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Update in the treatment of the complications of cirrhosis

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Abstract

Cirrhosis consists of two main stages: compensated and decompensated, the latter defined by the development/presence of ascites, variceal hemorrhage and hepatic encephalopathy. Survival is entirely different depending on the stage. Treatment with non-selective beta-blockers prevents decompensation in patients with clinically significant portal hypertension, changing the previous paradigm based of the presence of varices. In patients with acute variceal hemorrhage at high risk of failure with standard treatment (defined as those with a Child-Pugh score of 10–13 or those with Child-Pugh score of 8–9 with active bleeding at endoscopy), pre-emptive transjugular intra-hepatic porto-systemic shunt (TIPS) improves mortality and has become the standard of care in many centers. In patients with bleeding from gastrofundal varices, retrograde transvenous obliteration (in those with a gastrorenal shunt) and/or variceal cyanoacrylate injection have emerged as alternatives to TIPS. In patients with ascites, emerging evidence suggests that TIPS might be used earlier, before strict criteria for refractory ascites are met.. Long term albumin use is under assessment for improving prognosis of patients with uncomplicated ascites and confirmatory studies are ongoing. Hepatorenal syndrome is the least common cause of acute kidney injury in cirrhosis, and first line treatment is the combination of terlipressin and albumin. Hepatic encephalopathy has a profound impact on the quality of life of patients with cirrhosis. Lactulose and rifaximin are first and second-line treatment for hepatic encephalopathy. Newer therapies such as L-ornithine L-aspartate and albumin require further assessment.

Keywords

cirrhosis; portal hypertension; variceal hemorrhage; ascites; hepatic encephalopathy

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Cirrhosis consists of two main stages: compensated (asymptomatic) and decompensated, the latter defined by the development/presence of ascites, variceal hemorrhage and hepatic encephalopathy [1]. Survival is entirely different depending on stage. While the median survival in the compensated stage exceeds 15 years, the median survival in the decompensated stage is around 1.5 years (ranging from 2 to 4 years) [2]. Therefore, compensated and decompensated cirrhosis should be considered separate entities.

The main pathophysiological mechanism leading to cirrhosis decompensation is the severity of portal hypertension. This was demonstrated in a sub-analysis of a prospective cohort study of patients with compensated cirrhosis with no or small varices, 29% of whom developed decompensation on follow-up [3]. In these patients, the main determinant of decompensation was a portal pressure (as determined by the hepatic venous pressure gradient) ≥ 10 mmHg, the pressure gradient that now defines “clinically-significant portal hypertension” (CSPH).

Until recently, the approach and management of patients with compensated cirrhosis had been mostly focused on preventing variceal hemorrhage in those with high-risk varices on endoscopy. However, ascites, not variceal hemorrhage, is the most common decompensating event [2, 3] even in a recent series of patients with cirrhosis due to nonalcoholic steatohepatitis [4]. Ascites is also the decompensating event associated with the highest mortality [5]. Therefore, a loftier goal in the patient with compensated cirrhosis would be the ability to prevent not only variceal hemorrhage, but also ascites. It follows that measures to decrease portal pressure, particularly in those with CSPH, would result in prevention of cirrhosis decompensation.

Non-selective beta-blockers (NSBB) such as propranolol and nadolol decrease portal pressure via both β1 (decrease in cardiac output) and β2 (splanchnic vasoconstriction) adrenergic blockade. Carvedilol, in addition to blocking β1 and β2 receptors, also has α1 adrenergic blockade activity that may act by decreasing intrahepatic resistance, thereby resulting in a greater decrease in portal pressure compared to propranolol [6].

In a landmark randomized double-blind, placebo-controlled trial (PREDESCI) that included patients with cirrhosis mostly due to chronic hepatitis C, and with clinically-significant portal hypertension (CSPH), NSBB were associated with a significant, 49% lower risk of decompensation compared to placebo [7]. Ascites was the decompensating event that was significantly lower in the NSBB arm (58% reduction in the risk of ascites). Additionally, the risk of developing high risk varices (the study excluded patients with large varices at entry) was 40% lower in the NSBB group. The specific NSBB used in those randomized to this arm was propranolol (67%) or carvedilol (33%) based on pre-randomization response to IV propranolol. Post-hoc analysis showed that carvedilol outperformed propranolol both in terms of reducing portal pressure and in preventing decompensation. These results further support the recent Baveno consensus statement that carvedilol should be the preferred NSBB to be used in cirrhosis. [8]

In the PREDESCI trial, patients with compensated cirrhosis at a higher risk of decompensation were selected based on the presence of CSPH. Determining the presence of

CSPH requires an invasive and nuanced procedure (catheterization of the hepatic vein) that, while invaluable in clinical research, is impractical and not recommended in daily clinical practice. This is particularly the case now that there are non-invasive methods that can accurately predict the presence of CSPH. Two multicenter studies have now demonstrated that liver stiffness measurements (LSM) (by transient elastography) and platelet count can predict the probability of having CSPH [9, 10]The risk of having CSPH can be calculated using a nomogram included in these studies and that have been translated into two easier to use cutoffs that will predict a >60% probability of having CPSH: a LSM >25 kPa or a LSM 20–25 kPa plus a platelet count <150/mm^3. Although the positive predictive value of these thresholds were described as being lower in obese patients with NASH cirrhosis, a recent large study in NASH cirrhosis shows that they are applicable to all patients with NASH cirrhosis [11].. Therefore, these cutoffs have been recommended by the Baveno consensus that state that, although the concept of CSPH is HVPG-driven, noninvasive tests are sufficiently accurate to identify CSPH in clinical practice.

