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REVIEW

Outpatient management after hospitalisation for acute decompensation of cirrhosis: A practical guide

Adonis A Protopapas, Alexandra Tsankof, Ioanna Papagiouvanni, Georgia Kaiafa, Lemonia Skoura, Christos Savopoulos, Ioannis Goulis

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Abstract

Acute decompensation in cirrhotic patients signifies the onset of clinically evident events due to portal hypertension. The transition from compensated to decompensated cirrhosis involves hemodynamic changes leading to multiorgan dysfunction, managed predominantly in outpatient settings with regular monitoring. The mortality risk is elevated in decompensated patients. Therefore, diligent outpatient management should focus on regular medical follow-ups, medication adjustments, patient education, addressing emergent issues and evaluation for liver transplantation. The ultimate goal is to improve quality of life, prevent disease progression, reduce complications, and assess possible recompensation. This guide provides valuable recommendations for medical experts managing decompensated cirrhotic patients post-hospitalization.

Key Words: Cirrhosis; Decompensated; Outpatient; Complications; Treatment

Core Tip: Decompensation in patients with cirrhosis is associated with higher morbidity and mortality. Apart from managing these patients during hospitalisation, it is equally important to provide them with effective outpatient care. Regular medical follow-ups after hospitalisation due to acute decompensation are essential for monitoring the condition of decompensated patients with cirrhosis, while a multidisciplinary approach can prevent disease progression and optimise patient outcomes.

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INTRODUCTION

Acute decompensation in patients with cirrhosis is defined by the presentation of clinically evident events due to portal hypertension [varices, ascites and hepatic encephalopathy (HE)]. An increase in the hepatic vein pressure gradient (HVPG) ≥ 10 mmHg defines clinically significant portal hypertension and marks the threshold for the emergence of portal hypertension-related complications. The progression from compensated to decompensated cirrhosis (DeCi) has been vastly analysed and is generally characterised by hemodynamic changes leading to gradual multiorgan dysfunction. Patients with DeCi can be managed with regular monitoring in an outpatient setting, but most of them will need hospitalisation, especially at the time of diagnosis. Subsequent management after the first decompensating event may be critical for the outcome of these patients. It has been noted that 5-year mortality risk stands at 20% for patients experiencing their first decompensation solely due to bleeding, 30% for those facing any non-bleeding event, primarily ascites, and rises to 88% for individuals encountering multiple events[1]. Therefore, patients should be informed of further complications and screening methods. Outpatient management of decompensated cirrhotic patients typically involves several components to address their medical needs and optimise the patient's health outside of a hospital setting. Patients should be instructed to adhere to regular medical follow-ups (every 3-6 months) and monitor their condition (symptoms, physical state, *etc.*). At the same time, clinicians should adjust medications (adherence or side effects), provide information and education regarding medical status and address any emerging issues ranging from referral to other medical specialists to scheduling invasive techniques such as endoscopic variceal ligation or transjugular intrahepatic portosystemic shunt (TIPS) and evaluation for liver transplantation (LT). Overall, outpatient management aims to optimise the patient's quality of life, prevent disease progression, and reduce the risk of complications through a comprehensive, multidisciplinary approach. Furthermore, a recent addition to these goals could optimally be to guide the patient to what is becoming the final frontier: Recompensation. This guide serves as a valuable resource for medical experts, offering a general set of recommendations for the initial handling of DeCi patients following hospitalisation, with the aim of guiding physicians through the early steps of managing these patients, which seem to be the most crucial. Figure 1 summarises the cornerstones of outpatient management of patients with DeCi.

ETIOLOGIC TREATMENT

Regarding the etiologic treatment of DeCi, it should be treated accordingly based on causality as soon as possible. Regulation of etiological factors can substantially decrease HVPG and reduce the risk of further decompensation or even lead to recompensation. Nevertheless, there is a scarcity of high-quality studies examining the definition and clinical implications of hepatic recompensation[2-4].

Table 1 summarises etiological treatments for the most common causes of cirrhosis in decompensated patients. The influence of general risk factors like obesity, alcohol consumption, smoking and control of comorbidities on disease progression and hepatocellular carcinoma (HCC) development should be explained, and the patient must be heavily encouraged to act upon them with the help of an expert health professional (psychiatrist, nutritionist, *etc.*) when needed. Furthermore, physicians should carefully examine drugs used for comorbidities since many of them should be avoided or minimised in patients with DeCi, with non-steroidal anti-inflammatory drugs being the most notable example of drugs that are universally contraindicated in these patients[2,5].

Dietary interventions are encouraged for metabolic-associated steatotic liver disease (MASLD), usually in accordance with nutritionists, as well as physical activity (moderate-intensity aerobic exercise) and pharmacological treatment according to the underlying medical history[6]. Diabetic patients with decompensated MASLD should monitor glycemic control through insulin therapy since most antidiabetic drugs are contraindicated in decompensated Child-Pugh B and C. Regarding the newest MASLD treatment options, such as semaglutide, tirzepatide and resmetirom[7-9], most studies show promising results in patients without DeCi. Therefore, further comprehensive studies are warranted to ascertain the viability and safety of implementing these treatment options in patients with DeCi.

Alcohol cessation treatment should be discussed with patients by redirecting them to specialised centres, as abstinence decreases the risk of liver-related complications and is usually required for enlisting for LT[10]. Abstinence has been shown to significantly affect many outcomes, such as decompensation, recompensation, and survival, while also being the most effective therapy that leads to the improvement of patients and delisting from LT lists[11].

Table 1 Etiological treatments in decompensated patients

Cause	Treatment option
Alcohol	Discontinue alcohol consumption (long-term abstinence for more than six months)
HBV	Early HBV suppression with nucleoside analogues
HDV	Bulevirtide (not currently approved for patients with DeCi)
HCV	Sofosbuvir-velpatasvir. PI-based regimens in case of treatment failure (?)
MASLD	Weight loss, exercise, management of comorbidities. Resmetirom, semaglutide (?), tirzepatide (?)
PBC	Ursodeoxycholic acid, fibrates
AIH	Corticosteroids

HBV: Hepatitis B virus; HDV: Hepatitis D virus; HCV: Hepatitis C virus; MASLD: Metabolic-associated steatotic liver disease; PBC: Primary biliary cholangitis; AIH: Autoimmune hepatitis; DeCi: Decompensated cirrhosis; PI: Protease inhibitor.

