REVIEW ARTICLE

Management of Liver Decompensation in Advanced Liver Disease (Renal Impairment, Liver Failure, Adrenal Insufficiency, Cardiopulmonary Complications)

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Abstract

Systemic complications often occur in patients with advanced liver disease. In particular, the development of renal complications (acute kidney injury, hepatorenal syndrome), acute-on-chronic liver failure, cardiopulmonary diseases, or relative adrenal insufficiency can be serious in patients with advanced liver disease and may determine the patient's quality of life and prognosis. Therefore, the early diagnosis of possible complications is the key to the prompt initiation of specific treatments that can improve quality of life and survival. For this purpose, networking with reference centers where multidisciplinary units are available is essential so that every patient is evaluated in clinical discussions involving specialists from different fields.

Key Points

Acute kidney injury (AKI) is frequent in patients with advanced liver disease and impacts negatively on patients' survival. Early differential diagnosis and adequate classification are critical.

Hepatorenal syndrome (HRS) is a severe complication in patients with cirrhosis and ascites. Early intervention with vasoconstrictors in combination with albumin infusions are determining factors in the success of therapy and increased survival.

Acute-on-chronic liver failure (ACLF) is a common and severe complication in patients with chronic liver disease, but the pathophysiology, clinical course, and prognosis differ from acute hepatic decompensation. Liver transplantation should be evaluated according to the possible risk-benefit, considering the degree of ACLF.

Cardiopulmonary complications associated with portal hypertension are often underdiagnosed and include liver hydrothorax, hepatopulmonary syndrome, portopulmonary hypertension (PoPH), and cirrhotic cardiomyopathy.

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1 Introduction

Systemic complications often occur in patients with advanced liver disease. The liver has essential but diverse functions in metabolism, detoxification and excretion, the formation and inactivation of mediators, and non-specific defense mechanisms. Because of the high blood flow through the liver from the hepatic artery and portal vein, severe or advanced liver disease can cause changes in the systemic, portal, or cardiopulmonary circulation. Patients with advanced liver disease may develop several hemodynamic changes, leading to a hyperdynamic circulation, which is based on a progressive decrease in mean arterial pressure, a compensatory increase in cardiac output, and hypo-responsiveness to vasopressors. The current knowledge has linked these hemodynamic changes with the increase in portal pressure, bacterial translocation phenomena, and a progressive chronic systemic inflammatory state. These alterations manifest in extrahepatic symptoms that are often decisive for the disease course. In particular, renal and cardiopulmonary complications of advanced liver disease can be serious and may determine the patients' quality of life and prognosis [1]. This review summarizes the diagnosis and management of the most important complications of advanced liver disease: renal impairment, liver failure, adrenal insufficiency, and cardiopulmonary disease.

2 Acute Kidney Injury

2.1 Definition and Classification

Acute kidney injury (AKI) is a common condition in patients with advanced liver disease and negatively impacts patient survival, therefore early differential diagnosis (hepatorenal syndrome [HRS], acute tubular necrosis, prerenal failure, or nephrotoxicity) and proper classification are critical. AKI in cirrhosis is defined as an increase in serum creatinine (sCR) levels of ≥ 0.3 mg/dL (≥ 26.5 mmol/L) in 48 h, or an sCr increase of $\geq 50\%$ from baseline levels in the last 7 days [2].

Classification of the severity of AKI is essential. The International Club of Ascites-Acute Kidney Injury in cirrhosis (ICA-AKI) criteria provide a relevant and straightforward staging system for AKI in patients with liver cirrhosis based on the relative increases in sCr (Table 1) [2]. More recent studies indicate that stage 1 disease should be further subdivided into two subgroups with different outcomes, mainly sCr stage 1A (SCr < 1.5 mg/dL) and stage 1B (SCr ≥ 1.5 mg/dL) [3].

2.2 Prevalence

AKI is a frequent clinical problem that usually presents at and during hospitalization in cirrhotic patients; the estimated prevalence is 27–53% [3, 4]. Therefore, it is vital to determine the nature of kidney failure in patients with advanced liver disease. Some types of kidney failure in patients with liver disease, such as HRS or acute tubular necrosis, are more aggressive and have a worse prognosis and higher short-term mortality.