Therefore, the greatest paradigm change in the management of compensated cirrhosis is to forego screening endoscopy and instead, to screen for the presence of CSPH by using noninvasive tools and to start carvedilol (dose 3.25 to 25 mg/day) in those with CSPH. In patients with compensated cirrhosis with contraindications/intolerance to NSBB, one would revert to the old paradigm by which the patient would have a screening endoscopy and high-risk varices would undergo ligation, which would only prevent variceal hemorrhage but not ascites (Figure 1).

1) Variceal Hemorrhage

a) Prevention of a first variceal hemorrhage in patients with decompensated cirrhosis: when to start.

While in patients with compensated cirrhosis the presence of varices has become less relevant for therapeutic decisions, in patients with decompensated cirrhosis an upper endoscopy is still indicated in all cases. Small varices in decompensated cirrhosis carry the same risk of bleeding as large varices in compensated cirrhosis. Therefore, Baveno VII consensus [8] recommends that in patients with ascites, NSBBs may be used to prevent first variceal hemorrhage in varices of any size. Considering the greater portal pressure-reducing effect [12] and the easier titration, carvedilol is preferred in cirrhosis [8].

b) Advances in the treatment of acute esophageal variceal hemorrhage and the concept of pre-emptive TIPS

Mortality from acute esophageal variceal hemorrhage has markedly decreased from 40% at 6 weeks in series published in the 1980s [13] to 15–20% in the 1990s [14], but this has not further improved in the 2000s [15]. The advances in hemostatic treatment with drugs, endoscopy and TIPS resulted in most deaths no longer being due to ongoing bleeding, but to infections and worsening liver and kidney failure [14], which made it difficult to further reduce mortality. A breakthrough arose with the concept of pre-emptive TIPS [16]. The idea was that most patients experiencing early rebleeding were also those at higher risk of dying, i.e. those with worse liver failure that would not tolerate a second hit. Hence, the proposal

was to place TIPS pre-emptively in patients that were at high risk of rebleeding (Child-Pugh B with active bleeding or Child-Pugh C) [17], even if bleeding was initially controlled with pharmacological and endoscopic treatment.

Four trials have been conducted assessing pre-emptive TIPS (pTIPS) as compared with standard therapy (pharmacological and endoscopic therapy, using TIPS only as rescue therapy). Meta-analysis of the four trials [18] shows a large effect on mortality (RR: 0.33, or a 67% reduction in the relative risk of death), but with a wide confidence interval (0.08–1.36), reflecting the small number of patients (n=302) included in those trials.

Another recent individual patient meta-analysis, using data from additional observational studies, suggested a minimal threshold of Child-Pugh B of 8 points (with active bleeding at endoscopy) for pTIPS to improve survival [19]. On this basis, recent North American consensus on the use of TIPS [20] and Baveno [8] recommend pTIPS in patients with Child Pugh class C<14 points or Child class B >7 with active bleeding at initial endoscopy. This seems reasonable until the results of a large UK randomized trial (n=294) of pTIPS (https://fundingawards.nihr.ac.uk/award/NIHR130883) become available.

2) Prevention of recurrent bleeding (secondary prophylaxis)

In patients not undergoing pTIPS during the index admission, the standard first line therapy is the combination of NSBBs and endoscopic variceal ligation [8] with TIPS reserved for treatment failures. An exception may be patients with portal vein thrombosis. In these patients, a recent RCT [21] showed that TIPS was superior to NSBBs + variceal ligation in preventing rebleeding and was associated with increased portal vein recanalization, without differences in survival or encephalopathy. This suggests that TIPS might be the preferred first-line option in patients with portal vein thrombosis.

a) The controversy regarding the therapeutic window for beta-blockers

The potential of NSBBs to induce acute kidney injury (AKI) in patients with ascites was recognized early after the first proposal of propranolol for the treatment of varices [22]. However, it was not until 2010 that a prospective observational study raised for the first time the possibility of harm with NSBBs in patients with refractory ascites [23], ushering the concept of the “therapeutic window” [24]. However, subsequent meta-analysis of observational studies showed no association between NSBBs and mortality in patients with refractory ascites [25]. Furthermore, a recent RCT in patients with ACLF challenged the concept of a therapeutic window, showing a decreased 28-day mortality in patients treated with carvedilol as compared with placebo [26]. Arterial pressure has shown to be an excellent biomarker to determine when NSBBs might not offer benefit. A recent observational study [27] showed that transplant-free survival was not improved if NSBB were associated with MAP<65 mmHg or systolic blood pressure <90 mmHg.