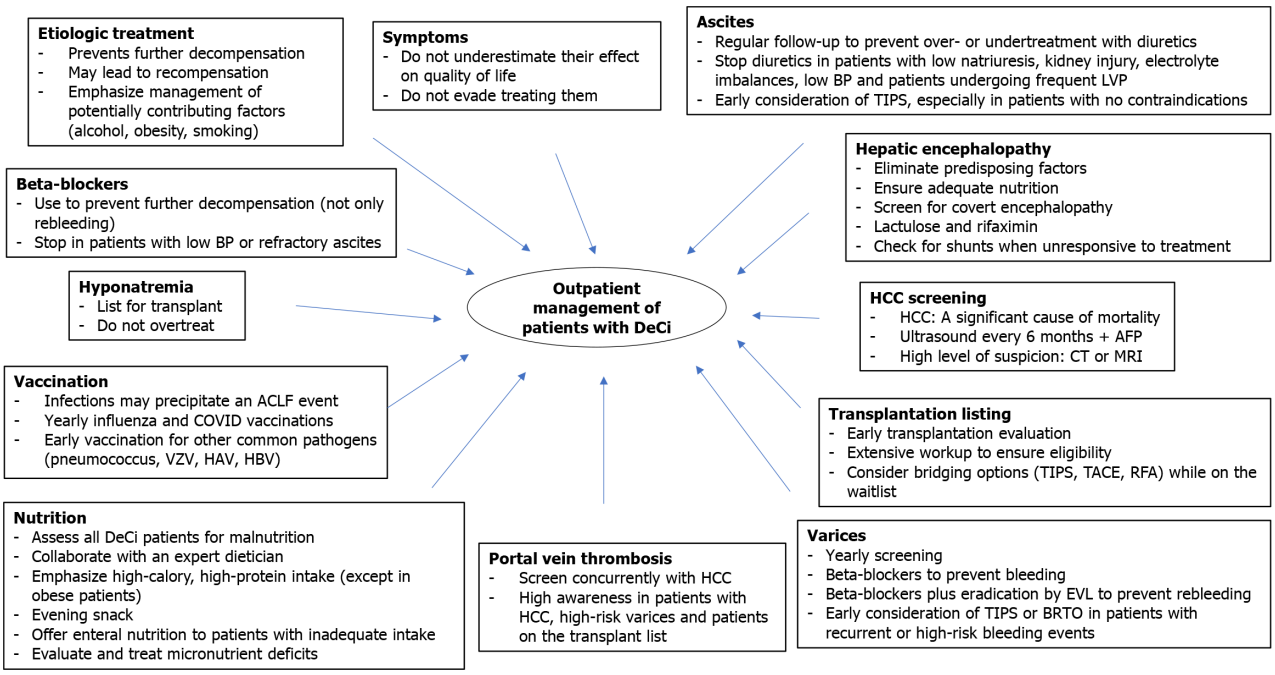

Figure 1 Main features of outpatient management of patients with decompensated cirrhosis. BP: Bacterial peritonitis; LVP: Large-volume paracentesis; TIPS: Transjugular intrahepatic portosystemic shunt; DeCi: Decompensated cirrhosis; HCC: Hepatocellular cancer; AFP: Alpha-fetoprotein; CT: Computed tomography; MRI: Magnetic resonance imaging; ACLF: Acute-on-chronic liver failure; COVID: Coronavirus disease; TACE: Transarterial chemoembolisation; RFA: Radiofrequency ablation; VZV: Varicella zoster virus; HAV: Hepatitis A virus; HBV: Hepatitis B virus; EVL: Endoscopic variceal ligation; BRTO: Balloon-occluded retrograde transvenous obliteration.

In hepatitis B virus (HBV) patients, early nucleoside analogues (NUCs) administration has proven to improve survival in all disease stages. Several studies have demonstrated the positive effects of long-term NUC therapy on hepatic function, including normalisation of alanine transaminase levels, as well as decreases in liver stiffness[12]. Concurrently, several studies have shown that NUC therapy can be used effectively in patients with DeCi to prevent decompensation, achieve recompensation and increase survival[13,14]. Clinicians should remember to use the high dose of entecavir (1 mg) and also screen patients who receive tenofovir disoproxil fumarate for kidney injury, osteoporosis or hypophosphatemia, findings which must prompt them to switch to entecavir or tenofovir alafenamide. Regarding hepatitis D virus infection, in cases of DeCi, the use of pegylated-interferon is not recommended due to the potential risk of triggering flares and precipitating episodes of acute-on-chronic liver failure (ACLF). Off-label monotherapy of bulevirtide in decompensated patients has been reported with optimistic results, but more data are required to ascertain its safety in this specific population[15]. Its use could be considered in case-by-case scenarios and conjointly with LT listing.

In hepatitis C virus-related DeCi, patients can achieve a sustained virological response (SVR) following treatment with the sofosbuvir-velpatasvir-ribavirin regimen in > 90% of cases. Many studies suggested an improvement in model for end-stage liver disease (MELD) scores after SVR achievement in the short term, but results regarding long-term improvement vary. Across four retrospective evaluations of sofosbuvir-based therapies in patients with decompensated

liver function, achieving SVR following direct-acting antiviral therapy resulted in 31.6% of Child-Pugh B patients and 12.3% of Child-Pugh C patients transitioning to Child-Pugh stage A[16]. Notably, attainment of SVR12 significantly diminished the risk of transplantation or death and enhanced the probability of clinical amelioration[16]. However, some patients may not respond to the indicated drug regimen. Then, the clinician will face the prospect of using a regimen with a protease inhibitor (PI), which is contraindicated by guidelines in patients with DeCi[17]. Nevertheless, due to the need to achieve viral eradication in these patients, there have been studies using PI-based regimens that exhibited significant efficacy and safety[18-20], leaving the decision in the hands of the clinician. Furthermore, considerable thought must be given to commencing therapy for patients awaiting LT. There are guidelines in place that, depending on the severity of the disease and average time to transplant, stipulate whether antiviral treatment should be commenced before LT or conserved for the post-LT period[17].

Treatment of DeCi due to autoimmune liver diseases, such as autoimmune hepatitis and primary biliary cholangitis (PBC), focuses on managing symptoms, preventing disease progression, and addressing complications. Patients with autoimmune hepatitis and DeCi typically receive corticosteroid monotherapy since azathioprine should be avoided in DeCi due to the risk of cytopenias[21]. Additionally, corticosteroids should be used carefully and in low doses, especially in patients with Child-Pugh C., due to their adverse events, most notably their association with a higher incidence of infections[22]. Patients with PBC may benefit from monotherapy with ursodeoxycholic acid or its combination with fibrates as secondary therapy[23,24]. Obeticholic acid is contraindicated and should be discontinued in patients with DeCi [25].

