended for severe hyponatraemia (<125 mmol/L) (Angeli 2018, Gerbes 2019).

In contrast, the importance of overall calory and in particular protein intake seems to be widely underestimated. Malnutrition and sarcopenia is frequent among cirrhotic patients and independently linked to an increased morbidity and mortality. In non-obese patients a calory intake of 30-35 kcal/kg body weight including 1-1.5g/kg body weight is indicated. This should be accompanied by late evening snack to avoid hypoglycemic and catabolic phases during the night, which provokes encephalopathy as well as further deterioration of sarcopenia and ascites (Merli 2019).

Diuretics

The first line of treatment is aldosterone antagonists, which directly target hyperaldosteronism and are superior to loop diuretics as monotherapy. Spironolactone is the most widely used drug and can be used up to a dosage of 400mg per day (Angeli 2018). Common side effects include hyperkalaemia, renal impairment and gynecomastia. In patients with severe gynecomastia, eplerenone can be used as an alternative and equally effective treatment. However, the approved dosage is limited to 50 mg/day. In case of inadequate response or severe ascites and/or hyperkalaemia on monotherapy, loop diuretics may be added (Angeli 2018). The dosage should be limited to the equivalent of 160mg of oral furosemide per day. Torasemide may offer a more favourable pharmacokinetic profile. However, there are no data to support that this translates into a superior outcome in cirrhotic patients. Combination therapy with spironolactone and loop diuretics is more effective, offers a better control of potassium levels, but is also more frequently associated with an excessive response with the need for dose reductions (Angeli 2010, Santos 2003). Treatment should be aimed at weight loss of 500-1000 g per day and should be adjusted after ascites control is achieved (Angeli 2018).

Large volume paracentesis (LVP)

In patients with refractory ascites, repeated LVP can be performed to control clinical symptoms. LVP is generally a safe procedure. Major bleeding is rare and routine assessment of the patient's coagulation status is therefore not required (Lin 2005, Villa 2022). However, ultrasound guidance is recommended to avoid inadvertent puncture of abdominal vessels. While, a maximum drainage volume has not been established, there is a certain risk of a circulatory dysfunction following LVP of more than 5 litres, as indicated by a decrease in mean arterial pressure, increase in aldosterone levels and the risk of acute kidney injury (AKI) (Ginès 1988). This can be prevented by albumin infusion of 6-8 g/L of removed ascites (Angeli 2018, Bernardi 2012, Sola-Vera 2003). However, the longer term administration of albumin in patients with severe ascites, requiring paracentesis, has been shown to improve survival (Caraceni 2018b).

Transjugular intrahepatic portosystemic shunt (TIPS)

TIPS insertion is the most effective treatment for CSPH after liver transplantation. Ascites control can be achieved in more than 70% of patients (García-Pagán 2020). A stent graft is placed through the jugular vein to create a bypass between a hepatic vein and a portal vein branch.

This results in an immediate decrease in PPG, usually below the threshold of CSPH. Initially, there were some safety concerns due to a significant mortality rate and complications such as liver failure and encephalopathy (Lebrech 1996). Since then, significant benefits have been achieved, including technical safety, stent patency rates, and patient selection. In the past, TIPS malfunction was a common problem. However, this changed when bare metal stents were replaced by PTFE-coated stents (Bureau 2004). There has been a long-lasting debate as to whether TIPS is only a symptomatic treatment in patients with refractory and recurrent ascites. Finally, an individual patient meta-analysis (refractory ascites) and a well-designed randomised trial (recurrent ascites) convincingly demonstrated an improved survival compared to repeated LVP (Bureau 2017a, Salerno 2007). Thus, today, TIPS is considered the first-line treatment for patients with refractory or recurrent ascites (Angeli 2018, de Franchis 2022). The survival benefit underscores the ability of TIPS to alter the natural history of ACLD by curing CSPH, a major driver of disease progression. TIPS reduces the risk of further decompensation (Larrue 2023) and may prevent hepatic decompensation in patients with ACLD undergoing extrahepatic surgery (Piecha 2024). In addition, some studies suggest that there is a decrease in systemic inflammation after TIPS (Berres 2015, Kornfehl 2024, Tiede 2024), which is linked to an improved survival, ascites control and improvement of sarcopenia (Hey 2023, Kornfehl 2024, Tiede 2024). However, disadvantages need to be considered and patients must be carefully selected (García-Pagán 2020) (Table 3). The most discussed complication of TIPS may be hepatic encephalopathy. Spontaneous portosystemic shunts (SPSS) and their absolute size are linked to the risk of encephalopathy (Praktikjnjo 2020a). Therefore, it seems obvious that this is also the case when TIPS is used as an iatrogenic shunt. In fact, the incidence of post-TIPS HE ranges from 35 to 50% (Bureau 2021, Ehrenbauer 2023, Montagnese 2022). While post-TIPS HE does necessarily increase mortality, it certainly does affect quality of life, in associated with rehospitalisation and is one of the most common reasons for the need of TIPS diameter reduction (Agrawal 2015, Gairing 2022, Nardelli 2024, Pereira 2016). Refractory or recurrent HE is usually considered as a contraindication for TIPS (Angeli 2018). However, the mechanisms of HE are complex and TIPS has both negative and positive effects in this regard (e.g. reduction of bleeding, inflammation and sarcopenia). Recent studies suggest that with fully covered stents and subsequently a marginal risk of dysfunction, the benefits and disadvantages of TIPS may even be balanced, as the HE incidence was not different from patients treated with LVP (Bureau 2017a). Overall, it remains difficult to predict the occurrence and course of HE after TIPS. Some authors stated that assessment for minimal HE may help to select patient selection (Berlioux 2014, Nardelli 2016). However, this has not been confirmed by others (Ehrenbauer 2023). More

relevant seems to be the stage of liver cirrhosis as indicated by MELD, serum cholinesterase or the new Freiburg index of post TIPS survival (FIPS) (Bettinger 2021, Cai 2022, Stockhoff 2022). The use of stents with a smaller diameter can reduce the risk for post-TIPS HE (Schepis 2018, Wang 2018). 8 mm instead of 10 mm is now widely considered as the standard of care, especially due to improved outcome (Trebecka 2019b, Praktijnjo 2021b). Treatment efficacy remains similar as long as a 50% PPG reduction is achieved (Queck 2023, Wang 2018). In high-risk patients underdilatation to 6 or 7 mm or a reduction of preexisting SPSS may be considered (Lv 2022, Praktijnjo 2021a, Schepis 2018). Recently, an individualised approach has been suggested. A PPG reduction of 60-80% was identified as the optimal target to maximise the chance of ascites control without increase in the incidence of Post-TIPS HE (Kabelitz 2025). Finally, primary prophylaxis with rifaximin significantly reduced post-TIPS HE in a recently published randomised controlled trial (Bureau 2021). While the risk of HE may be overestimated, many physicians tend to underestimate the risk for cardiac decompensation, which can be expected in 20% of patients (Billey 2019, Schneider 2023). Due to the newly introduced shunt, the cardiac index increases by approximately 50% (Huonker 1999), at least in the early phase after TIPS. Therefore, patients with significant cardiac impairment and moderate or severe pulmonary hypertension should not undergo TIPS insertion (Angeli 2018). In addition, the presence of aortic valve stenosis seems to be associated with a particularly high risk (Billey 2019). Different risk scores have been proposed in the past with varying degrees of prognostic accuracy. In general, the prevalence of diastolic dysfunction seems to be a valid parameter that is associated with the likelihood of decompensation (Billey 2019, Schneider 2023). Thus, echocardiography should be performed prior to TIPS. Smaller diameter stents may help to further reduce the risk of decompensation. TIPS results in reduced portal blood flow. In rare cases this can lead to hepatic infarction (Tuifua 2022). Insufficient arterial perfusion must be ruled out when evaluating patients for TIPS. However, the more common clinical challenge is the reduction of liver function leading to hepatic failure with progressive increase in bilirubin levels. High grades of intrahepatic inflammation, serum bilirubin, serum cholinesterase as well as low albumin levels have been associated with poor post-TIPS survival (Bettinger 2021, Bureau 2011, Stockhoff 2021, Stockhoff 2022). Therefore, patients with very advanced stages of liver disease may not be suitable candidates for TIPS. However, most of these studies lack a control group. Thus, it remains unclear whether TIPS treatment impairs survival or whether the poorer outcome does rather reflect the prognosis of the more advanced liver cirrhosis (Bettinger 2021, Bureau 2011, Stockhoff 2021, Stockhoff 2022). In fact, some retrospective studies suggest that in patients with very advanced liver disease (e.g. as indicated by FIPS or CHE)

survival is not impaired, but also no longer improved by TIPS insertion (Stockhoff 2021, Stockhoff 2022). Thus, TIPS could still be considered as a symptomatic treatment in these cases when liver transplantation is not available. Importantly, these studies also did not include patients with end-stage liver disease (e.g., bilirubin levels >100 µmol/L). While TIPS may not necessarily worsen prognosis in advanced stages of cirrhosis, it certainly becomes less effective and is associated with more complications. Current guidelines recommend to use TIPS for ascites only as soon as patients enter the stage of recurrent or refractory ascites. However, the required frequency of paracentesis is linked to higher rate of ascites persistence after TIPS (Piecha 2024). Given the positive effects at earlier stages including the reduction of further decompensation, future studies need to determine whether it should be considered earlier in the natural history of cirrhosis.

Table 3. Absolute and relative contraindications for TIPS insertion

Relative TIPS contraindications
• Cardiac ◦ Mild aortic valve stenosis ◦ E/A > 2 or E/A < 0.8 ◦ Two of the following: ▪ E/e' > 14 ▪ LAVI > 34 mL/m2 ▪ TR > 2.8 m/s ▪ sep e' < 7 cm/s or lat e' < 10 cm/s • Liver function ◦ MELD ≥ 18 ◦ Bilirubin ≥ 50 μmol/L ◦ Platelets ≤ 75.000/μL • Primary or metastatic hepatic malignancy • Contrast agent allergy • Hyperthyreosis • Age ≥ 65 years old
Absolute TIPS contraindications
• Cardiac ◦ LVEF ≤ 30% ◦ Moderate to severe aortic or pulmonary valve stenosis • Renal ◦ Chronic kidney failure > CKD4, except hepatorenal syndrome • Hepatic encephalopathy ◦ Acute ≥ 2. grade ◦ Recurrent/chronic encephalopathy ≥ 2. grade without specific trigger ▪ ≥ 2 episodes within 6 months • Liver function ◦ Bilirubin ≥ 80 μmol/L • Life expectancy ≤ 1 year • Unrelieved biliary obstruction • Active infection • Significant pulmonary hypertension (mPAP >35 mmHg) • Extensive primary or metastatic hepatic malignancy

Citations

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Home-based ascites drainage systems