b) Treating gastric varices

Hemorrhage from gastric varices is much less frequent than hemorrhage from esophageal varices, and there are few RCTs to support treatment decisions. The management of gastroesophageal varices type 1 (GOV1, those extending into the lesser curvature) is

comparable to the management of esophageal varices [8]. Gastrofundal varices which consist of varices in the fundus with (GOV-2) or without (IGV-1)extension into the esophagus,) have specific vascular anatomy and distinct management (Figure 2). First-line endoscopic treatment is cyanoacrylate injection [28]. TIPS is effective, although usually requires variceal embolization, and can be used as first-line especially in centers with limited experience with cyanoacrylate.

Retrograde transvenous obliteration (RTO) was for many years a routine treatment in Japan and Korea, but a rarity in Western countries. In the last decade it has become widely used in many centers in North America and Europe [28]. RTO requires the presence of a gastrorenal shunt (Figure 2), that is cannulated retrogradely allowing the obliteration of the varices. The original technique (balloon-occluded RTO or BRTO) required maintaining an intravenous catheter with an inflated balloon for a prolonged time (6– 36 hours), which created significant logistical issues. The technique has evolved with the development of plug assisted RTO (PARTO) and coil assisted RTO (CARTO) [29] that achieve complete variceal obliteration in less than an hour and have contributed to a wider applicability. By redirecting flow from the gastrorenal shunt to the liver, RTO may improve liver function and hepatic encephalopathy and, thus, can be performed in patients that are poor candidates for TIPS. However, it can result in an increase in portal pressure, with the development of new ascites, hydrothorax and esophageal varices. A recent RCT compared RTO with repeated cyanoacrylate injection in the prevention of gastric variceal rebleeding in 64 patients, showing a higher efficacy of RTO, withoutdifferences in survival, complications or in the rate of worsening esophageal varices [30].

3) Ascites and Acute Kidney Injury

Ascites is the most frequent complication of cirrhosis, with an annual incidence of 5–10% in compensated cirrhosis [1, 31] While the prognostic significance of ascites detected only by ultrasound (mild or grade 1) is still undetermined, clinically-evident ascites (moderate or grade 2 and large or grade 3) is associated with a survival of only 30% at 5 years [1].

Ascites is a risk factor for spontaneous bacterial peritonitis (SBP) and other infections, hyponatremia and acute kidney injury (AKI), including the hepatorenal syndrome (HRS-AKI). It also predisposes to malnutrition, thus contributing to sarcopenia, frailty, and disability. These complications explain not only its higher mortality but also its association with frequent hospitalizations, poor quality of life and a heavy socio-economic burden.

AASLD and EASL guidelines provide consensus recommendations on diagnosis and treatment of ascites [32, 33]. Herein we discuss some issues that are still not fully clarified.

From a therapeutic perspective, ascites can be classified as responsive, recurrent or refractory (Table 1) [32, 33]. However, while responsive and refractory ascites represent the relatively homogeneous ends of the spectrum with a clear clinical phenotype and prognosis, the current definition of recurrent ascites does not fully reflect the heterogeneity of patients in this category. Further characterization of these patients will allow for a more precise allocation of patients to different treatments.

a) First line treatments

At present, no treatment is recommended for grade 1 ascites, as there is no evidence that any treatment will improve patient outcomes. In fact, these patients are strictly still compensated and could be treated with NSBB (see above). In patients with grade 2 and 3 ascites, a moderate low-sodium diet and diuretics are recommended with the goal of eliminating ascites or at least decreasing to grade 1. Rather than pursuing strict sodium restriction that will aggravate the already reduced caloric/nutrient intake of these patients [34], a major goal is to avoid excessive salt intake with food, even though this may be insufficient to obtain a negative sodium balance. Regular nutritional counselling is essential in patients with ascites and should be started even with grade 1 ascites.

Diuretic therapy is based on aldosterone antagonists alone or, more frequently, in combination with loop diuretics. However, with the epidemiological changes in the etiology of cirrhosis, there is an increase in concomitant renal injury, even subtle, due to hypertensive and/or diabetic nephropathy that will require lowering the dose of aldosterone antagonists and increasing the dose of loop diuretics with as yet uncertain effects. Recommendations on the use of diuretics are reviewed in recent AASLD and EASL guidelines [32, 33].

b) Second line treatments

There is more controversy regarding the management of patients who stop responding to diuretics or develop diuretic-related side-effects. Currently, two major options, still under evaluation, have emerged: TIPS, and long-term treatment with intravenous albumin (LTA).