HCC SCREENING

Studies tracking patients over the long term have discovered that each year, around 1%-8% of individuals with cirrhosis develop HCC[26]. Characteristically, approximately 1 in 3 patients with cirrhosis will develop HCC during their lifetime [27]. Early diagnosis allows for effective treatment and significantly reinforces the survival probability of the patients[28]. Therefore, establishing an appropriate protocol for HCC screening and ensuring patient adherence can substantially affect the survival of patients with DeCi[29].

Most HCC surveillance guidelines suggest an abdominal ultrasound should be performed by an experienced radiologist every six months in all patients with DeCi. Other methods, such as computed tomography (CT) or magnetic resonance imaging (MRI), are not cost-effective for surveillance and have shown a significant rate of false-positive findings and should be considered in inadequate ultrasound results due to obesity, intestinal gas, or chest wall deformity [2,30]. Nevertheless, all patients with findings suspicious of HCC should undergo MRI or CT evaluation.

Regarding CT and MRI surveillance, the Liver Imaging Reporting and Data System (LI-RADS) is generally used. It is a standardised system developed by the American College of Radiology to standardise the interpretation and reporting of imaging studies for patients at risk of developing HCC. The LI-RADS criteria incorporate various imaging features such as size, arterial phase hyperenhancement, washout appearance, capsule appearance, and enhancing "pseudocapsule" to stratify liver lesions into different categories, ranging from LR-1 (definitely benign) to LR-5 (definitely HCC). Additionally, LI-RADS provides categories for lesions that are not specifically diagnostic of HCC but are suspicious for HCC (LR-3) or indeterminate (LR-2), as well as categories for lesions that are definitely or probably not HCC (LR-4 and LR-M). Imaging techniques can identify each patient based on the modified Barcelona Clinic Liver Cancer staging system, leading to a treatment strategy[30]. While the diagnosis of HCC in patients with cirrhosis may be established based on typical imaging findings, indeterminate lesions should undergo histological evaluation to confirm diagnosis. The recent emergence of immunotherapy in HCC and the need for immunohistochemical markers to guide management may, in the near future, re-establish histology as common practice for HCC diagnosis.

Several serological markers have been studied and are used for early prognosis and surveillance. Most studies have tested for alpha-fetoprotein (AFP); however, its use is ambiguous because a significant portion of tumours present without an elevated AFP, while an elevation of AFP can also be observed in a variety of acute and chronic liver diseases [31]. Nevertheless, the higher the AFP level, the higher the specificity for HCC, with levels > 400 ng/mL displaying sensitivity close to 99%[32,33]. Therefore, while there has been disagreement between guidelines regarding its routine use [34,35], its use, especially in high-risk populations, can further enhance the sensitivity of HCC screening in clinical practice[36].

Des-gamma-carboxy prothrombin levels have shown better diagnostic accuracy than AFP in early-stage HCC[37]. At the same time, they can also be used as a complementary marker to AFP to increase the diagnostic rate (such as the GALAD score)[38]. The GALAD score is derived from gender, Age, AFP-L3, AFP and des-gamma-carboxy prothrombin and was shown to be a highly accurate model for the detection of HCC. The GALAD score is complementary to ultrasound for detecting HCC, and it can be particularly important in a group of patients with advanced-stage hepatic dysfunction or obesity who are at risk for false-negative ultrasound[39]. However, these markers are currently unavailable or costly in most countries and cannot be routinely used for HCC surveillance for the time being. Overall, patients must be advised to adhere to the general suggestions of HCC surveillance through an abdominal ultrasound every six months. Doctors should continuously emphasise the importance of regular screening because early detection can significantly improve treatment outcomes and overall prognosis by allowing timely intervention and potentially life-saving treatments.

PORTAL VEIN THROMBOSIS

Portal vein thrombosis (PVT) develops in 10%-25% of patients with cirrhosis, mainly patients with DeCi[40,41]. Furthermore, in the presence of malignancies, particularly HCC, alongside liver cirrhosis, the incidence of PVT can escalate to as high as 35%[40]. While PVT is recognised as a common complication of cirrhosis, its impact on hepatic decompensation and overall mortality remains a topic of ongoing debate. PVT management guidelines from major hepatology associations are summarised in Table 2.

Ultrasonography and Doppler ultrasonography are first-line imaging techniques to evaluate PVT in cirrhotic patients [42]. Contrast-enhanced ultrasonography has high detection rates when compared to CT imaging, ultrasonography, and Doppler ultrasonography, but its use is limited due to low sensitivity (may not reliably detect small thrombi), operator dependence (depending on operator expertise), high cost and limited availability[43,44]. Considering these factors, Doppler ultrasound remains the preferred imaging modality for the screening of PVT due to its high sensitivity, wide availability, and cost-effectiveness. However, it may be utilised in cases where Doppler ultrasound is inconclusive or there are specific reasons for using contrast-enhanced ultrasonography[43]. Nevertheless, a diagnosis of PVT by ultrasound must be further evaluated by cross-sectional imaging to determine the extent of thrombosis and exclude the possibility of HCC-related PVT[45].

Various guidelines exist on the subject of PVT, with the Baveno VII being the most recent one. PVT treatment is contingent upon several factors, including the acuteness of the thrombosis and the patient's overall health status. Additionally, consideration should be given to the patient's eligibility for LT, as this can influence the treatment approach. We suggest anticoagulation (AC) is strongly considered in the following cases: (1) Recent (< 6 months) PVT completely or partially occlusive of the PV trunk; (2) Chronic PVT (> 6 months) in patients with known thrombus progression [even in minimally occlusive obstruction that progresses to the superior mesenteric vein (SMV)]; (3) Symptomatic PVT; and (4) Potential LT candidates (to prevent re-thrombosis or progression of thrombosis with the goal of facilitating adequate portal anastomosis in LT and reducing post-transplant morbidity and mortality).

AC should be continued until portal vein recanalisation or for at least six months, with prolonged use post-recanalization in patients awaiting LT. In all cases, the clinician should take into account the advantages of averting recurrence and potentially enhancing survival while weighing against the risk of bleeding. Some guidelines suggest helpful monitoring through imaging every 2 to 3 months to assess treatment response and every three months if a conservative approach is chosen. If this strategy is adopted, AC should be heavily considered in the case of PVT progression[2,3,45,46]. Prior to AC initiation, all patients should be screened for the presence of varices and treated accordingly. Finally, regarding the timing of AC, patients should receive treatment within two weeks of PVT diagnosis, ideally as soon as variceal bleeding prophylaxis [beta-blockers or endoscopic variceal ligation (EVL)] has been initiated[45,47].