In patients who are not candidates for TIPS, continuous or daily ascites drainage may be considered as an alternative treatment to repeated LVP. In contrast to TIPS, CSPH and ascites formation are altered. However, ascites control can be achieved without the need for repeated medical interventions. There are mainly two different systems available. The first one is an implantable pump that drains fluid from the peritoneal cavity to the bladder (alfapump). The subcutaneous system can be charged and programmed with an external device. Early studies reported a higher incidence of renal failure and infections (Bellot 2013, Bureau 2017b, Solbach 2018, Stirnimann 2017). The frequency of these complications decreased with more experience and the use of prophylactic antibiotics. Continuous ascites drainage has been associated with less need for paracentesis and improved quality of life (Bellot 2013, Bureau 2017b, Solbach 2018, Stirnimann 2017, Wong 2020). However, the pump comes with significant cost and the need for surgery. Moreover, it is currently not available in Europe. The other option is a tunneled peritoneal catheter (PeCa). These are widely used for drainage of malignancy-associated fluid collections in the abdominal and pleural cavities (Lungren 2013, Maleux 2016). The system is less expensive, can be easily implanted with local anesthesia or light sedation, and can be removed in the same manner. It can therefore also be used as a bridging treatment (e.g. until transplantation or TIPS is available). Studies in patients with cirrhosis have shown a reduced need for paracentesis (Macken 2019, Solbach 2017) and an overall good control of ascites. Infections are frequent in the treated patients. However, randomised controlled trials are lacking and it remains uncertain whether PeCa implantation itself increases the risk for peritonitis. Of note, a retrospective study found no significant differences in the rate of infection between patients with PeCa and those treated with LVP. However, the detection rate of pathogens in the ascites was higher and more gram positive bacteria were found (Tergast 2022). Recently, a new PeCa version has been introduced that uses a silver coating. Preliminary data suggest that this significantly reduces the risk for peritonitis and the need for PeCa explantation (Schütte 2024). Due to the continuous or intermittent daily drainage of ascites, both PeCa and the ascites pump are associated with hyponatraemia and renal impairment. In contrast to the more common hypervolemic hyponatraemia, these patients have a true sodium depletion due to the loss via ascites drainage. Sodium replacement may be required (Tergast 2023, Tergast 2022). Both

hyponatraemia and renal impairment correlate with the amount of fluid that is removed per day. If possible, drainage volume should be limited to a maximum of 1.5 L/day (Tergast 2023).

Portal hypertensive bleeding

Clinical manifestation and relevance

Oesophageal and gastric varices are very common and are present in approximately 40% of patients with CHILD A and 70% of those with CHILD B/C cirrhosis (Kovalak 2007). However, varices due to portosystemic shunts may also be present at various sites in the gastrointestinal tract (Jansson-Knodell 2021, Kochar 2008, Norton 1998). Patients remain asymptomatic and eventually present with variceal hemorrhage, which is a traumatic and life-threatening event (Reverter 2014). After ascites and encephalopathy, it is one of the most frequent events of hepatic decompensation (Jepsen 2010, Mandorfer 2021). Improvement in endoscopic and medical management have reduced short-term mortality from 30-50% to 10-20% (Chalasani 2003, D'Amico 1997, Graham 1981, Reverter 2014, Stokkeland 2006). However, recurrent bleeding is associated with significant morbidity related to other cirrhosis-associated complications such as encephalopathy, hydropic decompensation and hospitalisation (Angeli 2018, Garcia-Tsao 2024, Montagnese 2022). Bleeding of gastric varices is less frequent than from oesophageal varices. However, when bleeding does occur, it is often more difficult to control and is associated with higher mortality (Sarin 1992). Besides varices, recurrent bleeding may also occur in portal hypertension, gastropathy and intestinopathy (Merli 2004, Urrunaga 2014).

Pathogenesis

The development of oesophageal and ectopic varices is the result of CSPH and the need for portosystemic collaterals. The risk of varices is closely related to HVP levels. The risk of bleeding increases with values >15mmHg (Ripoll 2007).

Diagnostic work-up

Endoscopy is necessary to diagnose oesophageal and gastric varices. The risk of bleeding is closely related to the size of the varices, liver function and the presence of red colour signs (de Franchis 2022, Villa 2022). Thus, during

endoscopy oesophageal varices should be classified as either small or large (>5 mm). In addition, they can be classified according to Paquet as grade I (varices extending just above the mucosal level), II (varices not completely compressed after air insufflation), or III (varices protruding more than one third of the luminal diameter and/or are in contact with each other) (Angeli 2018, Paquet 1982).

Gastroesophageal varices (GOV) and isolated gastric varices (IGV) are usually classified according to Sarin depending on their localisation as GOV1 and GOV2, as well as IGV 1 and IGV2 (Sarin 1992). These may differ in their bleeding risk and associated mortality rate (Angeli 2018).

Treatment

Acute variceal bleeding

Acute variceal bleeding demands urgent treatment. Initially, immediate resuscitation is required, including placement of large intravenous lines to prevent organ failure (Angeli 2018, Cárdenas 2001, de Franchis 2022). The most important factor in bleeding control in portal hypertensive hemorrhage is control of portal hypertension. In the emergency setting, the quickest way to lower portal pressure is to use vasoactive drugs that cause arterial splanchnic vasoconstriction and, thus decrease portal inflow. In general, terlipressin and somatostatin (analogues) can be used (Angeli 2018, Avgerinos 1997, de Franchis 2022, Levacher 1995). Doing so before the endoscopy facilitates the subsequent sclerosing therapy or endoscopic variceal ligation (EVL). It is usually recommended that these medications be continued for five days, as this covers the time period of highest risk for rebleeding (Angeli 2018, de Franchis 2022, Dell'Era 2008). However, in low-risk patients, 24 hours may also be sufficient (Azam 2012). Blood (Angeli 2018, Mallet 2017) transfusion should usually not be given unless the hemoglobin level falls below 7 g/dL or the patient develops symptomatic anaemia (Villanueva 2013). Immediate antibiotic treatment (e.g., ceftriaxone) improves bleeding control and reduces the risk of rebleeding (Bernard 1995, Bernard 1999, Hou 2004). In addition, initiation of HE prophylaxis with lactulose is recommended (de Franchis 2022, Sharma 2011). Rifaximin is an alternative treatment option (Maharshi 2015). Routine use of procoagulant factors is usually not required. In fact, fresh frozen plasma can easily lead to volume overload, which further aggravate CSPH (Angeli 2018, de Franchis 2022). There is also no need to use proton pump inhibitors (PPI) in the absence of gastric ulcers. PPIs may be associated with smaller post-ligation ulcers. However, they do not alter the risk of rebleeding (Shaheen 2005). Their role in preventing ulcers in patients in the intensive care unit has

also been questioned, recently (Krag 2018). Whether they are even harmful in cirrhotic patients still remains a matter of debate (Gairing 2024, Peña Rodríguez 2024, Tergast 2018). There are conflicting data regarding the use of tranexamic acid. In a large randomised trial in patients with upper GI bleeding, no effect on survival. However, patients treated with tranexamic acid experienced venous thromboembolic events at a higher frequency (Afolabi 2020). Importantly, nearly half of the patients had suspected variceal bleeding. In contrast, a smaller randomised trial in patients with cirrhosis found a greater chance to control variceal bleeding. However, survival remained unchanged (Kumar 2024).

After initial resuscitation, patients should undergo endoscopy to confirm the diagnosis, achieve bleeding control (if necessary) and prevent early rebleeding. However, the optimal timing of endoscopy remains to be determined. A recent study showed that for upper gastrointestinal bleeding, there was no benefit to performing endoscopy within 6h compared to 6-24h. However, less than 10% of the patients enrolled had variceal bleeding (Lau 2020). If bleeding control cannot be achieved and/or in case of early treatment failure (within) 24hour, the patient should be considered for treatment with rescue TIPS and/or coiling/sclerosis of the varices. If an interventional radiologist is not immediately available, balloon tamponade can be used as bridging therapy (Angeli 2018, de Franchis 2022). However, it comes with the need for endotracheal intubation and the risk of oesophageal necrosis or perforation. A better alternative in this case is the application of a self-expanding metal stent (SEMS). SEMS has been associated with a better bleeding control and survival when compared to balloon tamponade (Escorsell 2016). All patients, regardless from initial bleeding control, should be evaluated for preemptive TIPS ("early TIPS"). There are compelling data that patients with a CHILD B cirrhosis and active bleeding at index endoscopy or CHILD C cirrhosis (<14 points) benefit from TIPS insertion within 72h after variceal bleeding (García-Pagán 2010, Nicoară-Farcău 2021). This is also the case in patients with acute-on-chronic liver failure (ACLF). Elevated bilirubin levels and acute hepatic encephalopathy do not necessarily represent a contraindication for TIPS under these circumstances (Trebicka 2020a).

Primary prophylaxis

Either NSBB or EVL can be used for primary prophylaxis of variceal bleeding. The likelihood of bleeding is not different between the two options. However, NSBB do have other advantages as they also treat the underlying CSPH (Shah 2014, Villanueva 2019). NSBB may reduce intestinal permeability and systemic inflammation (Jachs 2021, Reiberger 2013a). The combination of EVL and NSBB was not superior to NSBB treatment alone

in the majority of prospective studies (Lo 2010). However, a recent large prospective trial from India suggested a lower risk of bleeding in patients with decompensated liver cirrhosis and high-risk varices. NSBBs cause arterial splanchnic vasoconstriction via β_2 blockade and cardiodepression via β_1 blockade (Tevethia 2024). Both act synergistically to reduce portal pressure. Carvedilol, which also has an additional α_1 blockade, has been shown to be more effective than propranolol (Kim 2016, Reiberger 2013b). It is also easier to titrate it to an effective dose (Turco 2023). Primary prophylaxis of variceal bleeding is indicated in patients with either large varices or small varices and red spots or CHILD C cirrhosis (de Franchis 2022). If primary prophylaxis with NSBB is established and well tolerated, follow-up endoscopy is not required at least among those with compensated cirrhosis. Of note, in patients with only small varices and CHILD A/B cirrhosis, NSBB does neither prevent bleeding nor the development of large varices (Groszmann 2005). However, the prospective PREDESCI study and a recent meta-analysis data demonstrated that NSBB may still prevent hepatic decompensation (i.e., ascites) in patients with CSPH (Villanueva 2019, Villanueva 2022). While this was especially true for those with small varices, some recently proposed algorithms support the use of NSBB when CSPH is diagnosed with non-invasive tools (i.e., LSM). This may eliminate the need for endoscopy (Garcia-Tsao 2021). There has been an intense debate about the safety of NSBB in advanced stages of cirrhosis (Sersté 2010), suggesting the existence of a therapeutic window (Ge 2014). In those with cirrhosis-associated circulatory dysfunction, additional cardiodepression and α_1 blockade certainly have detrimental effects with an increased risk of acute kidney injury (Téllez 2020, Tergast 2019). However, the question remains as how to define the window. Some have suggested the presence of refractory ascites or SBP, but this has not been confirmed by others (Leithead 2015, Mandorfer 2014, Sersté 2010, Tergast 2019). Even in the case of ACLF, NSBBs have shown beneficial effects (Mookerjee 2016, Tergast 2019). However, systemic arterial pressure seems to be good indicator. In patients with a systolic pressure below 90 mmHg or a MAP of <65 mmHg patients have an increased risk of AKI but not beneficial effect on ACLF or survival (Tergast 2019).