Limited evidence indicates that TIPS placement at a stage earlier than refractory ascites is more effective and safer. First, a meta-analysis of individual data from RCTs all performed using bare stents, showed a more favorable impact on survival in the two trials that also included patients with recurrent ascites, compared to those enrolling only patients with refractory ascites [35]. Second, the only RCT assessing the new covered TIPS stents, included patients (median MELD 12) who had had no more than 6 large-volume paracenteses (LVP) in the last 3 months, showing a significant improvement in 1-year transplant free survival [36], even though some of the patients included could have met criteria for refractory ascites.

At present, TIPS should be considered in patients with *recurrent* ascites irrespective of the presence or absence of varices or history of variceal hemorrhage [8].

On the other hand, a large open-label Italian RCT (ANSWER), in patients with uncomplicated persistent grade 2/3 ascites despite moderate diuretic doses (median MELD 12), showed that LTA, in addition to standard medical treatment, significantly increased the number of patients remaining free of LVP and prolonged the interval between LVPs. Importantly, there was a decrease in the rate of complications of ascites, hospitalizations and death [37]. However, several factors limit LTA outside Italy, mainly the cost and logistics/ adherence to weekly intravenous infusion. Also, a placebo-controlled RCT performed in somewhat sicker patients with ascites (median MELD 17) showed no benefits of LTA (biweekly) plus midodrine in the need for LVP, complications of ascites or death [38]. Ongoing/future trials will help better define the patient population that will benefit from TIPS vs. LTA.

c) Treatment for refractory ascites

In patients with refractory ascites, TIPS should always be considered. Unfortunately, only in some of these patients can TIPS be performed safely and its use is limited by contraindications such as renal failure, cardiac diseases, and recurrent hepatic encephalopathy. With the aim of reducing side-effects, the use of small diameter PTFE-covered stents have provided promising results and a staged approach can be used with reassessment for need to further dilate the stent according to clinical response [20].

Standard of care is also based on periodic LVP followed by albumin supplementation to prevent circulatory dysfunction [39]. The administration of vasoconstrictor drugs aiming to expand effective volemia, including midodrine or clonidine, has been investigated in small studies which have not produced sufficient data to recommend their use [40, 41].

Finally, in patients with no other treatment options and need for frequent LVP, palliative care with implantation of a peritoneal catheter or, at least in some centers, the automated alpha-pump (not available in the USA) could be considered [42, 43].

d) General approach to the management of ascites

Treatment of cirrhosis etiology, when available, should be implemented as this represents the most effective approach and may lead to cirrhosis recompensation [8, 44]. Also, liver transplant evaluation should be undertaken with development of ascites. Finally, implementation of a “liver home” providing coordinated care among all caregivers should be encouraged and a remote monitoring and intervention strategy using digital systems should be further explored [45].

e) Acute kidney injury (AKI)

AKI is defined by an increase in serum creatinine of ≥0.3 mg/dL within 48 hours or ≥50% increase in serum creatinine that is known or presumed to have occurred within the preceding 7 days and is graded in three stages [46] Notably, in patients with cirrhosis, serum creatinine overestimates glomerular filtration rate because of a combination of decreased creatinine production and muscle wasting.

AKI is present in 25–50% of hospitalized patients with cirrhosis and is associated with a poor prognosis. The main causes of AKI are, in order of frequency, hypovolemia, acute tubular necrosis, and hepatorenal syndrome (HRS-AKI) [32].

The AASLD and EASL guidelines provide consensus recommendations on classification, differential diagnosis and management of AKI [32, 33]. Herein we discuss some specific aspects related to HRS-AKI, the type of AKI unique to patients with cirrhosis and ascites.

HRS-AKI is the least common type of AKI, representing about 15–30% of all AKI cases [18]. Diagnosis of HRS-AKI is challenging and is usually a diagnosis of exclusion (Figure 3) [32, 33, 46]. Patients with cirrhosis, ascites and AKI not responding to withdrawal of nephrotoxic drugs, reduction or withdrawal of diuretics, treatment of infections, and fluid replacement in presence of severe volume depletion, should receive plasma expansion with albumin (1 g/kg up to a maximum of 100 grams) for 2 consecutive days. HRS-AKI is a likely diagnosis

in patients who do not respond and should be started on vasoconstrictors (Figure 3). Terlipressin is the vasoconstrictor of choice as it has shown to be superior to the combination of midodrine and octreotide [47], achieving the reversal of AKI-HRS in about 30–50% of cases [47, 48]. Norepinephrine represents a valid alternative [49], but its administration usually requires admission to an intensive care unit (ICU) and a recent report has shown that it is less effective than terlipressin at least in patients with ACLF [50].

Treatment with terlipressin is combined with intravenous albumin and is not infrequently associated with potentially severe side-effects, mainly related to tissue ischemia and pulmonary edema [48]. The risk of ischemic side-effects can be reduced by administering terlipressin in intravenous continuous infusion instead of boluses every 4–6 hours [51]. However, in US centers this may require transfer to a more advanced level of care. Treatment should be avoided in patients with hypoxemia and in those with ongoing coronary, peripheral or mesenteric ischemia. Careful assessment of volume status and oxygenation should be performed at bedside (e.g. point-of-care ultrasound) throughout treatment.