The type of AC depends on the patient's characteristics, cirrhosis severity (Child-Pugh score, varices status) and other comorbidities (renal dysfunction, *etc*.). Generally, choices include direct oral anticoagulants (DOACs), low-molecular-weight heparin (LMWH) and vitamin-K antagonists (VKAs). Oral administration is usually preferred owing to its convenience by patients and medical personnel, aside from Child-Pugh C patients due to the lack of evidence regarding DOACs and VKAs, in which subcutaneous administration of LMWH is recommended[48]. DOACs can be used in Child-Pugh A patients as a first choice and with caution in Child-Pugh B patients. VKAs can also be used in Child-Pugh A patients, but international normalised ratio fluctuations must be perceived with caution in Child-Pugh B patients, thus they are not recommended in this category of patients[48,49]. More studies are needed to introduce evidence of superiority between DOACs regarding patients with DeCi. Patients who are not responding to AC and are candidates for LT or develop recurrent portal hypertension-related bleeding complications should be considered for TIPS insertion or other endovascular techniques to facilitate recanalisation, allow better surgical outcomes and alleviate portal pressure[3,45].

VACCINATION

Cirrhotic patients are considered immunosuppressed and are at higher risk of complications with grave morbidity from several infectious diseases. Concomitantly, infectious complications may precipitate further decompensation events or ACLF while also being associated with higher mortality rates[50]. General vaccination guidelines include hepatitis A virus, HBV, influenza, severe acute respiratory syndrome coronavirus 2, varicella zoster virus and pneumococcus doses according to national vaccination programs regardless of age[51]. Furthermore, vaccination should also be suggested for diphtheria, tetanus, and poliomyelitis, while Mumps-Measles-Rubella antibodies should be tested and supplemented with a booster dose if needed[51]. It is crucial to implement antibody testing after the vaccination and suggest booster doses in most cases since patients with immunosuppression develop weaker immune responses[52]. Despite the existing suggestions, vaccination rates for pneumococcus, hepatitis A virus, and HBV in cirrhotic patients are insufficient. Even amongst high-risk cohorts, such as those with concomitant diabetes or patients awaiting LT, vaccination rates were less than 40% for all pathogens[53,54]. A proposed vaccination schedule for patients with DeCi is outlined in Table 3.

VARICES

In Child-Pugh A patients, esophageal varices can manifest in approximately 42% of cases, while in Child B/C patients, the prevalence increases to 72%[55]. Variceal bleeding occurs in up to one-third of cirrhotic patients, with each episode

Table 2 Portal vein thrombosis management guidelines from major hepatology associations

	Baveno VII[3]	AASLD[45]	ACG[46]	EASL[165]
Indication for screening	LT candidates concomitantly with HCC screening	-	Upon diagnosis of cirrhosis First decompensation	LT candidates concomitantly with HCC screening
Indication for treatment	Recent (< 6 months) PVT completely or partially occluded Symptomatic PVT Potential LT candidates	Recent (< 6 months) PVT (or SMV) completely or partially occluded Symptomatic (ischemic) PVT	Evidence of thrombophilia Progression into the mesenteric veins Evidence of bowel ischemia	SMV thrombosis or history of bowel ischemia Potential LT candidates

AASLD: American Association for the Study of Liver Diseases; ACG: American College of Gastroenterology; EASL: European Association for the Study of the Liver; LT: Liver transplantation; HCC: Hepatocellular carcinoma; PVT: Portal vein thrombosis; SMV: Superior mesenteric vein.

Table 3 Proposed vaccination schedule for patients with decompensated cirrhosis

Vaccination	Schedule
HAV	At 0 and 6 months (2 doses)
HBV	At 0, 1 and 6 months (3 doses)
Influenza	Annually
COVID-19 - Moderna (mRNA 1273)	At 0 days and 28 days (2 doses)
COVID-19 - BioNTech/Pfizer (*BNT162b2* mRNA)	At 0 days and 21 days (2 doses)
VZV	At 0 months and 2 months (2 doses)
Pneumococcus	PCV15 followed by PPSV23 1 year after

HAV: Hepatitis A virus; HBV: Hepatitis B virus; COVID-19: Coronavirus disease 2019; VZV: Varicella zoster virus; PCV15: 15-valent pneumococcal conjugate vaccine; PPSV23: 23-valent pneumococcal polysaccharide vaccine.

carrying significant mortality[2]. The progression from small to large varices is notable, particularly in patients with Child B/C cirrhosis, where rates reach up to 22% at one year and 51% at three years, compared to 2% and 16%, respectively, in compensated patients[56].

In the matter of varices monitoring and treatment, Baveno VII states that non-selective beta-blockers (NSBBs) are the primary choice for bleeding prophylaxis in high-risk varices in decompensated patients and are preferred over EVL. In a randomised controlled trial involving 152 patients, those assigned to carvedilol (without banding) exhibited lower rates of variceal bleeding compared to individuals receiving band ligation every two weeks until variceal eradication (10% *vs* 23%) over a 20-month follow-up period[57]. EVL is recommended in severe cases of patients with large varices who cannot tolerate NSBBs. Caution should be adhered to in patients with acute kidney injury (AKI), infection or sepsis, hypotension, as well as acute bleeding so that NSBB use is halted. In patients with decompensation and low-risk varices, NSBBs are also recommended to prevent further decompensation. Additionally, rebleeding prophylaxis is managed by the combination of NSBBs and EVL, with the goal of complete eradication of varices[3]. However, in patients developing recurrent variceal bleeding from oesophageal varices while on prophylaxis and patients with bleeding from gastric varices, TIPS insertion should be considered to prevent further bleeding[3,58,59]. Finally, in terms of which NSBB to choose, carvedilol has displayed superiority over propranolol in terms of preventing further decompensation, but its more potent hemodynamic activity warrants even greater care when administering it to patients with low blood pressure or kidney dysfunction[60-62].

With regard to gastric varices, there is a lack of evidence regarding primary and secondary bleeding prevention. The only adequately powered study showed superiority of cyanoacrylate injection over propranolol for primary prevention of gastric variceal bleeding, although no difference in terms of survival was observed[63]. Most guidelines consider NSBBs as first-line therapy for primary prevention due to their effects on the prevention of liver decompensation, while TIPS and balloon-occluded retrograde transvenous obliteration should be considered for secondary prevention[3,59].

Generally, if there is evidence of hepatic decompensation, endoscopy should be done at that time and repeated annually[64-68], especially in patients not receiving NSBBs. In decompensated patients being managed with NSBBs, surveillance endoscopic practices are not clearly stated and need to be defined on a case-by-case basis (medical history, HCC, PVT, *etc.*)[3]. Conversely, the British Society of Gastroenterology guidelines clearly state that follow-up endoscopy is not warranted in patients on NSBBs for primary bleeding prevention[68].