3 Hepatorenal Syndrome

3.1 Definition and Classification

HRS is a severe complication in patients with cirrhosis and ascites and is defined as the occurrence of renal failure in a patient with advanced liver disease in the absence of another known cause of renal failure. Two forms of HRS have been described depending on the acuity and progression of kidney injury. The first form is characterized by acute impairment of kidney function, HRS-AKI, while the second is characterized by more chronic kidney dysfunction, HRS-non-AKI [1]. HRS-AKI has well-established diagnostic criteria in patients with decompensated cirrhosis. According to the International Club of Ascites, HRS-AKI can be defined as an acute impairment of kidney function in a patient with ascites without response to expansion with 48 h albumin, absence of shock, not taking nephrotoxic drugs, and absence of structural kidney damage. Ruling out structural kidney damage is challenging as kidney biopsy is a risky procedure and is not always available. To overcome this limitation, kidney Doppler ultrasound can be employed. Recently, several biomarkers have emerged, with urinary neutrophil gelatinase (NGAL) being the most promising. Several studies have shown that urinary NGAL [5], a marker of tubular damage, can be useful for differential diagnosis. Nevertheless, the optimal cut-off for diagnosis has not been established, and diagnosis based on biomarkers needs further evaluation. Finally, HRS non-AKI is characterized by gradual renal failure and glomerular filtration < 60 mL/min for < 3 months [6].

3.2 Pathogenesis

Portal hypertension is a hallmark of this disease [7, 8]. As cirrhosis progresses, systemic inflammation becomes more intense, leading to systemic and splanchnic vasodilation, reducing the effective circulating volume (ECV) and decreasing renal perfusion [9]. A decrease in cardiac output further aggravates this decrease in ECV due to cirrhotic cardiomyopathy and an increase in vasodilation due to bacterial translocation and systemic inflammation [10].

3.3 Treatment

3.3.1 Vasoconstrictors

Vasodilation is a fundamental aspect of the pathophysiology of HRS, therefore treatment is based on the use of

Table 1 Classification for staging of patients with cirrhosis and AKI. Adapted from Angeli et al. [2] and Huelin et al. [3]

AKI stage	Criteria
1	Increase in sCr ≥0.3 mg/dL (26.5 mmol/L) or an increase in sCr ≥1.5-fold to twofold from baseline Stage 1A: <1.5 mg/dL (75% resolution) Stage 1B: >1.5 mg/dL (50% resolution)
2	Increase in sCr more than two- to threefold from baseline
3	Increase in sCr more than threefold from baseline or sCr ≥4.0 mg/dL (353.6 mmol/L) with an acute increase ≥0.3 mg/dL (26.5 mmol/L) or initiation of renal replacement therapy

AKI acute kidney injury, *sCr* serum creatinine

vasoconstricting drugs. The main options include terlipressin, norepinephrine, and the combination of midodrine/octreotide. In Europe, the vasoconstrictor of choice is terlipressin, combined with intravenous albumin (20–25%) 20–40 g/day [11]. Intravenous albumin plays various roles: it increases the ECV, improves renal perfusion, and has immunomodulatory properties to reduce systemic inflammation [12]. Terlipressin compensates for pathological vasodilation by increasing ECV so that the combined use of terlipressin with albumin results in higher response rates than with albumin alone (77% vs. 33%; $p = 0.03$) [13]. Terlipressin can be administered by intravenous boluses at an initial dose of 1 mg every 4–6 h. However, continuous intravenous administration at an initial dose of 2 mg/day may reduce the rate of its adverse effects [14].

3.3.2 Diagnostic Algorithm and Treatment

In most cirrhotic patients with the mildest form of AKI (AKI 1A), the condition resolves with close monitoring and withdrawal of nephrotoxic drugs. However, in patients with more aggressive forms of AKI (AKI 1B, 2, 3), the withdrawal of nephrotoxic drugs is insufficient, and albumin expansion at a test dose of 1 g/kg should be administered for 48 h. HRS must be considered if the patient does not recover from renal failure or progresses despite this volume expansion (Fig. 1) [15]. Of note, non-selective β-blockers have also been associated with HRS and should be discontinued [9, 16]. Renal replacement therapy should be considered in the management of HRS patients who do not respond to vasoconstrictors or in those with end-stage kidney disease. The indications for renal replacement therapy are the same in patients with cirrhosis as in the general population (severe electrolyte or acid-base imbalance, volume overload, and symptomatic azotemia) [17]. These indications can be useful bridging therapy in very ill patients prior to liver transplantation.