Although the absence of structural kidney damage is a diagnostic criterion for HRS-AKI, it could develop in patients with pre-existing subtle organic nephropathy particularly with a higher prevalence of metabolic and alcoholic cirrhosis. Furthermore, the kidneys of patients with HRS-AKI may have a certain degree of histological damage [52]. This will make even more challenging the diagnosis and treatment of HRS-AKI and will likely lead to an even worse response.

Because treatment of HRS-AKI has no effect on mortality, patients should be evaluated for liver transplantation. In patients not responding to vasoconstrictors and albumin, candidacy for renal replacement therapy and/or transplantation (liver or kidney/liver) should be discussed by a multidisciplinary team.

4) Hepatic Encephalopathy

Hepatic encephalopathy (HE) is defined as brain dysfunction caused by hepatic insufficiency and or portosystemic shunting and is one of the most common and incapacitating complications of advanced liver disease [53, 54]. It ranges in severity from covert HE (reliably detectable only by neuropsychometric testing and affecting 20–80% of patients with cirrhosis) to overt HE (defined as ≥West Haven grade II and affecting up to 40% of patients with cirrhosis) [53, 54]. The AASLD and EASL guidelines provide consensus recommendations on multiple facets of diagnosis and treatment of HE [53, 54]. Here we highlight current concepts of pathophysiology-linked-to-clinical diagnosis and treatment of overt HE in patients with cirrhosis (Type C HE) to guide further reading.

a) Pathophysiology

Though not fully understood, the pathophysiology of HE is known to be multifactorial and is elegantly updated in a recent review [55]. Hyperammonemia and gut dysbiosis are key mechanisms in the pathogenesis of HE, and are linked to the mainstays of treatment, as well as novel therapies for HE.

b) Hyperammonemia

Hyperammonemia in stable outpatients with cirrhosis has been shown to predict not only the risk and frequency of HE, but also the risk of hospitalization for liver-related complications and mortality [56, 57]. In addition, ammonia scavengers combined with standard of care have been shown to reduce the risk of recurrent HE [58]. These findings support hyperammonemia as a key protagonist in HE. However, the only bed-side value for measured blood ammonia in cirrhosis with altered mental status is when it is normal, as this should direct a search for alternate reasons for altered mentation [54].

c) Gut Microbiome

The gut microbiome interacts with the host, food and medications, and significantly impacts cognitive function in cirrhosis and HE [53–55]. Dysbiosis in cirrhosis includes increased pathogenic and decreased autochthonous taxa, and impaired microbial functionality. Although poorly understood, the gut microbiome can predict clinical outcomes such as hospitalization, organ failure and death in cirrhosis [59]. Key HE therapies are thought to act through modulation of the gut microbiome function and associated dysbiosis and endotoxemia. Although rifaximin does not significantly reduce bacterial burden per se, it mitigates dysbiosis by driving a shift from pathogenic to beneficial metabolite linkages [60]. Probiotics also mitigate dysbiosis and endotoxemia, and have had some success in the prevention of recurrent HE [61, 62] Fecal microbial transplantation (FMT) can restore bacterial diversity and function, and reduce HE recurrence in cirrhosis, and is an exciting future direction in HE therapeutics [63].

d) Hepatic Encephalopathy in Acute-on-Chronic Liver Failure

Hepatic encephalopathy is a leading cause of hospitalization and readmission in patients with decompensated cirrhosis [64]. However, HE in the context of acute-or-chronic liver failure (ACLF), is characterized by distinct pathophysiology (exaggerated inflammatory responses with infection, sepsis, neuroinflammation, vasoconstriction, hyponatremia and oxidative stress) and worse prognosis (higher mortality) [65, 66]. Though more studies are needed, there is mounting evidence that these distinct features of HE in ACLF may warrant specific therapies targeting hyperammonemia and inflammation [55].

e) Medical management

AASLD and EASL guidelines cover the treatment and secondary prevention of HE in detail, with lactulose as first-line and rifaximin as second line treatments, as well as nutritional measures to mitigate sarcopenia and addressing large portosystemic shunts [53, 54]. It is important to recognize racial and ethnic disparities in access to rifaximin for HE in the US, highlighting the need for legislative efforts to improve access to care [67].

Standard and other therapies for HE warrant mention and have been succinctly summarized in recent reviews (Table 2) [55, 68]. The targets of other therapies include (i) gut absorption of ammonia (osmotic laxatives), (ii) gut dysbiosis and production of ammonia (FMT, probiotics, engineered bacteria, carbon microspheres) (iii) nitrogen scavenging and ammonia clearance through ureagenesis (hepatic) and glutamine (hepatic and muscle) synthesis (L-Ornithine L-Aspartate (LOLA), ornithine phenylacetate, sodium/glycerol phenylbutyrate),

(iv) toxin binding (albumin, albumin dialysis), and (v) direct vigilance modulators such as golexanolone, a GABA-A receptor antagonist [55, 68]. Selected clinically available therapies are briefly discussed.