BETA-BLOCKERS

In the management of cirrhotic patients, beta-blockers are often used to prevent further decompensation. The beneficial actions of beta-blockers in portal hypertension-related events derive from their effect on cardiac output and splanchnic arterial flow. However, their use should be approached with caution and individualised based on the patient's condition and risk factors[69]. In comparison to conventional NSBBs like propranolol and nadolol, carvedilol stands out due to its inherent anti-alpha adrenergic vasodilatory properties, which enhance its ability to lower portal pressure. Carvedilol is a unique beta-blocker that possesses both non-selective beta-blocking activity (beta-1 and beta-2 receptors) and alpha-blocking activity, leading to downregulation of intrahepatic resistance and an additional decrease in HVPG. Those advantages have translated into clinical outcomes, with multiple studies showing a lower risk of further decompensation and better survival with carvedilol, thus essentially making it the top treatment option among beta-blockers in patients with DeCi[60-62,70]. Carvedilol is advised to be started at a dose of 6.25 mg/day for one week, followed by a dose increase to a maximum of 12.5 mg/day after the second week[71]. Propranolol, the previous first-choice, has the advantage that it confers less effect on blood pressure and, therefore, may be more suitable for patients with advanced DeCi. It can be slowly titrated to doses from 20 mg/day to 160 mg/day, with a target resting heart rate of 55-60 beats per minute[72]. However, patients with DeCi usually cannot tolerate doses higher than 80 mg/day[73].

In patients with ascites, NSBBs should be dose-reduced or discontinued in case of persistently low blood pressure (systolic blood pressure < 90 mmHg or mean arterial pressure < 65 mmHg) or hepatorenal syndrome (HRS)-AKI. Once blood pressure returns to baseline or HRS-AKI resolves, NSBBs can be re-initiated or re-titrated[74,75]. Healthcare providers should emphasise regular heart rate and blood pressure monitoring to patients in order to identify potential harmful effects, thus ensuring timely treatment adjustment or cessation.

ASCITES

Ascites is the most common cause of decompensation in cirrhotic patients (5%-10%/year in compensated patients), and *vice versa*, cirrhosis is the leading cause of ascites (approximately 80%)[1]. Ascites management in decompensated patients can be defined as a stepwise process, according to ascites severity. The treatment steps involved in this process are outlined in the following paragraphs.

Dietary salt restriction

Clinical trials comparing various dietary approaches have not shown a significant advantage in using low-sodium diets alongside diuretics[76]. Extreme sodium restriction can increase the risk of diuretic-induced hyponatremia and renal failure. Restricting dietary sodium can result in ascites resolution in approximately 10% of patients, particularly those experiencing their initial episode of ascites[77]. The prevailing view suggests that sodium intake should be moderately restricted (between 80-120 mmol/day) primarily to prevent excessive salt consumption[78]. A practical tip in order to avoid decreased energy intake would be to advise patients to avoid salted/canned foods and not add salt during and after cooking.

Diuretics

For patients experiencing their initial episode of moderate ascites, the recommended treatment entails initiating an anti-mineralocorticoid drug alone, with the first option being spironolactone. It should be commenced at a dosage of 100 mg/day, with incremental increases every 72 hours (in 100 mg increments) up to a maximum of 400 mg/day if there is inadequate response to lower doses. A significant side effect that can be exceedingly bothersome and can affect > 10% of patients is gynecomastia[79]. In this case, the patient can be switched to eplerenone, which has shown similar efficacy in controlling ascites, albeit with no consensus regarding optimal dosing[80].

For patients who fail to respond to anti-mineralocorticoids, defined as a body weight reduction of less than 2 kg per week, or those who develop hyperkalemia, furosemide should be added, starting at a dose of 40 mg/day and increased stepwise up to a maximum of 160 mg/day (in 40 mg increments)[81]. Patients with persistent or recurrent ascites should receive a combination therapy of an anti-mineralocorticoid drug and furosemide, with dosage adjustments based on individual response. Torasemide may be considered for patients showing insufficient response to furosemide.

During diuretic therapy, aiming for a maximum weight loss of 0.5 kg/day in patients without oedema and 1 kg/day in those with oedema is recommended. Once ascites resolution is achieved, diuretic dosage should be tapered down to the lowest effective level[82]. Close monitoring, both clinically and biochemically, is crucial during the early weeks of treatment, especially upon initial presentation. In cases where patients present with gastrointestinal bleeding, renal impairment, HE, hyponatremia, or abnormalities in serum potassium levels, correction of these issues should precede the initiation of diuretic therapy[83]. Subsequently, diuretic therapy should be cautiously initiated in such patients, with frequent clinical and biochemical assessments. Diuretic therapy is generally contraindicated in patients with persistent overt HE, severe hyponatremia (serum sodium concentration < 125 mmol/L), AKI, worsening HE, or incapacitating muscle cramps. Furthermore, furosemide should be discontinued in the event of severe hypokalemia (< 3 mmol/L), while anti-mineralocorticoids should be discontinued if severe hyperkalemia (> 6 mmol/L) occurs[82].

Large volume paracentesis

Large volume paracentesis (LVP) has been randomly defined as the removal of > 5 L of ascitic fluid. Frequent LVP is a standard procedure used in the management of recurrent/refractory ascites. While it can provide symptomatic relief and

improve patient comfort, it is not without risks. Some of the potential side effects and complications associated with frequent large-volume paracentesis include hemodynamic instability (hypotension and circulatory collapse) due to the rapid removal of large volumes of ascitic fluid, renal dysfunction (particularly common in patients with pre-existing kidney disease), electrolyte imbalance (hyponatremia, hypokalemia, and hypomagnesemia), HE, infections [spontaneous bacterial peritonitis, cellulitis (SBP)], and hematomas[84-86]. Plasma volume expansion is essential to prevent post-paracentesis circulatory dysfunction, typically achieved by infusing albumin (8 g/L of ascites removed). Even in cases where LVP removes less than 5 L of ascites, there is a low risk of post-paracentesis circulatory dysfunction. Yet, it is generally not recommended to administer albumin in these patients[87,88]. After LVP, patients should receive the minimum effective dose of diuretics to prevent ascites accumulation.