3.3.3 Use of Non-steroidal Anti-inflammatory Drugs in Patients with Cirrhosis

Pharmacological nephrotoxicity, mainly from non-steroidal anti-inflammatory drugs (NSAIDs), is a frequent complication in patients with advanced liver disease. Portal hypertension and vasodilation that occur in cirrhosis results in a decrease in ECV. This is compensated for by the intrarenal release of prostaglandins, which produce vasodilation of the afferent artery and better renal perfusion. However, anti-inflammatory drugs block this compensatory mechanism and can compromise renal perfusion. Although the impairment of renal perfusion associated with NSAIDs is usually mild and transient, in about one-third of cases it has a persistent or progressive course; in these patients, the prognosis

is potentially serious and the mortality rate is significantly higher [18].

4 Acute-on-Chronic Liver Failure (ACLF)

Acute-on-chronic liver failure (ACLF) is a syndrome in cirrhosis characterized by acute decompensation (AD), organ failure(s), and high short-term mortality [19]. According to the European Association for the Study of the Liver, based on the CANONIC study, ACLF is defined as hepatic and extrahepatic failure triggered by precipitating factors (hepatic and/or extrahepatic) in patients with acutely decompensated cirrhosis. In addition, the short-term mortality associated with ACLF is high (> 15% at 28 days), which differentiates it from acutely decompensated cirrhosis, where mortality is much lower. Acute organ failure, according to the Liver Failure Consortium scoring parameters is liver failure (bilirubin > 12 mg/dL), kidney failure (sCr > 2 mg/dL), severe encephalopathy, coagulopathy (international normalized ratio > 2.5), circulatory failure that requires vasoactive drugs, and respiratory failure (ratio of arterial oxygen partial pressure [PaO_2] to fractional inspired oxygen [FiO_2] < 200) [20].

The clinical presentation of ACLF is very heterogeneous and is classified according to the number of affected organs. Grade 1: organ failure in only the kidney or another organ accompanied by kidney and/or cerebral damage; grade 2: failure in two organs; grade 3: failure in three organs; grade 4: failure in four organs. This classification is essential for determining prognosis because a higher grade of ACLF corresponds to a worse prognosis (28-day mortality rate >15%) [Table 2]. ACLF is not a static process but a dynamic process, and up to 50% of ACLF cases improve or resolve, 20% worsen, and 30% remain stable [21].

4.1 ACLF Pathophysiology

Hepatic or extrahepatic precipitating factors (such as infections, alcohol, etc.) stimulate the release of factors that mediate inflammation and there is a higher degree of systemic inflammation than in decompensated cirrhosis. This massive release of inflammatory factors produces systemic inflammation and cellular oxidative stress, which cause tissue damage due to hypoperfusion, immune-mediated tissue damage, and direct mitochondrial damage, eventually causing multi-organ failure [22–24].