Secondary prophylaxis

In contrast to the setting of primary prophylaxis, the combination of NSBB and EVL is widely accepted to be superior to either NSBB or EVL alone (Puente 2014). This affects both mortality and the risk of rebleeding. Patients should also be evaluated for TIPS insertion, which should be performed if secondary prophylaxis fails or if adequate secondary prophylaxis is not possible for any reason. If TIPS is chosen as a treatment option, it should

be used as soon as possible after the bleeding event. It has been shown to be highly effective in preventing rebleeding and it improves survival (de Franchis 2022, Sauerbruch 2015). If TIPS is not an option, patients may be considered for retrograde balloon-assisted obliteration of portosystemic shunts (e.g., BRTO) (Table 4).

Table 4.

Primary prophylaxis	Acute portal hypertensive bleeding	Secondary prophylaxis	Recurrent bleeding
Indication - Large Varices (>5 mm) - Small Varices (<5 mm) and CHILD C or red spots - Evidence for CSPH (only NSBB!) Treatment - NSBB or EVL NSBB and EVL can be considered in CPS B/C?	Initial treatment - Resuscitation - Blood Transfusion if HB <7 g/dL or by clinical indication - Terlipressin (1-2 mg i.v.) - Antibiotic Treatment - Lactulose - PPI only if gastric ulcers suspected Hemostasis - Endoscopy within 12 h - Danis-Stent - Rescue-TIPS	Early/preemptive TIPS - Within 72h if - CHILD C (<14) - CHILD B (≥8) + active bleeding in index endoscopy Conservative - Combination of NSBB and EVL - BRTO	TIPS

Hepatic encephalopathy

Clinical manifestation and relevance

Hepatic encephalopathy (HE) describes a clinical syndrome characterised by a broad spectrum of neuropsychiatric abnormalities in patients with liver disease. Patients may present with overt HE defined by obvious, clinically apparent changes that can range from impaired orientation to coma. In contrast, those with covert HE can usually be only be diagnosed by a careful history or, in the case of minimal HE (mHE), only by a specific neuropsychometric assessment (Montagnese 2022, Vilstrup 2014). HE is highly prevalent among patients with cirrhosis. The annual incidence of overt HE cirrhotic patients has been estimated to be around 2-10% (Benvegnù 2004, Tapper 2019) with a considerable range depending on the severity of liver disease and the underlying aetiology (Rose 2020, Vilstrup 2014). In patients with decompensated liver cirrhosis overt HE is prevalent in 10-14% at the time of diagnosis (Jepsen 2010, Saunders 1981). Minimal HE may be diagnosed in approximately 40% of patients with cirrhosis

(Ehrenbauer 2024, Gairing 2023). HE is associated with impaired quality of life, significantly increased morbidity and health-care related costs (Hirode 2019, Lv 2024, Shaheen 2019). The recurrence rate is high despite the use of prophylactic measures (Kang 2017, Sharma 2009). Even mHE can be linked to significant impairments of activities in daily living including driving skills (Redfield 2024). Moreover, mHE is a risk factor for the subsequent development of overt HE (Redfield 2024). After the first episode of overt HE, mortality increases up to 85% within five years (Jepsen 2010).

Pathogenesis

The pathogenesis of HE is complex and, so far, still incompletely understood. Several factors may contribute to the development of HE. However, there are two components that widely are considered to be central to the pathophysiology: impaired hepatic detoxification and portosystemic shunts (Praktiknjo 2020a, Rose 2020). According to the EASL guidelines, HE can be classified as type A, B or C depending on the pathogenesis. Type A is present in acute liver failure where impaired detoxification plays a major role. Type B occurs in those with large portosystemic shunts, which impair outcome, especially if their cumulative area exceeds 83 mm² (corresponding to a single shunt with a diameter of 10 mm) (Praktiknjo 2020b). Type C HE is present in cirrhosis (mixture of SPSS and impaired liver function) (Montagnese 2022). Regardless of the predominant cause of HE ammonia is one of the central molecules involved in the pathogenesis. The main source of ammonia is the gut where it is a product of protein digestion and bacteria urease activity. However, it is also produced and required in certain amino acid metabolisms in several organs including the liver itself. Excess ammonium is usually eliminated in the liver via the urea cycle. In case of excess production or impaired elimination i.e. due to hepatic impairment or portosystemic shunts, ammonium molecules may enter the brain and subsequently the astrocytes, where it is metabolised to glutamine. The resulting increase in intracellular osmotic pressure forces fluid into the astrocytes, causing swelling and dysfunction. This can be exacerbated by hypoosmotic serum, for example as a result of hypoproteinaemia and hyponatraemia (Rose 2020, Gallego-Durán 2024). Ammonia detoxification via the glutamine dehydrogenase may also be accompanied by increased neuronal levels of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) (Sørensen 2024). Furthermore, ammonia has been linked to oxidative stress resulting from neutrophil dysfunction, which increases neuronal vulnerability and neuroinflammation. Increased systemic inflammation also contributes to neuroinflammation (Rose 2020, Gallego-Duran 2024) (Figure 4).

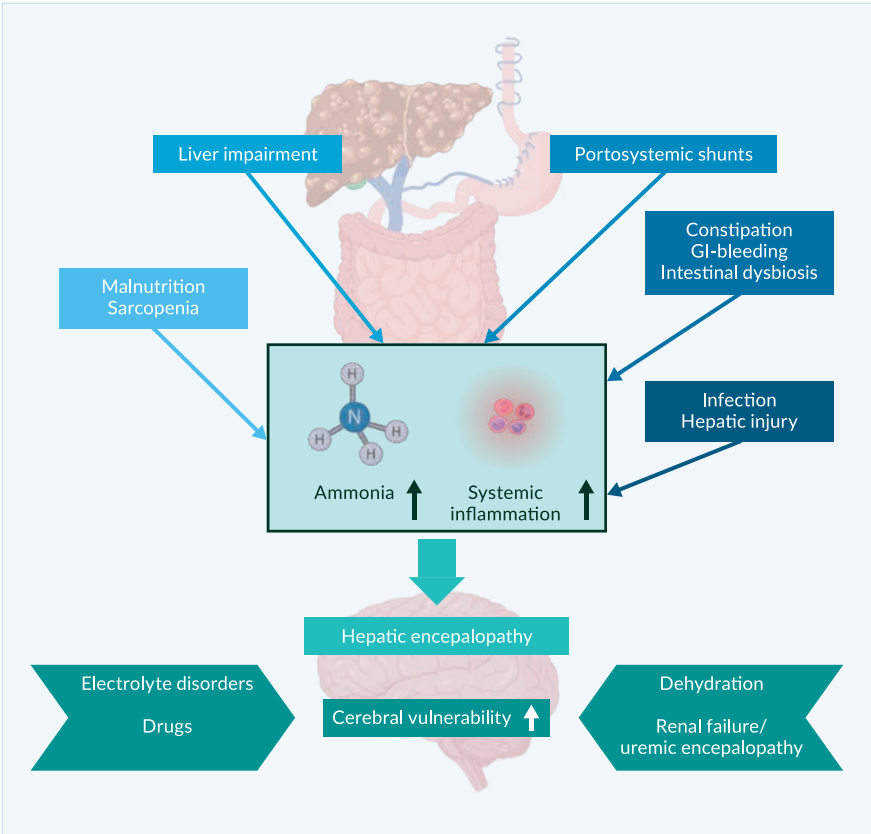


Figure 4.

Diagnostic work-up

The diagnosis of HE requires the exclusion of all relevant differential diagnoses. Contributing factors such as hyponatraemia and gastrointestinal bleeding must also be identified. The diagnostic relevance of ammonia has been debated over decades. However, its measurement can help to attribute neurocognitive impairment to cirrhosis or rule in differential diagnoses (Montagnese 2022). Moreover, elevated serum ammonia levels indicate a higher risk of overt HE development (Ballester 2023). Given the high inter-laboratory variability, recent studies have suggested using the ratio of ammonia to the local upper limit of normal rather than absolute ammonia levels (Ballester 2023, Tranah 2022).

However, at this stage, overt HE remains a diagnosis to be made clinically. It should be graded according to the West Haven criteria. This can be challenging and time consuming in routine clinical practice. The joint EASL/AASLD guidelines suggest a more practical approach based on the patient's level of orientation. Those with impaired orientation

regarding the time are considered to have HE grade II, while an insufficient orientation with regard to space can be classified as HE grade III. HE grade IV is characterised by hepatic coma in which the patient is unresponsive to painful stimuli (Vilstrup 2014). To diagnose HE grade I, clinicians need to be familiar with the patient's usual cognitive level (e.g. with the help of a relative), as neurocognitive impairment is by definition not obvious (Table 5) (Vilstrup 2014).

Table 5. Suggested application of West Haven Criteria for Hepatic Encephalopathy in clinical practice.

West Haven Criteria	Description	Suggested criteria for clinical practice
Unimpaired	No history of HE and no current encephalopathy	Tested and proved to be normal
Minimal	• Descreet motor and cognitive impairment as detected by psychometric or neuropsychological tests • Neurophysiological alteration without clinical evidence of mental change	• Abnormal results of established psychometric or neuropsychological tests • No clinical manifestations
Grade I	• Trivial lack of awareness • Phases of euphoria or anxiety • Shortened attention span • Impaired performance of basic math (addition or subtraction)	Patient presents with cognitive or behavioral decline with respect to his or her standard on clinical examination but is oriented in time and space
Grade II	• Lethargy or apathy • Disorientation for time • Obvious changes in personality • Occurrence of inappropriate behavior • Dyspraxia • Asterixis	Disoriented for time whilst the other symptoms mentioned might also occur
Grade III	• Somnolence to semi-stupor, but responsive to stimuli • Confusion • Gross disorientation	Disoriented for space whilst the other symptoms mentioned might also occur
Grade IV	• Comatose state (unresponsive to verbal or noxious stimuli)	No response even to painful stimuli

Adapted from: Vilstrup, H., Amodio, P., Bajaj, J., Cordoba, J., Ferenci, P., Mullen, K. D., Weissenborn, K., and Wong, Philip. (2014). Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study Of Liver Diseases and the European Association for the Study of the Liver. Hepatology 60 (2): p 715-735. DOI: 10.1002/hep.27210

Specific neuropsychometric tests must be used to assess mHE. The gold standard is the Psychometric Hepatic Encephalopathy Score (PHES), which can be obtained using the Portosystemic Encephalopathy Syndrome Test (PSE), which consists of a comprehensive test battery of 5 subtests (Weissenborn 2001). The PSE may provide the most comprehensive and accurate assessment of neurocognitive status. However, it is also quite time-consuming. A number of alternative tests have been proposed in the past, varying in their diagnostic accuracy for mHE and their predictive value for oHE (Table 6) (Ehrenbauer 2024). Among these, the Animal Naming Test (ANT) has been shown to be of significant value when used as a screening tool in clinical practice. Patients are asked to name as many animals as possible in one minute. Adjustments, e.g. for the educational level, need to be considered when using this test and different norms have been suggested for different regions (Campagna 2017, Ehrenbauer 2024, Labenz 2019). Another app-based alternative is the stroop test, which showed a high correlation with PHES and can be done by patients without supervision by dedicated staff and is also available in an abbreviated version (Acharya 2023, Ehrenbauer 2024, Labenz 2024).