TIPS

Patients with recurrent or refractory ascites may benefit from TIPS insertion, as it improves survival and control of ascites. TIPS's use in patients with DeCi has been associated, when used in the right patients, with significantly lower portal hypertension-related complications and enhanced survival[89,90]. Therefore, regardless of varices presence or history of variceal bleeding, all patients with recurrent ascites (requiring > 3 LVP within one year) should be considered for TIPS[91,92]. TIPS typically leads to enhanced effective blood volume and renal function within 4-6 weeks, resulting in increased renal sodium excretion. However, TIPS-induced natriuresis might be delayed in elderly patients or those with reduced pre-TIPS glomerular filtration rate and intrinsic kidney disease. One major complication following TIPS insertion using bare stent grafts is HE, occurring in up to 50% of cases. This incidence can significantly decrease to around 18% with polytetrafluoroethylene-covered stent grafts of 8 mm, as evidenced by recent randomised trials. Notably, this effect is superior to larger stent grafts underdilated to 8 mm, as underdilated 10 mm stent grafts tend to expand almost entirely within 1-6 weeks. Hence, small-diameter polytetrafluoroethylene-covered stents are recommended in patients with a high risk of HE to reduce the risk of TIPS dysfunction and HE. Following TIPS insertion, diuretics and salt restriction should be continued until ascites resolution, along with thorough clinical monitoring. Patient selection for elective TIPS insertion is crucial, as is the expertise of the performing centre[3,93]. TIPS is not recommended for patients with specific contraindications, including elevated serum bilirubin, low platelet count, current or chronic HE, concomitant active infection, progressive renal failure, severe cardiac dysfunction, or pulmonary hypertension.

Alfapump®

Alfapump® is an implantable device that redirects ascitic fluid from the peritoneal cavity to the urinary bladder. Alfapump® has proven effective in significantly reducing the frequency and volume of paracentesis in patients with advanced cirrhosis and refractory ascites. However, adverse effects directly associated with the device have been reported in approximately 30%-50% of cases. Its implantation is recommended for patients with refractory ascites that are unsuitable for TIPS insertion, particularly in specialised centres. Nevertheless, close monitoring of patients is essential due to the elevated risk of adverse events, including renal dysfunction and technical challenges[94]. One study comparing TIPS and Alfapump® suggested TIPS had a better one-year transplant-free survival but had fewer negative prognostic factors at baseline[95]. Alfapump® is currently available in multiple European countries, while a clinical trial is underway (POSEIDON) for market introduction in the United States and Canada, with an expected completion date in 2024[96].

Antibiotics

Patients deemed to be at high risk for SBP, identified by Child-Pugh C status and an ascitic protein count < 1.5 g/dL, should be offered primary antibiotic prophylaxis for SBP[97]. These patients and individuals who have recuperated from an episode of SBP should commence treatment with norfloxacin (400 mg once daily), ciprofloxacin (500 mg once daily, orally), or co-trimoxazole (800 mg sulfamethoxazole and 160 mg trimethoprim daily, orally) to prevent subsequent episodes of SBP[98].

Midodrine

Midodrine has also been used as a vasoconstrictor in cases of repeated LVP to decrease the frequency of paracentesis and the risk of paracentesis-induced circulatory dysfunction. Several studies have noted its favourable use, as well as a meta-analysis which stated the significant urine output improvement and weight loss after midodrine use, as well as a substantial decrease in MELD scores in patients treated with midodrine compared to those receiving standard medical treatment[99-103]. Despite these exciting facts, no difference was found in paracentesis-induced circulatory dysfunction risk or short-term mortality[103]. Midodrine remains not officially indicated in most guidelines, and its use is defined in a case-by-case evaluation. However, its lack of significant side effects makes it an enticing option for patients with recurrent ascites that can not be treated with TIPS. Vaptan use has remained a controversial treatment option because of the lack of potent results regarding mortality and reduction of complications. Promising results had been stated in some phase-two studies[104], whereas larger randomised controlled trials did not yield significant results in terms of efficacy and indicated the possibility of electrolyte imbalances such as hypernatremia, dehydration, kidney failure, and osmotic demyelination syndrome. As expected, it is especially contraindicated in patients with HE, while the only official indication of vaptans (tolvaptan) is reserved for cases of syndrome of inappropriate antidiuretic hormone release[105, 106].

Sodium-glucose cotransporter 2 inhibitors

Sodium-glucose cotransporter 2 inhibitors have been investigated for their potential use in ascites management, partic-

ularly in patients with cirrhosis. While the current evidence is limited, some cases have shown promising results in reducing ascites volume and improving renal function due to the improvement of diuresis and natriuresis in patients with cirrhosis[107-109]. Additionally, careful monitoring for potential side effects, such as dehydration and electrolyte imbalances or urinary tract infections, is crucial[110]. Therefore, while SGLT-2 inhibitors hold promise, their use in ascites management requires extensive investigation before they can be routinely recommended in clinical practice. Nevertheless, their role in heart failure may justify their use in patients with concomitant DeCi, especially since diastolic dysfunction in these patients is significantly correlated with circulatory and renal dysfunction[111].

HE

In patients recovering from an initial episode of HE, maintenance therapy should aim to administer enough lactulose to attain 2 to 3 soft bowel movements per day. Rifaximin (550 mg, twice daily), as an addition to lactulose, is recommended for secondary prevention after experiencing one or more additional episodes of overt HE within six months of the initial episode[112]. Due to the significant effect of malnutrition on HE development, education regarding nutrition should be provided to every at-risk patient. Patients should consume 35-40 kcal/kg/day, 1.2-1.5 g of protein/kg/day, and avoid overnight fasting[113]. Alternative agents, such as branched-chain amino acids, probiotics, other antibiotics, or intravenous L-ornithine L-aspartate, are available; however, the effectiveness of these treatments remains a topic of debate due to inconclusive evidence[114].

Additionally, patients with DeCi should be screened for covert encephalopathy using a validated tool such as the Animal Naming Test and treated with the same regimen as patients with episodes of overt encephalopathy[115,116]. Additionally, patients undergoing TIPS may benefit from treatment with rifaximin to prevent post-TIPS HE[3,115]. Lastly, significant care must be taken to explain to the patients the risks of certain everyday activities, chief among them driving, which should ideally be prohibited for patients with a history of overt HE[117,118]. Nevertheless, current guidelines emphasise the need for the assessment of the patient's fitness to drive by local authorities[115].

In patients exhibiting persistent, difficult-to-treat, or multiple episodes of HE, clinicians should consider the possibility of spontaneous portocaval shunts, which contribute to HE by increasing the amount of ammonia and other substances that bypass the liver entirely. Existing data indicates that shunt embolisation represents a beneficial therapeutic approach for individuals with cirrhosis and HE[119]. However, it is typically regarded as a transitional measure to transplantation in most cases.

HYPONATREMIA

Patients with DeCi commonly experience hyponatremia (serum sodium concentration < 130 mmol/L), which is associated with an ominous prognosis and increased morbidity. Therefore, these patients should promptly undergo evaluation for LT. While the evidence supporting its management is limited, hyponatremia is typically treated by addressing volume depletion if present and optimising diuretic doses. Fluid restriction is only recommended for patients whose serum sodium levels remain below 125 mmol/L despite optimisation efforts[120].