f) L-Ornithine L-Aspartate

L-Ornithine L-Aspartate (LOLA), a urea cycle substrate and an activator of glutamine synthetase, has been studied in both oral and intravenous form in the treatment and prevention of HE [69]. Interestingly, LOLA is now available as an over-the-counter oral supplement in the US. Therefore, it is worth understanding its potential therapeutic role in HE although there remains uncertainty regarding its benefit [68].

g) Albumin

Recent evidence shows that weekly albumin infusions in outpatients with HE is associated with improved neurocognitive testing and HRQOL, and less severe HE with improved survival in those with uncomplicated ascites [70, 71]. At present however, there are no guideline recommendations for albumin use in the prevention of recurrent HE in cirrhosis [53, 54].

h) Primary prevention of HE

There are scant data on the primary prevention of HE, but it has been recently re-examined in a large cohort of patients undergoing TIPS. Contrary to prior findings [72], initiation of rifaximin treatment 2 weeks before TIPS insertion reduced the risk of HE events within 6 months by approximately 50% [73]. Current EASL guidelines support the consideration of this strategy for prevention of HE post TIPS, although the role of treatment and risk of HE beyond 6 months is not known [54]. Outside of TIPS, a soluble solid dispersion of rifaximin has been studied for the prevention of cirrhosis-related hospitalizations or mortality and recurrent HE [74], and is currently under investigation for the prevention of HE in cirrhosis (ClinicalTrials.gov Identifier: NCT05071716).

Conflicts of interest:

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Abbreviations used in this paper:

ACLF	acute-on-chronic liver failure
AKI	acute kidney injury
CSPH	clinically significant portal hypertension

HE	hepatic encephalopathy
HRS	hepatorenal syndrome
LOLA	L-ornithine L-aspartate
LSM	liver stiffness measurement
LTA	long-term treatment with intravenous albumin
LVP	large-volume paracenteses
MELD	Model for End-stage Liver Disease
NASH	nonalcoholic steatohepatitis
NSBB	nonselective b-blocker
pTIPS	pre-emptive transjugular intrahepatic portosystemic shunt
RTO	retrograde transvenous obliteration
TIPS	transjugular intrahepatic portosystemic shunt

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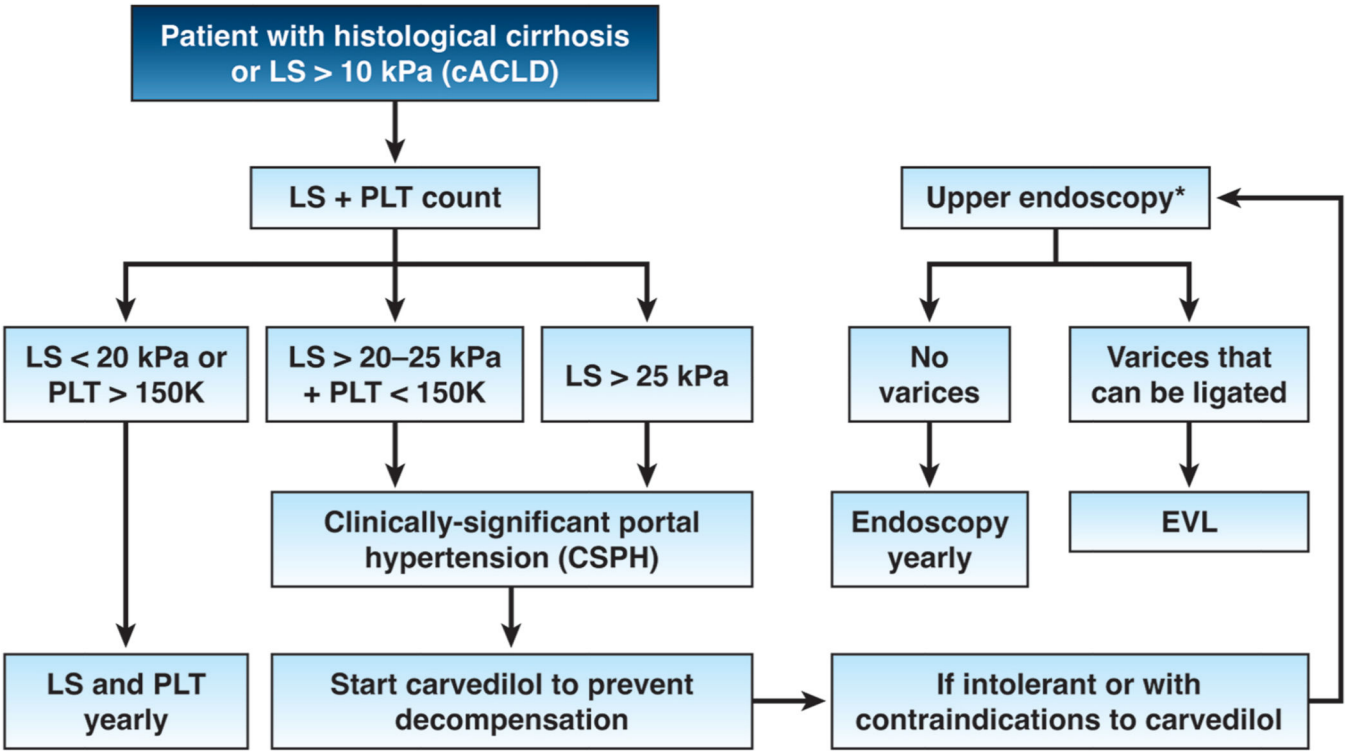

Figure 1.