Table 6. Selected tests for mHE assessment

Test	Test description	Time and equipment required	Cut-off values
PSE Syndrome Test	The PSE-Syndrome Test, yielding the Psychometric hepatic encephalopathy score (PHES) is a neuropsychological paper-pencil based test which is the surrogate goldstandard for diagnosing mHE. The test is evaluating psychomotor speed and visuomotor and -spatial orientation in 5 subtests. It is validated in numerous languages/ countries.	15–20 minutes Timer, pencil, test sheets	Score < -4 to -3 depending on regional norm values
Animal Naming Test (ANT)	The ANT is a word-fluency test in which patients had to name in one minute as many animals as possible. Recent studies recommend ANT for selecting patients for further HE diagnostics. It is the only bedside test.	2–3 minutes with explanation Timer	Age and education norms available only for Italy <23 animals (Germany) <14 animals (India) <20 animals (China)
EncephalApp (Stroop)	The EncephalApp is a smartphone-based version of the classic paper-based Stroop test that assesses psychomotor speed and cognitive flexibility. Here, patients had to react on a coloured font of a word that names a different color.	5–15 minutes Smartphone and EncephalApp	Age and education norms available only for USA >185.1s (Germany)
Critical Flicker Frequency (CFF)	A psychophysiological test in which patients have to react to a rapidly flickering light when it seems flickering to them. Problems can arise due to high variability of the test runs. There are competing study results with regard to the predictive value.	5–15 minutes HEPAtonorm analyzer	<39 Hz Age and education norms available only for Germany
Inhibitory Control Test (ICT)	The ICT is a computer-based test which evaluates working memory and sustained attention. Difficulties with the test are complex test clarification and long duration.	20 minutes Computer and ICT software (via www.hecme.tv, curently offline)	>24 Weighted Lures Age and education norms available only for Germany and USA
Continuous Reaction Time Test (CRT)	CRT measures the time between an auditory stimulus and a motor response. The score, the CRT index, looks at the variability of reaction times. Here, a high variability should indicate a cognitive deficit. One advantage of this test is its independence of age and education.	15 minutes Computer and EKHO CRT equipment	CRT-Index <1.9

Treatment

If the trigger of HE can be identified, it should be treated first. This includes correcting electrolyte imbalances and stopping certain medications (Montagnese 2022, Vilstrup 2014). Most of the available specific medical treatments for HE target ammonia (Rose 2020).

Lactulose

Lactulose is a non-resorbable disaccharide that has long been used as a symptomatic treatment for constipation. Its mode of action consists of acceleration of intestinal transit time as an osmotic laxative and of the decrease of the intestinal pH. The latter results in a higher proportion of NH_4^+ compared to NH_3 , which leads to a lower ammonium resorption. It also leads to favourable changes in the gut microbiota (Elkington 1969). Lactulose has proven efficacy in the treatment of acute HE as well as in secondary prophylaxis (Als-Nielsen 2004, Gluud 2016). Intra-rectal administration can be used in the treatment of acute HE. Oral dosing is usually titrated up to a target of 2-3 soft bowel movements per day. However, tolerance is limited, especially for long-term treatment, as it is often associated with abdominal discomfort. A small but randomised trial documented that a single dose of polyethylene glycol led to an even faster resolution of HE than standard treatment with lactulose (Rahimi 2014).

Rifaximin

Rifaximin is an antibiotic that is only minimally absorbed in the gut. It is thought to work by decontaminating the gut, which is associated with reduced ammonia production by gut bacteria. In severe cases, rifaximin might help speed recovery from HE and might even reduce mortality when added to lactulose (Sharma 2013). More importantly, rifaximin has been shown to be effective for secondary prophylaxis in combination with lactulose (Bass 2010, Kang 2017).

L-ornithine-L-aspartate (LOLA)

LOLA contains two amino acids that are required for urea synthesis and glutamine synthesis, both of which are natural pathways for ammonia elimination. It has therefore been suggested that LOLA supports ammonia detoxification. There has been a long ongoing debate about the efficacy of LOLA in HE therapy, particularly when used as an oral preparation (Vilstrup 2014). A well-conducted meta-analysis including 36 trials and 2377 patients found a significant positive impact of LOLA on mortality and HE resolution

when compared with placebo or no intervention. However, the authors noted that the quality of the individual studies included was limited (Goh 2018). Recently, a well-performed prospective double-blind, randomised controlled trial demonstrated the efficacy of intravenous LOLA in severe HE (grade III+IV) when added to rifaximin + lactulose. Treated patients benefited from faster HE recovery and lower mortality (Jain 2022).

Branched-chain amino acids (BCAA)

BCAA facilitate albumin and muscle protein biosynthesis, which may help to reduce ammonia production (Kawaguchi 2013). Meta-analyses support the beneficial effect of BCAA on HE recovery, while mortality remains unchanged (Gluud 2017).

Embolisation of portosystemic shunts

If medical treatment fails, embolisation of SPSS is an effective treatment that should be considered (Montagnese 2022). The procedure is generally safe (Ke 2022, Laleman 2013, Privitera 2018). However, it also worsens portal hypertension and may subsequent complication such as ascites.

Dialysis

In cases of severe HE, hemodialysis can remove ammonia very quickly. This also leads to electrolytes rebalance and removal of urea, which may contribute to encephalopathy in patients with renal impairment. Systems that use albumin and its binding capacity may be even more effective (Hassanein 2007).

Fecal microbiota transplant (FMT)

FMT may be a future treatment option for patients with recurrent HE. Some promising pivotal studies have been published, showing improvements in PHES and other psychometric tests (Bajaj 2017, Bajaj 2019). However, more studies are needed before this can be recommended for routine clinical practice.

Acute kidney injury in cirrhosis

Clinical manifestation and relevance

Kidney disfunction is very common in advanced stages of liver cirrhosis affecting 27-53% of hospitalised patients (Pose 2024). Kidney dysfunction is a continuum in cirrhosis and increasing creatinine levels correlate with the risk of short-term mortality. Thus, serum creatinine is part of several prognostic scores in cirrhosis including the MELD score and its squeals, which determine donor liver allocation in several eras of the world (Martin 2024). However, due to the low muscle mass in patients with liver cirrhosis, kidney dysfunction may also be present at lower creatinine levels (Angeli 2018). Therefore, a rapid rise in serum creatinine or a significant decrease in urine output should prompt immediate diagnostic and therapeutic intervention, even before a specific threshold is reached. Acute Kidney Injury (AKI) is defined as an increase in serum creatinine by more than 50% from the baseline within one week or an increase of $\geq 26.4 \mu\text{mol/L}$ ($\geq 0.3 \text{ mg/dL}$) within 24 (48) hours (Nadim 2024). While the majority of AKI episodes are mild (AKI 1), even the distinction between AKI1a (serum creatinine $<1.5 \text{ mg/dL}$) and AKI1b (serum creatinine $\geq 1.5 \text{ mg/dL}$) has important prognostic implications (Huelin 2017) . Renal failure in patients with acute decompensation of liver cirrhosis is indicated by serum creatinine levels above 2 mg/dL and should not be confused with HRS, as HRS indicates a very poor prognosis (Nadim 2024). Renal failure is also the most common manifestation ($> 50\%$) of Acute-on-Chronic Liver Failure (ACLF), a specific form of acute decompensation associated with very high short-term mortality (Moreau 2013). Patients may also present with a slow rise in serum creatinine referred to as Non-AKI (NAKI). Chronic kidney disease is defined by a glomerular filtration rate (GFR) of $< 60 \text{ mL/min}$, calculated using the Modification of Diet in Renal Disease 6 (MDRD6) formula, persisting for at least three months (Nadim 2024) (Table 7).

Table 7. Diagnostic criteria for kidney dysfunction in advanced liver cirrhosis

Subject	Definition		
Definition of Baseline sCr	• A value of sCr obtained in the previuos three months, when available, can be used as baseline sCr. • In patients with more than one value within the previous three months, the value closest to the admission time should be used as baseline. • In patients without a previous sCr value, the sCr on admission should be used as baseline.		
Definition of AKI	• Increase in sCr $\geq 0.3 \text{ mg/dL}$ ($\geq 26.5 \mu\text{mol/L}$) within 48 hours; or, • A percentage increase sCr $\geq 50\%$ which is knwon, or presumed, to have occured wihtin the prior seven days		
Staging of AKI	• Stage 1: increase in sCr up to 2-fold from baseline ◦ 1a: sCr $< 1.5 \text{ mg/dL}$ ◦ 1b: sCr $\geq 1.5 \text{ mg/dL}$ • Stage 2: increase in sCr >2-fold to 3-fold from baseline • Stage 3: increase of sCr >3-fold from baseline or sCr $\geq 4.0 \text{ mg/dL}$ ($353.6 \mu\text{mol/L}$) with an acute increase $\geq 0.3 \text{ mg/dL}$ ($\geq 26.5 \mu\text{mol/L}$) or initiation of renal replacement therapy		
Progression of AKI	Progression		Regression
	Progression of AKI to a higher stage and/ or need for RRT		Regression of AKI to a lower stage
Response to treatment	No response	Partial response	Full response
	No regression of AKI	Regression of AKI with a reduction of sCr to $\geq 0.3 \text{ mg/dL}$ ($\geq 26.5 \mu\text{mol/L}$) above the baseline value	Return of sCr to a value within $\geq 0.3 \text{ mg/dL}$ ($\geq 26.5 \mu\text{mol/L}$) of the baseline value
Diagnostic Criteria for HRS	• Presence of advanced cirrhosis and ascites • No improvement in sCr and/or urine output within 24 h following adequate volume resuscitation • Absence of strong evidence for an alternative explanation HRS-AKI: HRS + AKI criteria fulfilled HRS-AKD: HRS + increase in sCr $\geq 50\%$, or GFR $<60 \text{ mL/min/1.73 m}^2$ or markers of kidney damage $\leq 90\text{d}$ HRS-CKD: HRS + GFR $<60 \text{ mL/min/1.73 m}^2$ and/or markers of kidney damage for $>90\text{d}$		

AKI: acute kidney injury; sCr: serum creatinine; RRT: renal replacement therapy

Citations: EASL Guideline cirrhosis AND Position Paper

Pathogenesis

There are various types of AKI and triggers of kidney damage. However, patients with cirrhosis are particularly susceptible for AKI, which is a result of the systemic inflammation and hemodynamic alterations that can be observed among patients with CSPH and advanced liver cirrhosis and may even be further enhanced by comorbidities or treatment related effects e.g. LVP or diuretic treatment. The decrease in systemic arterial blood pressure leads to activation of RAAS and the sympathetic nervous system and vasoconstriction of the renal artery and afferent glomerular arterioles (Adebayo 2023, Pose 2024). This results in renal hypoperfusion. In the recent years, it became evident that systemic inflammation and in particular the inflammatory driving factors, namely PAMPs and DAMPs, have direct deteriorating effects on renal function. PAMPs and DAMPs may enter the renal blood flow and cause renal inflammation (Pose 2024, Solé 2019). Besides direct cellular damage this leads to further decrease of renal blood flow. Ultimately, the changes linked to CSPH, systemic inflammation and circulatory dysfunction will lead to renal damage that is called hepatorenal syndrome (HRS-AKI).