The management of hypovolemic hyponatremia involves addressing the underlying cause and administering normal saline. In other cases, such as hypervolemic hyponatremia, fluid restriction to 1 L per day is recommended to prevent further decreases in serum sodium levels. While albumin administration may be suggested for hypervolemic hyponatremia, there is limited data to support its use[121]. The use of hypertonic saline should be reserved for rare acute cases with life-threatening symptoms of hyponatremia. It may also be considered in patients with severe hyponatremia who are expected to undergo LT within a few days[122]. As stated in most hyponatremia treatment guidelines, it is important to remember that when correcting serum sodium concentration, it is essential to proceed slowly (≤ 8 mmol/L per day) to avoid irreversible neurological complications such as osmotic demyelination[123]. Overall, clinicians should not rush to correct asymptomatic hyponatremia in patients with DeCi and should focus on efforts to address the severe underlying liver disease.

NUTRITION

Nutrition guidance is significant for all patients with cirrhosis, but it becomes essential when it comes to patients with DeCi. These patients are at an increased risk of malnutrition and sarcopenia and should be evaluated for nutritional support, especially those with a body mass index < 18.5 kg/m^2 or Child-Pugh stage C. Simple assessments such as mid-arm muscle circumference can help identify sarcopenic patients, while patients with a recent CT examination (which is common in patients with advanced liver disease) can further benefit from the evaluation of skeletal muscle quantification [124]. While identifying patients with malnutrition or sarcopenia may be a task that a hepatologist can carry out, the next steps can only be appropriately followed by a multidisciplinary approach, with the aid of an expert dietician being critical.

After identifying patients at risk for malnutrition, a detailed nutritional assessment should be conducted by recording the dietary habits of the patients and identifying their nutritional needs. Extra care should be followed in patients with ascites to avoid taking ascites into account when determining total body weight, which can be resolved by weighing

patients after paracentesis or diuretic therapy or subtracting 5%-10% of body weight according to ascites status[125]. Generally, patients with cirrhosis are advised to attain a daily intake of ≥ 35 kcal/kg and 1.2-1.5 g of protein/kg. This translates to patients being advised to have 2-3 meals/day and an equal number of snacks, with late-night snacks being particularly emphasised to avoid prolonged fasting periods, which lead to muscle wasting[124]. Patients should be advised not to avoid foods, and even recommendations regarding salt could be reconsidered if they negatively affect their food intake. If patients cannot maintain adequate energy intake, enteral nutrition with high-protein supplements should be considered. These recommendations are not applied to obese patients with DeCi, where a hypocaloric, high-protein diet is recommended to facilitate weight loss without simultaneously inducing sarcopenia[126].

Another thing to consider is micronutrient deficiencies, which are common in patients with DeCi and depend on the aetiology of the disease. Lipid-soluble vitamin deficiencies are common in patients with PBC and primary sclerosing cholangitis, while thiamine is significantly depleted in patients with alcohol-related liver disease. A significant number of patients with DeCi have vitamin D deficiency, with many having concomitant osteoporosis, demonstrating the need for screening for these conditions in this group of patients.

SYMPTOM TREATMENT

Muscle cramps

Muscle cramps are a known complication in patients with cirrhosis, although their exact cause is not fully understood [127]. Several factors can contribute to the presentation of this symptom, such as electrolyte imbalance (hypokalemia or hypomagnesemia), malnutrition and sarcopenia, dehydration, and medications (such as diuretics). Management of muscle cramps in patients with cirrhosis typically involves addressing underlying factors. This may include electrolyte supplementation, ensuring adequate hydration, and optimising nutritional intake. In some cases, medications to relieve muscle cramps or underlying conditions contributing to them may be prescribed. However, treatment should be individualised based on the patient's circumstances and medical history[128]. Restoration of effective circulating blood volume with albumin has been shown to improve cramping. Albumin infusion or baclofen administration (10 mg/day, with a weekly increase of 10 mg/day up to 30 mg/day) are recommended in patients with muscle cramps[129]. Additionally, a recent randomised controlled trial showed evidence regarding the efficacy of pickle juice in alleviating muscle cramp severity without resulting in adverse effects such as electrolyte imbalances (commonly seen in rehydration attempts of decompensated patients)[130].

Depression/sleep disorders

Depression and sleep disorders are quite frequent and have a significant effect on the quality of life of patients with cirrhosis[131-133]. There is a considerable overlap of these conditions with the effects of HE; however, studies have shown a high prevalence of them even in patients with compensated cirrhosis, suggesting that there are other underlying factors to consider[133]. The Pittsburgh Sleep Quality Index and Epworth Sleepiness Scale can be used to evaluate the overall sleep quality of patients and daytime sleep quality[134], while the Patient Health Questionnaire-9 can be used to detect depression and evaluate its severity[135].

Most guidelines recommend cognitive behavioural therapy as the first-line treatment for sleep disorders[136]. Moreover, patients with sleep disturbances are encouraged to maintain a regular sleep-wake schedule. These patients should be exposed to bright light as early as possible in the morning and avoid bright light exposure at night. In addition, one study reported that mindfulness-based stress reduction and supportive group therapy remarkably improved the sleep quality of patients with cirrhosis[137]. Zolpidem improved sleep quality as measured by increased total sleep time, decreased sleep latency, and periodic limb movements in patients with Child-Turcotte-Pugh classification A and B cirrhosis. Nevertheless, the clinical usefulness of zolpidem was restrained by side effects, such as excessive sedation (11% of patients) and constipation (23% of patients)[138]. Accordingly, a randomised controlled trial showed that 3 mg of melatonin treatment for two weeks remarkably improved sleep quality and decreased daytime sleepiness compared with placebo treatment and before melatonin treatment in patients with liver cirrhosis[139].

Management of depression in patients with DeCi can be challenging due to the liver toxicity of various drugs used for its treatment. A multidisciplinary approach with psychologists and psychiatrists is needed. The hepatologist's role mainly involves the identification of such symptoms and aiding psychiatrists in deducing the appropriate drug dose according to DeCi severity[135]. With regards to drug classes, selective serotonin reuptake inhibitors are considered the safest option for patients with DeCi, albeit in significantly reduced doses[140], while other drug classes may be used after careful consideration and dose reduction. Nevertheless, in all cases, a strict surveillance program should be established in order to determine the optimal dose that balances drug efficacy and safety.