4.2 ACLF Treatment

Treatment is based on four pillars: management/removal of triggers, support techniques, artificial functionality
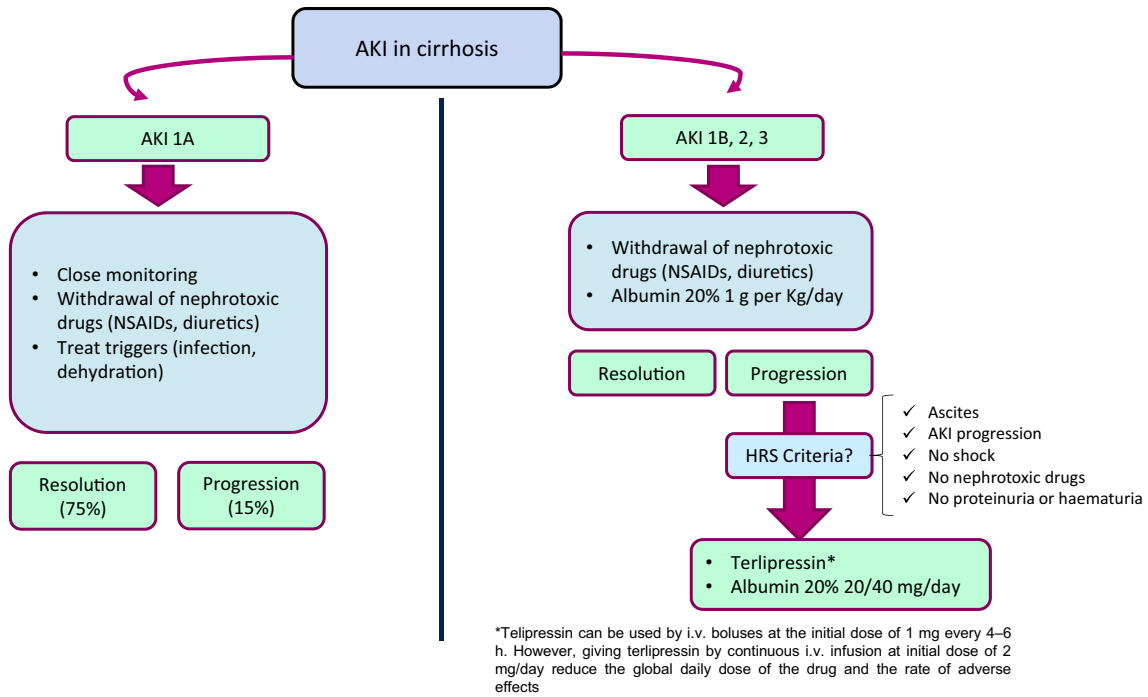
Fig. 1 Diagnostic and treatment algorithm for AKI in cirrhosis. *AKI* acute kidney injury, *NSAIDs* non-steroidal anti-inflammatory drugs, *HRS* hepatorenal syndrome, *IV* intravenous

techniques, and transplantation. Unfortunately, there is no specific treatment for ACLF. When infections are the suspected trigger, patients require intensive screening, early broad-spectrum antibiotic therapy, and daily reassessment. The prevention of ACLF progression, including early and aggressive treatment of infections, is crucial and the treatment response is conditioned by the degree of ACLF (52%,

42%, and 8% grade 1, grade 2, and grade 3, respectively) [24]. Patients with alcoholic hepatitis should be advised to abstain from alcohol and may benefit from the use of corticosteroids in the absence of active infections and when ACLF is severe. Patients with variceal bleeding require hemodynamic control, early antibiotic prophylaxis [25], and the application of transjugular intrahepatic portosystemic

Table 2 Acute-on-chronic liver failure classification. Adapted from Arroyo et al. [19]

Organ failure (OF)	Mortality at 28 days	ACLF Grade
Absence of OF	4.4%	No ACLF
Single OF (non-renal, without kidney / cerebral damage)	6%	No ACLF
Isolated renal OF	19%	Grade 1 ACLF
Single OF + kidney / cerebral damage	28%	Grade 1 ACLF
2 OFs	32%	Grade 2 ACLF
3 OFs	68%	Grade 3 ACLF
4 OFs	89%	Grade 4 ACLF

AKI acute kidney injury, *sCr* serum creatinine, *OF* organ failure, *ACLF* acute-on-chronic liver failure

shunts (TIPS) as needed. Notably, the insertion of a pre-emptive TIPS has demonstrated a clear survival benefit in patients with ACLF who fulfill specific criteria (Child–Pugh B > 7 with active bleeding at the time of endoscopy and Child–Pugh C < 14) [26].

It is important to detect hemodynamic failure with regard to organ support, which can lead to kidney failure and the need for vasoactive drugs. In addition, it is also important to consider possible neurological failure (hepatic encephalopathy) that should be monitored and treated early with specific treatment (osmotic laxatives [lactulose] and non-absorbable antibiotics [rifaximin]) [27].

Two fundamental studies—RELIEF [28] and PROMETHEUS [29]—assessed artificial liver support techniques in these patients but neither demonstrated a short-term survival benefit with this approach.