Diagnostic work-up

In all patients with cirrhosis and AKI the potential trigger should be identified and removed as soon as possible. Those progressing to stage 1b or higher should be assessed for the presence of HRS. HRS represents the maximal renal dysfunction in liver cirrhosis and is potentially reversible. Generally, two forms are still distinguished: HRS type I (HRS-AKI) is characterised by rapid renal failure, defined as a doubling of serum creatinine over 2.5 mg/dL (226 mmol/L) within less than two weeks. HRS type II (HRS-NAKI) is often associated with refractory ascites and shows moderate renal failure with serum creatinine levels between 1.5 and 2.5 mg/dL (133 to 226 mmol/L) with a stable or slowly progressive course. However, HRS is cannot be diagnosed immediately, serum creatinine must be > 1.5 mg/dL (> 133 mmol/L) and there must be no improvement after at least one day of withdrawal of all diuretics and adequate volume resuscitation (Nadim 2024). In the past, HRS was strictly diagnosed by exclusion, not associated with shock, nephrotoxic medications, parenchymal kidney disease (proteinuria > 500 mg/d, abnormal urine sediment, microhematuria, pathological kidney ultrasound). It is now accepted that HRS-AKI can also occur in the presence of other (chronic) kidney disease. Therefore, the absence of strong evidence for an alternative explanation as the primary cause of AKI is sufficient to establish the HRS-AKI diagnosis (Nadim 2024) (Figure 5).

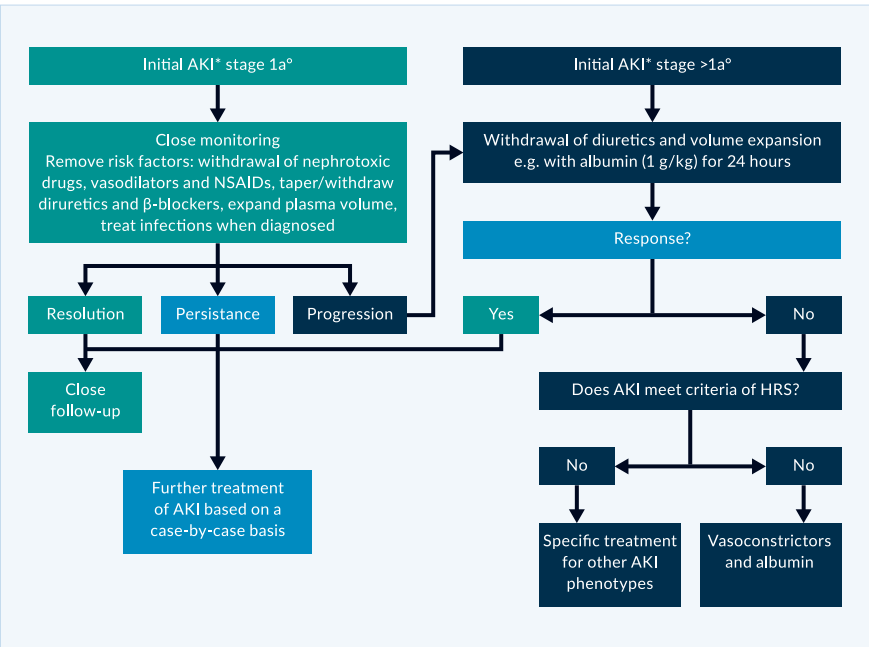


Figure 5. *AKI at the first fulfillment of KDIGO criteria.

Treatment

Any AKI should be treated by removing the precipitating factor and all nephrotoxic medications. The specific treatment of HRS type I (HRS-AKI) includes intravenous albumin administration of 20-40 g/day and additional therapy with vasoconstrictors. If there are no contraindications, terlipressin is the drug of choice, as it significantly improves short-term survival in combination with albumin infusions. This therapy should start with a terlipressin dose of 2–4 mg/day and be continued for at least three days. Terlipressin should be used at a maximum dose of 12 mg/day (Angeli 2018, Nadim 2024). Instead of repeated bolus application, terlipressin can also be given as a continuous infusion in HRS (initial dose 3 mg over 24 hours), which may reduce the required dose and side effects (Cavallin 2016). In patients under intensive care supervision, continuous norepinephrine administration may also be effective, although not in combination with terlipressin (Singh 2012, Wong 2021). Other vasoconstrictors are not recommended due to insufficient data.

While the administration of terlipressin in patients with HRS type I (HRS-AKI) is recommended in most guidelines worldwide, including Europe, the use of terlipressin as a vasoconstrictor for the treatment of HRS has not yet been approved in the United States. A recently published phase 3 study (CONFIRM) was designed to confirm the efficacy and safety

of terlipressin in combination with albumin in patients with HRS Type I. The study was randomised 1:2 with a placebo control for 14 days. The primary endpoint was the reversal of HRS, defined as two consecutive measurements of creatinine below 1.5 mg/dL, taken more than 2 hours apart, with survival without dialysis for at least 10 days after the completion of treatment. A total of 300 patients were randomised, 199 to terlipressin and 101 to placebo. Terlipressin led to a reversal of HRS in 32% of patients, while the primary endpoint was achieved in only 17% of patients in the placebo group. Liver transplantation was performed in 46 patients (23%) in the terlipressin group and 29 patients (29%) in the placebo group, with 50% vs. 45% mortality. Respiratory deterioration within 90 days accounted for 11% of deaths in the terlipressin group and 2% of deaths in the placebo group. The cardiodepressive effect of terlipressin is an additional side effect that may have influenced the results of the CONFIRM study (Wong 2021). This was particularly present among those with ACLF grade 3. Moreover, terlipressin was not linked to a higher rate of reversal of renal failure in this group but even a numerically higher mortality. Therefore, the use in ACLF grade 3 may not be recommended (Wong 2022).

In a recently published Danish study, 25 patients with ascites and impaired kidney function were randomised 2:2:1, group A received terlipressin combined with dobutamine, group B received dobutamine and terlipressin as sequential monotherapies, and group C received placebo. Dobutamine monotherapy increased cardiac output without affecting GFR. Terlipressin alone improved GFR and mean arterial pressure but decreased cardiac output. The combination of dobutamine and terlipressin had a favourable effect on cardiac output, but no additional effect on mean arterial pressure or GFR. This study showed that dobutamine alone does not have a favourable effect on systemic or renal hemodynamics in patients with ascites. However, it suggests that the combination with dobutamine may be an option for patients with terlipressin and cardiodepressive side effects (Israelsen 2020).

Patients with HRS type II (NAKI-HRS) are unlikely to benefit from this therapy and are treated similarly to patients with refractory ascites. Especially in these patients, but generally in all patients with HRS, a TIPS could be considered. Renal replacement therapy is indicated only in the presence of dialysis criteria, mainly as a bridge to liver transplantation, the only potentially curative treatment for HRS. For intended liver transplantation, albumin and terlipressin should be administered, as patients with renal insufficiency have a significantly poorer postoperative prognosis. In patients with HRS and prolonged dialysis dependency, the indication for sequential liver/kidney transplantation should be considered (Angeli 2018, Nadim 2024).

Infections and cirrhosis-associated immune dysfunction (CAID)

Clinical manifestation and relevance

Advanced liver cirrhosis is accompanied by a complex and, so far, not completely understood cirrhosis-associated immune dysfunction (CAID) (Albillos 2014, Albillos 2022). As a result, the incidence of infection is 4-6 times higher than in non-cirrhotic individuals (Fernández 2002, Fernández 2021). In the event of infection, mortality is 4x increased (Arvaniti 2010, Jalan 2014a) and the prognosis remains impaired even after the infections resolved (Kimmann 2019). Many cirrhotic patients develop multiple infections during hospitalisation and mortality almost doubles with each infectious episode (Bajaj 2012, Schultalbers 2020). Bacterial infections are a major cause of hepatic decompensation (e.g. variceal bleeding and worsening of ascites) (Fernández 2019, Moreau 2023) and the most common trigger of (ACLF) (Arroyo 2015, Moreau 2013). The most frequent sites of infection are spontaneous bacterial peritonitis (SBP) and urinary tract infections (UTI) (Schultalbers 2020). A particular threat is the emergence of multi-drug resistant bacteria (MDRB) (Fernández 2019, Hillert 2021, Piano 2019). These are highly prevalent in nosocomial infections and are associated with the development of sepsis and a poor survival (Fernández 2019, Piano 2019). The detrimental effects of infections are not limited to bacterial pathogens. More serious causes have also been documented for viral infections such as COVID-19 or influenza (Qiu 2020, Schütte 2019, Singh 2020). A particular poor prognosis has been described for invasive *Candida* infections (Barros 2023).

Pathogenesis

The liver and its resident immune cells play a central role in the immune system. They mediate immune tolerance, recognise systemic and gut-derived pathogens and orchestrate appropriate responses such as the production of pro-inflammatory cytokines and acute phase proteins. In patients with cirrhosis, liver dysfunction, reduced intestinal barrier function and increased systemic inflammation are the key drivers in the pathogenesis of CAID (Albillos 2022, Hasa 2022). Portal hypertension and intestinal dysbiosis facilitate translocation of gut bacteria and bacterial products into the portal vein. The resulting hepatic and systemic inflammation as indicated by increased levels of several pro-inflammatory cytokines such as TNF, IL-6 and IL-8. This is associated with the transition

from the compensated to the decompensated stage of cirrhosis and with the degree hepatic impairment (Albillos 2022, Hasa 2022). Ultimately the persistent inflammation leads to a compensatory but excessive immunosuppressive response (e.g. mediated by IL-10) that turns into a state of immune paralysis and immune cell exhaustion, making patients particularly vulnerable for infections (Albillos 2022, Hasa 2022). However, the mechanisms of CAID are much more complex as there are several other important contributing factors. The distortion of liver histology, the lower amount of total liver tissue as well as the increasing number of porto-systemic shunts interfere with the liver's role as an immune filter and initial place of antigen recognition (Albillos 2022, Hasa 2022). Impaired hepatic function lowers the capability of the synthesis of acute phase and complement proteins (Homann 1997). Functional changes can also be documented at the cellular level, affecting various innate and adaptive immune cells, including monocytes, neutrophils and lymphocytes. Overall, the number of circulating monocytes is increased but functionally impaired, with reduced phagocytic capacity and lysosomal enzyme production (Albillos 2022, Nakagawara 1984). Neutrophils are characterised by a higher degree of respiratory burst but lower phagocytic capacity and reduced circulating levels (Albillos 2022, Shawcross 2008). Circulating CD4+ T helper cells are also reduced, while certain subsets of CD8+ T cells are increased (Albillos 2022). T-helper cell impairment leads to reduced B-cell function and lower immunoglobulin levels in advanced stages of cirrhosis (Basho 2021). Importantly, these decreased IgG levels are associated with a higher risk of ACLF and death in patients with decompensated liver cirrhosis (Tergast 2021).