Restless leg syndrome

Restless leg syndrome (RLS) is a neurological disorder characterised by an irresistible urge for leg movement, often accompanied by uncomfortable sensations such as tingling, crawling, or itching. While RLS has been primarily associated with conditions like iron deficiency anaemia, chronic kidney disease, and peripheral neuropathy, its prevalence and clinical significance in cirrhosis are less well understood. Research on RLS in cirrhosis is limited, but there is some evidence to suggest that it may occur more frequently in patients with liver disease compared to the general population [141]. The exact mechanisms underlying the association between RLS and cirrhosis are unclear, but potential contributing factors may include alterations in neurotransmitter levels, hormonal changes, and metabolic disturbances. However, it is essential for healthcare providers to recognise and address RLS symptoms in cirrhosis patients, as they can significantly

impact quality of life and sleep quality.

Management of RLS in cirrhosis typically involves addressing underlying factors contributing to the disorder, such as iron deficiency or neuropathy, if present. Medications commonly used to manage RLS in the general population, such as dopamine agonists or alpha-2 delta ligands, may also be considered in cirrhosis patients. However, caution is warranted due to potential interactions with liver function and other medications[141]. At the moment, there are no clear guidelines regarding the syndrome in patients with DeCi. A promising agent may be pregabalin, with a recent study showing that a short course of low-dose (75 mg/day) pregabalin was effective (82%) in alleviating RLS in patients with cirrhosis[142].

TRANSPLANTATION LISTING

Individuals with cirrhosis should be referred for transplant evaluation upon experiencing their initial major cirrhosis-related complication, such as ascites, variceal bleeding, or HE. The prognostic MELD has proven to be a valuable tool in predicting short-term survival in individuals with chronic liver disease, making it the most critical indicator for transplantation. Based on current guidelines, a MELD score of 15 or higher is recommended for possible transplant patients [143,144]. However, even DeCi patients with lower MELD scores should start evaluation for LT due to the process being lengthy and in order to be prepared for the possibility of further acute decompensation or ACLF. Additionally, MELD scores can be used to assess the urgency of LT and the priority of each patient in the transplantation list.

Nevertheless, a number of disease complications are considered exceptions to the above-mentioned MELD rule due to their effect on patient's survival and quality of life, with patients experiencing them given priority points for LT. Such complications in patients with DeCi are hepatopulmonary syndrome, refractory ascites, recurrent encephalopathy, recurrent cholangitis in patients with PSC, refractory pruritus in PSC or PBC and HCC. Lastly, patients with severe portal hypertension-related complications, which severely limit their survival prognosis, may undergo a TIPS procedure in order to halt disease progression and prolong survival while on the waitlist[145].

While hepatic resection and locoregional therapy can manage HCC in some cases, most individuals with HCC confined to the liver should be evaluated for LT. For instance, individuals with HCC who meet Milan criteria (solitary HCC lesion less than 5 cm or up to 3 nodules smaller than 3 cm) and have no radiographic evidence of extrahepatic disease but who are not candidates for surgical resection (usually due to portal hypertension), should be considered candidates for LT and given priority[146]. In these patients, locoregional therapy can be used as an effective bridge to transplantation either by downstaging the disease and allowing for the Milan criteria to be met or by preventing disease expansion while awaiting LT[147,148].

Lastly, a thorough pre-transplant evaluation of comorbidities and potential contraindicative factors is crucial to maximise patient outcomes. Such assessments may uncover comorbidities or cirrhosis complications that may render the patient unsuitable for LT, or their management prior to LT may have a significant impact on post-LT outcomes. Clinicians should look to local transplant centre's guidelines in order to complete the required pre-transplant workup efficiently and as soon as possible[149].

FUTURE (KEEP AN EYE ON)

Statins

Encouraging the use of statins is recommended for patients with cirrhosis who have an approved indication for statins, as these agents may decrease portal pressure and improve overall survival[150]. Some studies have shown a protective role of statins, especially in type-2 diabetes mellitus patients with decompensated MASLD, as well as in patients with HBV cirrhosis[151,152]. In patients with Child-Pugh B and C cirrhosis, statins should be administered at a lower dose (maximum of 20 mg/day for simvastatin), and patients should be closely monitored for muscle and liver toxicity with regular checkups regarding creatine phosphokinase, alanine transaminase, and aspartate aminotransferase. However, in Child-Pugh C cirrhosis, the benefit of statins has not been proven yet, and their use should be more limited[153]. While statins may not be advised in cases of DeCi, their potential benefits in disease management have been demonstrated. Therefore, patients with evident treatment indications should not refrain from their use.

Rifaximin

Rifaximin is currently recommended only for the secondary prevention of HE or primary prophylaxis after TIPS insertion [3]. Research has linked rifaximin therapy with improved management of challenging refractory ascites, lower rates of decompensation, reduced occurrences of all-cause hospitalisations and readmissions, decreased risks of SBP and variceal bleeding, and a lower incidence of AKI-HRS[154-156]. Most currently, the LIVERHOPE trial showed simvastatin and rifaximin therapy alters the metabolomic profile of individuals with DeCi, resulting in a reduction and deactivation of various metabolites and metabolic pathways linked to the progression of cirrhosis and the onset of ACLF. A comprehensive multinational study spanning multiple centres and featuring an extended treatment duration is currently underway to provide deeper insights into the impacts of this combination therapy on clinical outcomes[157].

Anticoagulants

AC is not contraindicated in patients with cirrhosis who have an approved indication for AC, as it may reduce liver-related outcomes in patients with and without PVT and may improve overall survival[158]. Consequently, DOACs are

likely to emerge as the preferred choice for most cirrhotic patients, especially for the prevention of cardiovascular events in patients with Child-Pugh A/B cirrhosis[159,160]. However, DOACs are not recommended in patients with Child-Pugh C cirrhosis outside study protocols, with LMWH currently being the treatment of choice in these patients. The use of aspirin is also not discouraged in patients with cirrhosis and an approved indication for aspirin, as it may reduce the risk of HCC, liver-related complications, and death[161]. AC is both safe and efficacious for individuals with cirrhosis; nevertheless, clinicians should thoroughly assess each patient's individual characteristics before commencing treatment, including the severity of cirrhosis and renal function. Additionally, emerging evidence is showing that AC may improve survival in patients with cirrhosis regardless of indication, paving the way for their potential use as a therapeutic tool in patients with cirrhosis[162-165].

CONCLUSION

Outpatient management of patients following hospitalisation for acute decompensation of cirrhosis presents a complex but critically important challenge for healthcare providers. By implementing comprehensive, multidisciplinary approaches that prioritise close monitoring (every 3-6 months), personalised treatment plans, and ongoing education for patients and caregivers, we can hope to improve outcomes, reduce readmissions, and enhance the overall quality of care. Continued research, collaboration, and innovation will be essential in refining best practices and optimising long-term management strategies for decompensated cirrhotic patients.

FOOTNOTES

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