The presence of clinically-significant portal hypertension (CSPH, determined noninvasively) establishes the indication for carvedilol with the goal of preventing cirrhosis decompensation. cACLD= compensated advanced chronic liver disease (noninvasive surrogate of compensated cirrhosis); LS = liver stiffness; PLT= platelet count; EVL= endoscopic variceal ligation. *Patients with LS <20 kPa and PLT >150,000/mm3 can circumvent endoscopy because the risk of having high-risk varices is minimal

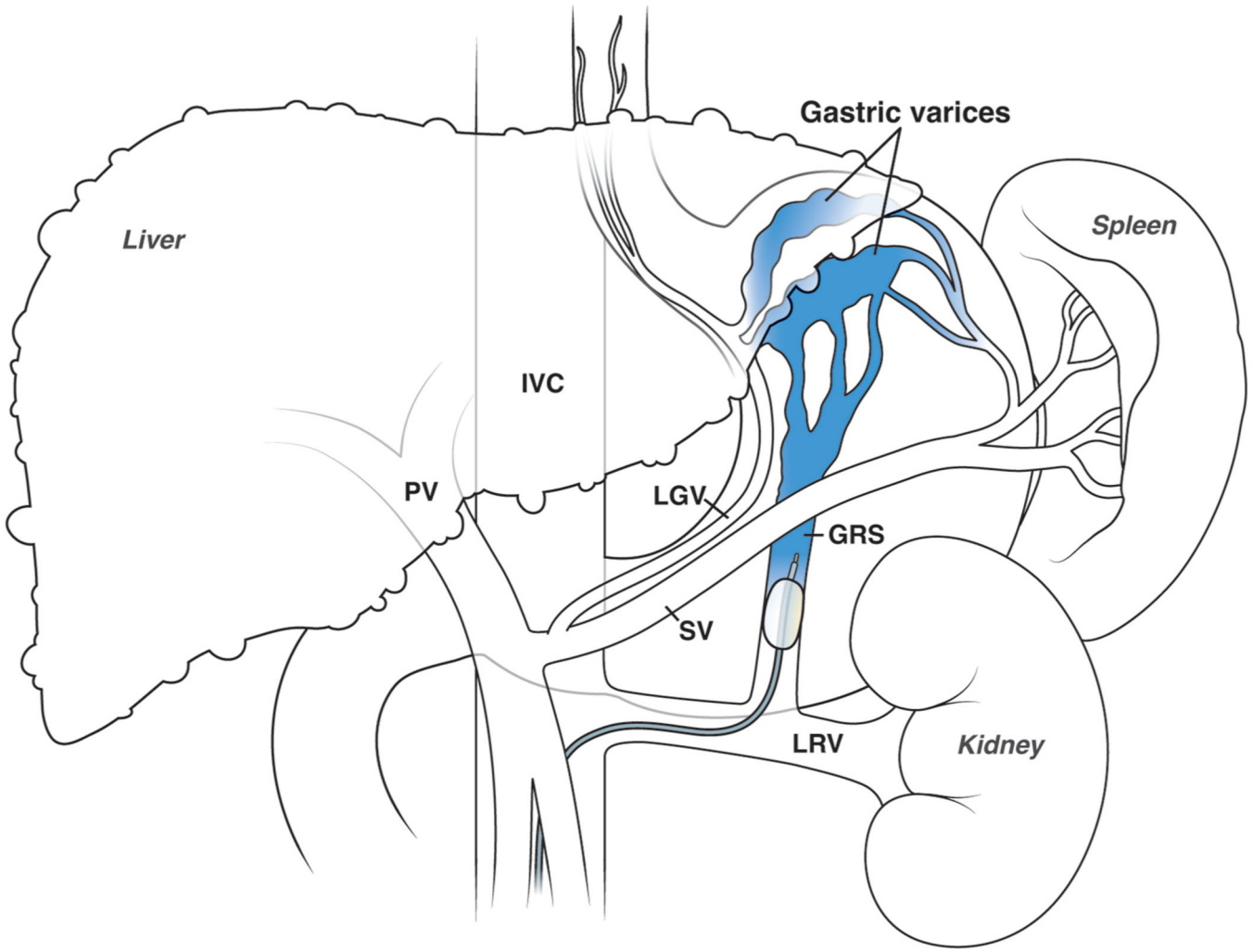

Figure 2.