Liver transplantation is the definitive treatment for ALCF, curing both the ACLF and the underlying liver disease. However, some concerns deserve consideration, particularly the brief accessibility of ACLF patients to liver transplantation, the complex evaluation of candidates, the poor survival outcomes of transplantation, and futility. The prognosis of patients with grade 3 ACLF is ominous regardless of their model for end-stage liver disease (MELD) score [30]. Liver transplantation positively impacts severe forms of ACLF and increases survival. Nevertheless, the result is highly conditioned by the degree of ACLF and number or type of organ failure in the patient, negatively impacting respiratory and hemodynamic function [31]. In addition, patients with three or more organ failures or CLIF-ACLF score > 64 must be carefully evaluated for other factors associated with poor survival after liver transplantation, including mechanical ventilation at the time of transplantation, lactate level > 4 mmol/L, normal leukocyte count, older age of the recipient, and use of marginal organs [32]. Therefore, early intervention is a fundamental factor in identifying and treating patients who may be appropriate candidates for transplantation.

5 Cardiopulmonary Complications in Cirrhosis

Up to 70% of patients with cirrhosis report dyspnea or hypoxemia at some point during disease progression [33]. Although several cardiopulmonary pathologies can coexist in patients with cirrhosis, some are pathophysiologically linked to portal hypertension: hepatic hydrothorax, hepatopulmonary syndrome (HPS), portopulmonary hypertension (PoPH), and cirrhotic cardiomyopathy.

5.1 Hepatic Hydrothorax

Hepatic hydrothorax is a relatively frequent complication (occurring in 5–10% of patients with cirrhosis) and is associated with high morbidity and mortality. Pathophysiologically, hepatic hydrothorax develops when ascitic fluid passes into the pleural cavity through communications in the diaphragm, assisted by the patient's malnourished state/wasting syndrome and the increase in abdominal pressure [34].

Treatment of hepatic hydrothorax is a challenge. Initial treatment is a low-sodium diet with a diuretic (spironolactone + furosemide) and thoracocentesis, but if the patient does not respond to repeated thoracentesis, TIPS and transplantation should be considered (Fig. 2). Unfortunately, TIPS placement is less effective in controlling hydropic decompensation in patients with hepatic hydrothorax than in patients with pure refractory ascites [35].

5.2 Hepatopulmonary Syndrome

HPS is a relatively frequent complication in cirrhotic patients. It is defined by analytical characteristics (PO_2 < 80 mmHg and a high alveolar-capillary gradient [> 15 mmHg]), structural features (arteriolar vasodilation and/or presence of intrapulmonary shunts), and the presence of portal hypertension due to either cirrhosis or non-cirrhotic causes [36].

The pathophysiology of HPS is characterized by systemic and pulmonary vasodilation and a progressive increase in cardiac output. This results in inadequate gas exchange, which is even more pronounced in the presence of a vascular shunt and inflammatory infiltrate at the interstitial level [36]. The characteristic signs and symptoms of HPS are platypneas with orthodeoxia or a state of desaturation when the patient is sitting due to a marked imbalance in the ventilation/perfusion ratio, caused by blood accumulating at the base of the lungs due to vasodilation. Diagnostic confirmation of this pulmonary vasodilation requires contrast echocardiography with agitated saline solution or scintigraphy with technetium-99m [37, 38]. Computed tomography angiography (CTA) can also reveal true intrapulmonary shunts, which support the diagnosis and opens up the therapeutic option of shunt occlusion.