Diagnostic work-up

Early diagnosis and prompt initiation of an adequate treatment is crucial to limit morbidity and maximise patients' chances of survival (Jalan 2014a). In the case of SBP, every hour of delay is associated with a 3% increase in mortality (Kim 2014). However, the clinical diagnosis of an infection in a cirrhotic patient can be challenging. Symptoms of hepatic decompensation, such as hepatic encephalopathy or worsening of ascites, may dominate the clinical picture. Thus, any new onset of hepatic decompensation or worsening of cirrhosis-related complications should be considered as an alarm signal and the patient should be evaluated for the presence of an infection, including a diagnostic paracentesis (Angeli 2018, Jalan 2014a). There has been a long debate about the utility of biomarkers. Pancytopenia is highly prevalent in patients with liver cirrhosis, limiting the value of leucocytosis. C-reactive protein (CRP) can indicate the presence of infection. However, as it is produced in the liver, false negatives must be

considered (Park 2005). In contrast, systemic inflammation leads to chronic elevations of CRP even in the absence of infection (Jalan 2014a). Unlike CRP, procalcitonin (PCT) levels are less dependent on liver function. While PCT correlates with infection in cirrhosis, e.g. SBP (Yang 2015), as well as with the outcome of infections (Girardi 2024), it can also be elevated due to systemic or hepatic inflammation (Sato 2020, Simbrunner 2023). Some other biomarkers such as presepsin and resistin have been suggested, but their role still remains to be determined (Fischer 2019). Overall, biomarkers are not able to replace careful clinical evaluation at this stage. If an infection is suspected, the diagnostic work-up should include a diagnostic paracentesis and culture of ascites fluid (if ascites is present), urine sediment examination and a chest x-ray (Fernández 2021).

Treatment

Spontaneous bacterial peritonitis (SBP)

SBP is diagnosed when the ascitic polymorphonuclear count exceeds 250/μL (Angeli 2018). Antibiotic treatment should be started immediately, but must be chosen carefully. An inappropriate choice of the antibiotic leads to a more than twofold increase in mortality (Fernández 2019). A small prospective randomised trial demonstrated a superior survival when patients were treated aggressively with daptomycin and meropenem instead of ceftazidime (Piano 2016). However, the widespread use of broad-spectrum antibiotics is certainly followed by a further emergence of MRBD (Piano 2019). Therefore, an individualised, risk-based approach seems necessary. As nosocomial infection has been confirmed as the most relevant risk factor for MRBD across different studies (Fernández 2012, Fernández 2019, Fernández 2021, Piano 2019), current EASL guidelines recommend a stratification into community-acquired, healthcare associated and nosocomial SBP (Angeli 2018). In addition, the severity of infection (e.g. sepsis and/or ACLF) should be taken into account. Third-generation cephalosporins appear to be sufficient for community-acquired SBP. However, if the infection is nosocomial and/or associated with organ failure, more aggressive treatment, e.g. a carbapenem +/- a glycopeptide antibiotic, should be used (Angeli 2018). Carbapenems have shown to be highly effective, including excellent and rapid distribution into the ascites fluid (Griemsmann 2022, Piano 2016). Glycopeptides should be considered particularly if there is an increased risk of infections with gram positive species (e.g. with enterococci) (Angeli 2018). This is the case, for example, among patients treated with high doses of PPIs (Tergast 2018, Wellhöner 2019), those with PeCa (Tergast 2022) and recent endoscopic procedures (Reuken 2012), and in alcoholic liver disease, where *Enterococcus*

faecalis is closely linked to disease progression (Duan 2019, Llorente 2017). The efficacy of antibiotics should be monitored by a diagnostic paracentesis 48 hours after treatment initiation, which should show a reduction in PMN count of at least 25% (Angeli 2018). Patients with SBP benefit from albumin treatment, which can counteract circulatory dysfunction in these patients (Mandorfer 2014, Salerno, Navickis, Wilkes 2013, Sort 1999). 1.5 g/kg body weight on day 1 followed by 1g/kg body weight on day 3 is usually recommended based on the original study protocol by Sort et al (Angeli 2018, Sort 1999). Once the SBP has resolved antibiotic prophylaxis should be initiated for as long as the ascites persists (Angeli 2018, Ginés 1990, Titó 1988). Some patients may even benefit from primary SBP prophylaxis (Fernández 2007). A potential risk factor for SBP is a low ascites protein level (Guarner 1999, Llach 1992, Runyon 1986). A recent prospective, multicentre study showed that primary prophylaxis with norfloxacin may improve survival among patients with CHILC cirrhosis. However, this was only the case if the ascites protein level was below 1.5 g/dL (Moreau 2018). Norfloxacin is usually recommended for SBP prophylaxis based on the available studies (Angeli 2018, Cohen 2009, Mücke 2020a). Some concerns have been raised about the emergence of infection and in terms of side effects (Mücke 2020b). Rifaximin is an alternative and promising treatment option (Facciorusso 2019, Wang 2019). However, current data remain insufficient to recommend it as the first-line treatment.

Urinary tract infection

UTI are among the most common types of infections in patients with decompensated liver cirrhosis (Fernández 2002, Schultalbers 2020). While the rate of clinical complications and mortality may be lower compared to other sites of infection, UTI may still trigger AKI and ACLF in a considerable proportion of patients (Angeli 2018, Merli 2016, Moreau 2013, Mücke 2018). Antibiotic treatment is generally recommended (Angeli 2018). Similar to SBP, the risk for MDR has to be considered when choosing the anti-infective drug. However, a prospective randomised study demonstrated that a broad-spectrum antibiotic treatment is only required in case of severe infections, i.e. sepsis (Merli 2016). For uncomplicated UTI, fosfomycin or nitrofurantoin may be considered as a sufficient treatment attempt (Angeli 2018). The use of albumin is not recommended in the absence of HRS-AKI (Angeli 2018, Guevara 2012, Thévenot 2015).

Pneumonia

Pneumonia is a particularly dangerous form of infection in cirrhosis (Merli 2016). Conversely, the likelihood of mortality in patients with

pneumonia is dramatically increased in the presence of liver cirrhosis (Boivin 2019, Di Pasquale 2013). Given the impact of the initial use of an inadequate antibiotic treatment and the considerable risk of MDR in nosocomial infections in these patients, an aggressive approach seems to be reasonable (Piano 2019). Thus, carbapenems could be considered early in nosocomial pneumonia and at least third-generation cephalosporins and/or piperacillin/tazobactam in healthcare-associated pneumonia (Angeli 2018, Jalan 2014a). However, local prevalence of MDR must be taken into account as well. As with other non-SBP infections, the use of albumin is not recommended and it may even complicate pneumonia due to the higher incidence of pleural and pulmonary edema (Angeli 2018, China 2021, Maiwall 2022).

Pulmonary complications

Clinical manifestation and relevance

There are four main pulmonary complications that can be linked to liver cirrhosis. Pneumonia as a result of CAID, hepatic hydrothorax, as atypical localisation of ascites related to small defects in the diaphragm, portopulmonary hypertension (PPHT) and hepatopulmonary syndrome (HPS). Pneumonia/CAID and hepatic hydrothorax/ascites are discussed above. PPHT is defined by an increase in the mean pulmonary arterial pressure (mPAP) to a level of more than 20 mmHg due to increased pulmonary vascular resistance (PVR) in patients with portal hypertension in the absence of other causes of pulmonary hypertension (Simonneau 2019). It may be present in 5-10% of patients with end-stage liver cirrhosis and is associated with poor survival (Colle 2003, Kawut 2008, Krowka 2006, Sussman 2006). Depending on the severity of PPHT, liver cirrhosis as well as cardiac and pulmonary comorbidities, patients may present with severe hypoxia and/or clinical signs of right heart failure (DuBrock 2023). HPS is defined by the presence of chronic liver disease (most commonly cirrhosis), intrapulmonary shunts (IPS) and either hypoxaemia or an increased alveolar-arterial oxygen gradient indicating impairment of intrapulmonary blood oxygenation (Angeli 2018). The presence of HPS is widely underestimated. However, in patients with decompensated cirrhosis, IPS and HPS can be found in up to 50% and 36%, respectively (Mauz 2024). Patients are often asymptomatic but may become clinically apparent with dyspnoea (Angeli 2018, Raevens 2022). However, the most specific symptom is platypnea, i.e. improvement of symptoms when lying down. Of note, HPS impairs survival regardless of the severity of liver disease (Raevens 2022).

Pathogenesis

The pathophysiology of PPHT is still incompletely understood. However, it is hypothesised that portosystemic shunting allows bypassing of the increased vasoactive substances (which are a response to the increased portal pressure, hepatic resistance and inflammation) from the portal tract to the systemic blood circulation. As a result, increased levels of vasoactive substances may also be present in the pulmonary arterial system, leading to vasodilation also at the capillary level. Intrapulmonary blood flow is increased while the capacity for oxygen exchange remains unchanged, resulting in a functional shunting from the right to the left heart. This is thought to be one of the key components of HPS (Thomas 2020, Zaka 2025). In addition, both systemic vasodilation and intrapulmonary result in a hyperdynamic state. Increased blood flow is accompanied by increased shear stress on the endothelial wall. In response, endothelin-1 is secreted leading to smooth muscle cell proliferation and/or increased muscle tone and intimal fibrotic changes (Farber 2004, Porres-Aguilar 2012, Thomas 2020). Ultimately, this may significantly contribute to PHHT (Neuhofer 2006) (Figure 6).

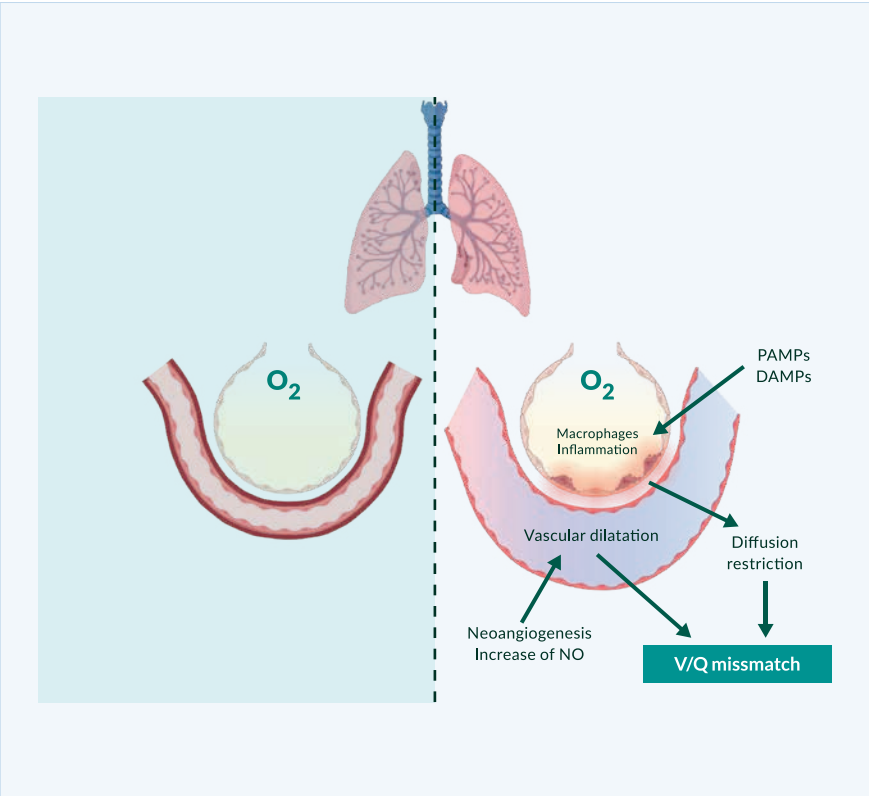


Figure 6.