No drug has shown efficacy in controlling this syndrome. TIPS appear to induce transient but not definitive improvements [39]. Currently, the only definitive treatment is liver transplantation, which is effective even in patients with severe HPS [40].
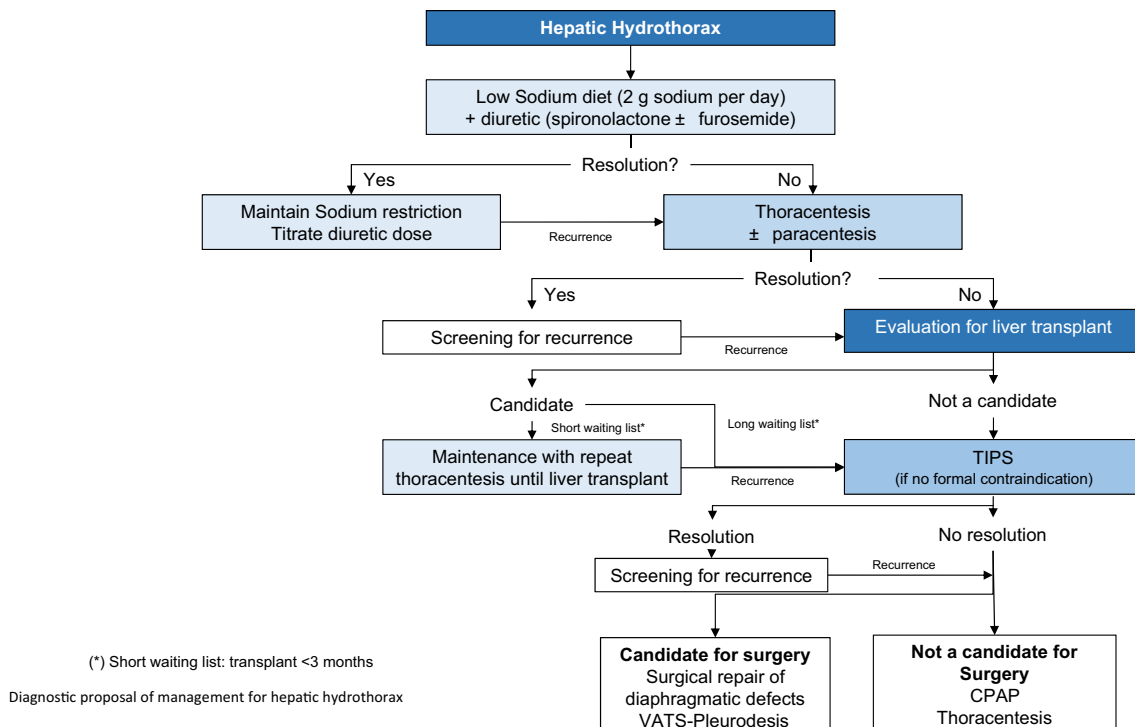
Fig. 2 Treatment algorithm of hepatic hydrothorax. *TIPS* transjugular intrahepatic portosystemic shunts, *CPAP* continuous positive airway pressure, *VATS* video-assisted thoracoscopic surgery

5.3 Portopulmonary Hypertension

PoPH is a severe form of Group 1 pulmonary arterial hypertension requiring vasodilator treatment and liver transplantation in selected cases. PoPH is defined as the presence of a mean pulmonary arterial pressure (mPAP) of ≥ 25 mmHg at rest, pulmonary vascular resistance ≥ 3 Wood Units, and pulmonary capillary pressure < 15 mmHg [41, 42]. Hemodynamic assessment is used to classify the severity of the disease as mild (mPAP < 35 mmHg), moderate (35–45 mmHg), or severe (> 45 mmHg).

The pathophysiology of PoPH is currently unknown but it is assumed that the hyperdynamic hypercirculation in cirrhosis induces shear stress in the pulmonary vascular endothelium [43]. Moreover, vasoconstriction mediated by enteric molecules that reach systemic circulation by portosystemic shunts can also contribute.

Any patient with portal hypertension, regardless of the cause, can develop PoPH. Nevertheless, it is important to rule out PoPH in candidates for liver transplantation, candidates for TIPS placement, those who present signs and symptoms of the disease, or those with suggestive electrocardiographic abnormalities such as right bundle branch block [44]. Therefore, the screening method of choice is the transthoracic echocardiogram.

Pharmacological treatment is not simple. Different drugs used in pulmonary hypertension have been tested and, to date, only macitentan has shown efficacy in randomized phase III studies (Table 3) [45]. Thus, treatment must be individualized depending on the experience of each center. Pulmonary vasodilators should be used cautiously in patients with ascites and patients closely monitored for possible adverse effects. Transplantation does not always reverse PoPH and it is difficult to establish which patients may benefit from transplantation. Therefore, severely ill patients are generally excluded and those with mild/moderate PoPH who respond well to vasodilators are selected.

5.4 Cirrhotic Cardiomyopathy

Systemic inflammation in patients with cirrhosis induces a series of changes that can lead to cardiac alterations [9]. Cirrhotic cardiomyopathy encompasses a set of common structural, functional, and electrophysiological alterations that have not been well defined. Consequently, the prognostic implications of this condition are not well known. The main echocardiographic feature is diastolic dysfunction, which is an early sign of cardiomyopathy in the setting of

Table 3 Pharmacologic treatment of portopulmonary hypertension. Adapted from Krowka et al. [36] and Krowka et al. [45]

Pharmacologic class	Drugs	Dosage	Hepatic Toxicity	Effect on portal hypertension	Improves
Endothelin receptor antagonists	Macitentan[a]	Oral (1/24 h)	Rare	Decreases intrahepatic resistance	Symptoms
	Bosentan	Oral (2/24 h)	Frequent		Functional capacity
	Ambrisentan	Oral (1/24 h)	Rare	Decreases portal pressure (animal)	Hemodynamics
PDE inhibitors	Sildenafil	Oral (3/24 h)	Rare	Decreases intrahepatic resistance	Symptoms
	Tadalafil	Oral (1/24 h)		Increases splanchnic flow	Functional capacity
					Hemodynamics
Guanylate cyclase stimulators	Riociguat[b]	Oral (3/24 h)	Rare	Decreases portal pressure (animal)	Symptoms
					Functional capacity
					Hemodynamics
Prostanoids	Epoprostenol	IV	Cytoprotective action	Increases splanchnic flow	Symptoms
	Treprostinil	Inhaled		Equalizes HVPG (humans)	Functional capacity
	Iloprost				Hemodynamics
	Selexipag/beraprost	Oral			

HVPG hepatic venous pressure gradient, *PDE* phosphodiesterase, *IV* intravenous

[a]PORTICO clinical study (phase IV) [60]

[b]PATENT-1 clinical study (phase III) [61]

normal systolic function [46], although the clinical relevance of diastolic dysfunction is not clear [47, 48]. In contrast, some patients can develop systolic impairment, which can be detected by sophisticated techniques such as dynamic stress tests, myocardial strain imaging, and cardiac magnetic resonance imaging [49–51]. In addition, systolic dysfunction (i.e., low cardiac output) is implicated in the pathophysiology of HRS [8]. Finally, prolonging the QTc interval is common in cirrhosis and is associated with a worse outcome [52] but the risk of sudden death is unclear. There are two clinical scenarios where a detailed cardiac function is mandatory: patients who are candidates for liver transplantation [53], and as part of the assessment for TIPS insertion [54].

6 Adrenal Insufficiency in Cirrhosis

Adrenal insufficiency mainly appears in critically ill cirrhotic patients and implies a worse prognosis. Cortisol is a pluripotent hormone involved in adaptation to stress and is secreted by the adrenal gland in response to adrenocorticotropic hormone (ACTH). Pituitary secretion of ACTH is stimulated by various cytokines and other inflammatory mediators during stress, leading to fluctuating cortisol levels during critical illness and sepsis. Relative adrenal insufficiency may appear in 50–77% of critically ill patients with cirrhosis [55, 56]. Indeed, although cortisol levels may be within the normal range, they are still insufficient to guarantee vascular tone and prevent vascular permeability in cirrhosis. Several hypotheses explain the high incidence of adrenal insufficiency in patients with cirrhosis, although the most

accepted is related to the state of chronic systemic inflammation and hypoperfusion of target organs in the most advanced stages of the disease. The diagnosis of adrenal insufficiency in cirrhosis is complex and relies on measuring plasma levels before and after adrenal stimulation with synthetic corticotrophin. At present, the diagnostic criteria are not clear. Nevertheless, baseline cortisol values of < 15 µg/dL or an increase in cortisol after ACTH of < 9 µg/dL in patients with baseline cortisol < 35 µg/dL have been proposed. There are contradictory data regarding the beneficial effects of hydrocortisone administration but it appears to shorten the length of stay in the intensive care unit [57–59].

7 Conclusions

Decompensated liver cirrhosis is a complex clinical scenario that requires specialized management. Increasing knowledge about the underlying pathophysiological processes and new therapeutic and prophylactic approaches may increase the survival of patients with cirrhosis. Renal impairment is crucial in the natural history of decompensation and should be recognized early. ACLF is a life-threatening complication where the treatment of precipitants and liver transplantation play the central therapeutic role. Cardiopulmonary complications are rare decompensation events but specific treatments are available.

Declarations

Conflict of interest Luis Téllez and Antonio Guerrero declare they have no conflicts of interest.

Ethics approval This article was based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material Not applicable.

Code availability Not applicable.

Authors' contributions All authors contributed to the conception and design, analysis and interpretation of data, drafting the article and revising it critically for important intellectual content, and final approval of the version to be published.

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