Diagnostic work-up

PPHT: Elevated right ventricular pressure (>40-50 mmHg) on echocardiography will raise suspicion of PPHT and can be used as a screening criterion for further investigation (DuBrock 2023). However, to establish the diagnosis of PPHT a right heart catheterisation is required. PPHT is characterised by a precapillary pulmonary hypertension. Diagnostic criteria include a mPAP >20 mmHg, pulmonary arterial wedge pressure (PAWP) ≤15 mmHg and PVR ≥2 WU (Humbert 2023). Other causes of PAH need to be excluded. Patients with PAH can be divided into three risk categories, as it is the case for PPHT. The risk categories are defined by clinical symptoms, specific results of echocardiography and hemodynamic parameters (Table 8) (Humbert 2023).

Table 8. Portopulmonary hypertension: Diagnostic criteria

I – Presence of portal hypertension
II – Elevated pulmonary arterial pressure compatible with pulmonary hypertension (mPAP in right-heart catheterisation >20 mmHg)
III – Increased pulmonary vascular resistance (>240 dyne s-1cm-5; >2 Wood Units)
IV – normal pulmonary occlusion pressure (PAWP ≤15 mmHg)
V – absence of other causes of pulmonary artery or venous hypertension hypertension (i.e., chronic thromboembolism, chronic lung disease/hypoxia, chronic left heart disease)

Degree of severity is determined by mPAP in right-heart catheterisation as mild (mPAP <34 mmHg), moderate (mPAP =35-44) or severe (mPAP ≥45 mmHg).

Abbreviations

mPAP: Mean pulmonary arterial pressure; PAWP: Pulmonary arterial wedge pressure; PVR: Pulmonary vascular resistance.

Citations

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HPS: Given the high prevalence, all cirrhotic patients with hypoxaemia should undergo screening for HPS. The first step is to assess for IPS. This can be done by contrast-enhanced echocardiography using microbubbles of >10 µm in diameter. In a healthy individual, these bubbles should remain and be absorbed in the pulmonary capillaries. In patients with IPS, bubbles appear in the left heart atrium within 3 to 6 cardiac cycles (Angeli 2018,

Raevens 2022). This easy and diagnostic tool cannot be used in the presence of intracardiac shunts (e.g. due to a patent foramen ovale). In this case, bubbles will appear in the left atrium after 1 or 2 cardiac cycles. In patients with IPS, the diagnosis of HPS requires the exclusion of other lung diseases, which usually requires a chest CT scan and functional lung assessments such as maximal forced expiratory volume and carbon monoxide diffusing capacity (Table 9) (Angeli 2018, Raevens 2022).

Table 9. Hepatopulmonary syndrome: Diagnostic criteria

I – Liver disease and/or portal hypertension
II – Pulmonary vascular defect with positive finding on contrast-enhanced echocardiography (i.e., microbubble opacification of the left heart chambers three to six cycles after right atrial passage) or abnormal uptake in the brain (>6%) with radioactive lung-perfusion scanning
III – Hypoxia with partial pressure of oxygen <80 mmHg or alveolar-arterial oxygen gradient >15 mmHg in ambient air (≥20 mmHg in patients older than 65 years)

III)The abbreviated formula for the alveolar-arterial gradient is as follows: $P(A-a)O_2 = (FIO_2 (Patm - PH_2O) - (PaCO_2 / 0.8)) - PaO_2$, where PAO_2 denotes partial pressure of alveolar oxygen, PaO_2 partial pressure of arterial oxygen, FIO_2 fraction of inspired oxygen, $Patm$ atmospheric pressure, PH_2O partial pressure of water vapor at body temperature, and $PaCO_2$ partial pressure of arterial carbon dioxide. Severity classification of HPS is based on the partial pressure of oxygen in arterial blood gas without supplementary oxygen (PaO_2) as mild ($PaO_2 \geq 80$ mmHg), moderate (PaO_2 60–79 mmHg), severe (PaO_2 50–59 mmHg) or very severe ($PaO_2 < 50$ mmHg).

Abbreviations

HPS: Hepatopulmonary syndrome; $P(A-a)O_2$: Alveolar-arterial oxygen gradient; PaO_2 : Partial pressure of arterial oxygen; PAO_2 : Partial pressure of alveolar oxygen; $PaCO_2$: Partial pressure of arterial carbon dioxide; FIO_2 : Fraction of inspired oxygen; $Patm$: Atmospheric pressure; PH_2O : Partial pressure of water vapor at body temperature.

Citations

European Association for the Study of the Liver. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. J Hepatol. 2018 Aug;69(2):406-460. doi: 10.1016/j.jhep.2018.03.024. Epub 2018 Apr 10. Erratum in: J Hepatol. 2018 Nov;69(5):1207. doi: 10.1016/j.jhep.2018.08.009. PMID: 29653741.
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Treatment

PPHT: In general, treatment strategy follows the clinical assessment of the risk category and the presence or absence of cardiovascular comorbidities (Humbert 2023). Medical treatment options include endothelin receptor antagonists, phosphodiesterase subtype 5 inhibitors and prostacyclin analogues (Angeli 2018, Humbert 2023). However, while

treatment is associated with improvement in hemodynamic parameters, all of these drugs can lead to decrease in systemic arterial pressure, which limits their tolerability in advanced liver cirrhosis, particularly when combination treatment is required (DuBrock 2023, Savale 2020). Best treatment results can be achieved by liver transplantation (Savale 2020). However, not all patients are suitable candidates, mainly because of the risk of right heart failure. Patients with mPAP of > 45-50 mmHg at the time of liver transplantation, have a posttransplant mortality of up to 100% (Krowka 2000). In contrast, transplantation appears to be safe in patients with mPAP of < 35 mmHg or of 35-45 mmHg but a PVR of < 3 WU (Angeli 2018, DuBrock 2023).

HPS: Up till now, there is no pharmacological treatment available. Patients with hypoxaemia can be treated with continuous oxygen supply (Angeli 2018, Raevens 2022). Moreover, coil embolisation of arteriovenous malformations has been suggested. However, complications such as pulmonary infarction and infections need to be considered (Grady 2015). Liver transplantation remains the only effective treatment option. Although perioperative mortality is higher compared with non-HPS patients, arterial oxygenation and six-minute walk distance significantly improves significantly. Recent data suggest that HPS can be expected to resolve in approximately 95% of cases (Aragon Pinto 2021, Raevens 2022).

Acute-on-chronic liver failure

Clinical manifestation and relevance

The poor prognosis of liver cirrhosis (Lange 2023) is particularly due to acute decompensations (AD), which represent a situational worsening of the disease state (Jalan 2021). These are characterised by the rapid onset of ascites, gastrointestinal bleeding, hepatic encephalopathy, bacterial infections, or a combination of these complications (Gu 2022). The CANONIC study demonstrated that there is a subgroup of patients with acutely decompensated liver cirrhosis who have a significantly worse prognosis (Moreau 2013). This subgroup of patients was termed ACLF, which is the most severe form of acute decompensation (Schulz 2022). ACLF was defined by the European Association for the Study of the Liver (EASL)–Chronic Liver Failure (CLIF) Consortium based on the results of the CANONIC study. The CANONIC study is a prospective observational study involving more than 1300 patients with acute decompensation (Moreau 2013). Various organ systems were classified into organ failure or organ dysfunction based on clinical and laboratory parameters. Analogous to the Sequential Organ Failure Assessment (SOFA) Score, the CLIF-C Organ Failure (OF) Score was

calculated (<https://www.efclif.com/scientific-activity/score-calculators/clif-c-aclf>). This score includes the function of the liver and kidneys (creatinine and bilirubin levels), cognition (West Haven criteria), circulation (MAP and catecholamine requirement), and coagulation (INR) (Table 10).

Table 10.

Organ system	Diagnostic criterium	Points		
		1	2	3
	Bilirubin	<106 µmol/L	106–205 µmol/L	>205 µmol/L
		<6 mg/d	6–12 mg/dL	>12 mg/dL
	Creatinine	<177 µmol/L	177–310 µmol/L	>310 µmol/L
		<2 mg/dL	2–3.5 mg/dL	>3.5 mg/dL
	Hepatic encephalopathy	Grade 0 (WH)	Grade I, II (WH)	Grade III, IV (WH)
	INR	<2.0	2.0–2.4	≥2.5
	Mean arterial pressure	>70 mmHg	<70 mmHg	Vasopressors
	S _p O ₂ /F _i O ₂	>357	214–357	≥214
	p _a O ₂ /F _i O ₂	>300	300–200	<200

Bold = Organ failure

Organ failure is defined as a score of 3 in the respective organ system. An exception is made for the kidneys, where organ failure is defined with a CLIF-C-OF score of 2 (corresponding to a creatinine level of > 2 mg/dL) (Jalan 2014b) (Figure 7). Patients with more than one organ failure or isolated kidney failure meet the criteria for ACLF. Additionally, isolated organ failures combined with kidney dysfunction (creatinine 1.5–1.9 mg/dL) or hepatic encephalopathy (grade I/II) are classified as ACLF Grade I. Patients with two manifest organ failures show ACLF Grade II, and those with three or more organ failures have ACLF Grade III. The 28-day mortality rate increases with the grade, reaching 68% in patients with four or more organ failures (Arroyo 2020). A more precise prognosis for ACLF can be made using the CLIF-C ACLF Score, which also considers age and leukocyte count (Jalan 2014b). Although the EASL-CLIF definition has been validated worldwide, two other definitions exist in the USA and Asia:

the North American Consortium for the Study of End-stage Liver Disease (NACSELD) and the Asian Pacific Association for the Study of the Liver (APASL). Both definitions are similar to the EASL-CLIF, with the distinction that NACSELD defines ACLF only when there are two manifest organ failures, whereas APASL does not consider extrahepatic triggers and organ failures (Arroyo 2020).

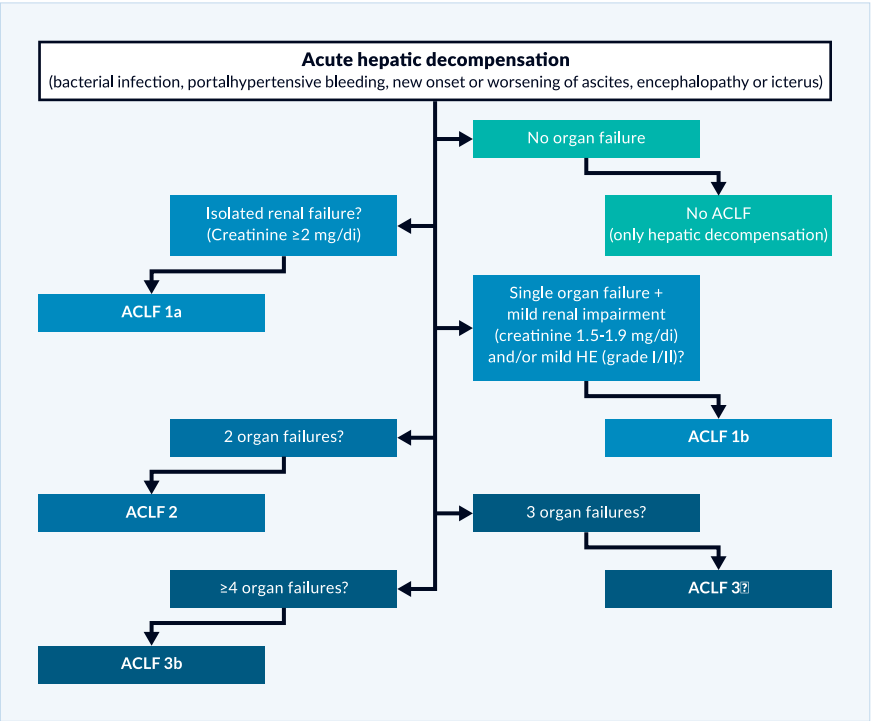


Figure 7.

Pathogenesis

ACLF affects approximately one in four patients (23%) hospitalised for decompensated liver cirrhosis. About 20% of patients admitted without ACLF develop ACLF within the following 90 days (so-called pre-ACLF), with 60% of these cases occurring within the next three weeks, as shown in the PREDICT study (Trebecka 2020b). Pre-ACLF patients exhibit a significantly elevated inflammatory profile (increased leukocyte counts and CRP levels) (Trebecka 2020b). Risk factors for the development of ACLF include the presence of ascites, low mean arterial pressure, anaemia, and a high MELD score. In addition, younger patients appear to be more commonly affected (Angeli 2018). The onset of ACLF is primarily attributed

to two pathophysiological phenomena: portal hypertension and systemic inflammation (Trebicka 2020b). Patients with ACLF show significantly higher concentrations of pro-inflammatory cytokines (Trebicka 2019a). The occurrence of events, especially infections, severe gastrointestinal bleeding, or alcoholic hepatitis, can lead to further reductions in effective blood volume, thereby inducing hypoperfusion of various organs (Trebicka 2021a). The kidney and brain are particularly early affected, thus playing a special role in the definition of dysfunction. These events are known as precipitating factors or triggers and play a crucial role in the prevention and treatment of ACLF. However, in 40% of cases no trigger can be identified (Trebicka 2021a).

Diagnostic work-up and treatment of triggers

A trigger can be identified in 60% of patients with ACLF (Trebicka 2021a). Possible triggers include liver-related factors such as alcoholic steatohepatitis (ASH) or a flare of viral hepatitis, as well as extrahepatic triggers such as infections. Combinations are also not uncommon (Trebicka 2021a). Any patient admitted with ACLF or who develops ACLF during hospitalisation should undergo a systematic examination for the presence of the most common triggers, including documented bacterial infections, alcohol-related hepatitis, gastrointestinal bleeding with hemodynamic instability, a flare of hepatitis B virus infection, recent intake of medication known to cause brain failure, and recent intake of medication known to cause kidney failure (Figure 8) (Moreau 2023).

Patients for whom systematic examination fails to identify expected triggers should be investigated based on clinical context and using a comprehensive list of all potential unusual cases (Figure 8) (Moreau 2023). The causal treatment of potential triggers plays a key role in preventing ACLF, as no specific preventive therapy has been established so far (Angeli 2018, Moreau 2023). The concepts of treating the most critical triggers are outlined below.

Infections can represent both a trigger and a complication of ACLF. Typically, these are bacterial infections, less commonly mycoses. When choosing antibiotic therapy, patient-specific factors, the suspected focus, and local resistance patterns should be considered (see above) (Moreau 2023). Patients with ACLF and suspected bacterial infections should receive broad-spectrum empirical antibiotic therapy as soon as possible, in line with local epidemiology. A rapid and comprehensive evaluation for infection is recommended for patients with ACLF and suspected bacterial infections (Moreau 2023). An empirical antifungal therapy may be indicated for ACLF patients developing nosocomial septic shock with additional risk factors for

fungal infection (Moreau 2023).

One of the most common triggers in Western countries is alcoholic hepatitis due to active alcoholism or an alcohol binge. Here, corticosteroids remain the treatment of choice, although their efficacy is still under debate. Severe cases with increased short-term mortality can be identified using the modified Maddrey score. In cases with a score > 32, steroid therapy with 40 mg of prednisolone/day can be initiated. Due to potential steroid-associated side effects, identifying patients who do not benefit from steroid therapy is essential. This can be assessed using the Lille score, calculated based on age, albumin, prothrombin time, creatinine, and bilirubin levels at the start and after seven days of prednisolone therapy (Trebicka 2022). With increasing severity of ACLF, the response to corticosteroids decreases, while the risk of infection increases. Therefore, corticosteroids are not recommended for patients with severe alcoholic hepatitis and ACLF-3, nor for patients with uncontrolled bacterial infections. If corticosteroids are administered to patients with severe alcoholic hepatitis and ACLF, close monitoring for infections is necessary (Moreau 2023, Trebicka 2022).

Acute variceal bleeding, accounting for 70% of upper gastrointestinal bleeding episodes in cirrhosis, has been identified as a common cause of death and ACLF in cirrhotic patients. Recent treatment advances, including endoscopic treatment, pharmacotherapy, and TIPS, have led to a decrease in the frequency of variceal bleeding over the past decade. However, ACLF significantly worsens survival in these patients. Indeed, ACLF doubles the risk of rebleeding and serves as a simple criterion for identifying patients at risk of rebleeding (Moreau 2023). Two independent studies have shown that TIPS, either preemptive/early or emergency, improves survival in patients with ACLF-1 or ACLF-2 and variceal bleeding, although few patients with ACLF-3 were included in these studies (Kumar 2021, Trebicka 2020a). Therefore, TIPS should be considered in the treatment of patients with ACLF and variceal bleeding, even in those with bilirubin levels over 5 mg/dL. As a result, affected patients should be transferred to hospitals with access to TIPS, potentially reducing their mortality rate by up to 75%. This data is well supported by a recent study showing that the survival benefit from preemptive/early TIPS increases with a higher MELD score (Moreau 2023).

Other triggers can include a flare of known viral hepatitis. Acute infections with hepatitis A or E can also be potential triggers. Therefore, patients with liver cirrhosis should be vaccinated against hepatitis A and B as appropriate (Moreau 2023). For patients with HBV-related ACLF, the use of nucleoside analogues is recommended as the treatment of choice (Moreau 2023).

Drug-induced liver injury (DILI) is often implicated as a potential trigger. Physicians should especially inquire about recent new medications,

including over-the-counter, natural remedies, and dietary supplements (Moreau 2023).

There is a high likelihood of having more than one trigger in patients with ACLF. Identifying these triggers is crucial for targeted treatment and preventing disease progression. Therefore, it is important to differentiate between the treatment of trigger-related complications and the treatment of ACLF itself (Moreau 2023).

Specific therapy and supportive measures

Specific therapy for ACLF aims to address the pathophysiology, particularly the inflammatory response. To date, only the use of Albumin is evidence-based in ACLF. Albumin binds to endotoxins and acts as a scavenger of reactive oxygen species. Its effectiveness is likely due to its positive effect on hemodynamics and inflammatory response (Klein 2020).

The ANSWER study demonstrated the positive effects of long-term albumin therapy in patients with decompensated liver cirrhosis. Patients who received weekly albumin infusions in addition to standard therapy showed significantly improved transplant-free survival. Additionally, fewer severe infections and complications occurred (Caraceni 2018a).

The ATTIRE study did not show a benefit of albumin infusion on 28-day mortality in patients with decompensated liver cirrhosis, despite achieving normal albumin levels. This study did not explicitly differentiate between patients with ACLF and those with AD. However, there was a lower number of patients with new or existing organ failures among patients who achieved normal albumin levels (China 2021). The RESOLVE trial, currently enrolling patients, aims to clarify the significance of long-term albumin therapy in patients with ACLF.

As albumin levels and concentrations are often significantly reduced in patients with ACLF, albumin infusion is recommended for treating ascites, prevention of HRS, and in cases of confirmed SBP.

Patients with ACLF, particularly those in ACLF Grade III, require intensive care. Guidelines for supportive therapy are not specific to ACLF and are derived from those for severe sepsis and multiple organ failure in non-cirrhotic patients. However, significant differences exist in the application of general guidelines to patients with liver cirrhosis. (Gustot 2015). Special attention is given to the risk of overhydration and tissue edema. To maintain adequate organ perfusion, slightly increased MAP values should be targeted. Isotonic crystalloids should be preferred over colloids in volume resuscitation (Gustot 2015, Garnacho-Montero 2015). Vasopressor use, especially norepinephrine, should be considered early in ACLF patients with septic shock (Choudhury 2017). Non-invasive ventilation

(NIV) and extracorporeal membrane oxygenation (ECMO) are considered in patients with respiratory failure, while renal replacement therapy is indicated in cases of renal failure, particularly in the presence of HRS or metabolic complications (Moreau 2023).

Liver transplantation remains the definitive treatment for patients with ACLF, offering potential for improved survival and quality of life. Early evaluation for liver transplantation is recommended, especially in patients with ACLF Grade II and III (Moreau 2023, Trebicka 2020c).

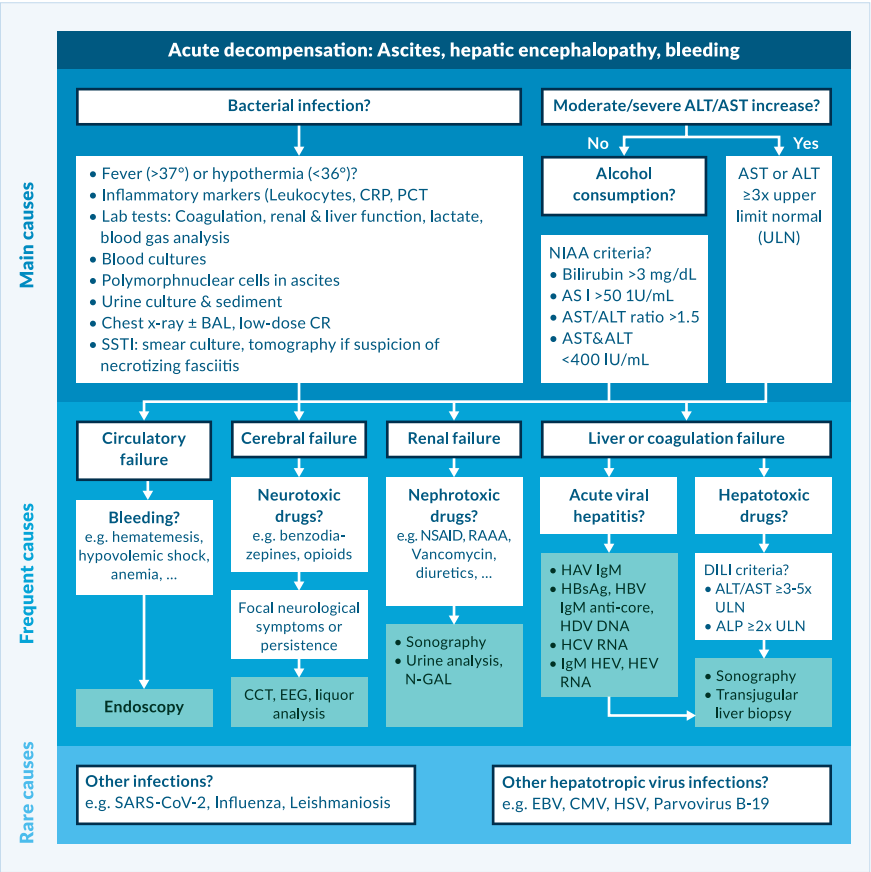


Figure 8.

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