RTO procedure (performed with balloon-occlusion or BRTO). A gastro-renal shunt (GRS), which usually connects the splenic vein (SV) and the left renal vein (LRV) creating the gastrofundal varices (GV) nidus in the fundus of the stomach, is a requisite for performing the procedure. The efferent of the GRS is catheterized and occluded with a balloon. Subsequent retrograde injection of a sclerosant obliterates the gastric varices.

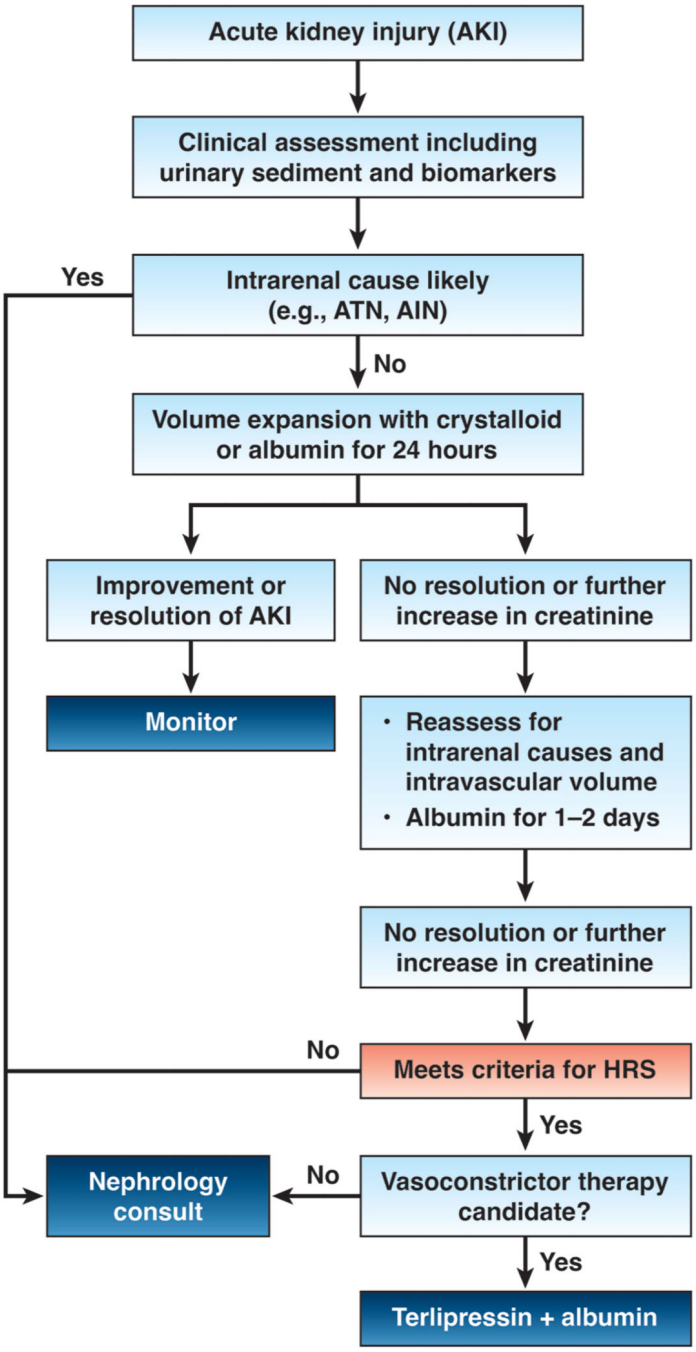

Figure 3.
Management algorithm in a patient with cirrhosis and ascites presenting with AKI.

Table 1.

Classification of ascites according to response to treatment

Responsive	Ascites that can be fully mobilized or limited to grade 1 with diuretic therapy associated or not to moderate dietary sodium restriction
Recurrent	Ascites that recurs on at least 3 occasions within a 12-month period despite dietary sodium restriction and adequate diuretic dosage
Refractory	Ascites that cannot be mobilized or the early recurrence of which (i.e., after large-volume paracentesis) cannot be satisfactorily prevented by medical therapy

Table 2.

A summary of therapeutic targets and related therapies in the treatment of hepatic encephalopathy in cirrhosis.

Therapeutic target	Therapies
Laxatives to decrease gut absorption of ammonia	Non-absorbable disaccharides (lactulose) Osmotic laxatives (polyethylene glycol)
Gut dysbiosis and gut production of ammonia	Antimicrobials- rifaximin (other antibiotics not favored, eg neomycin, metronidazole or vancomycin) Solid soluble dispersion rifaximin (in clinical trials) Lactulose (putative intraluminal pH effect) Fecal microbiota transplant (clinical protocols) Probiotics (limited success) Engineered bacteria (early-stage clinical trials) Carbon microspheres (early-stage clinical trials)
Nutritional measures	Adequate nutrition and protein intake to mitigate sarcopenia/malnutrition Branched-chain amino acids Avoid and treat hypokalemia and hyponatremia Zinc repletion (primes the urea cycle)
Closure of portosystemic shunts	Interventional radiology embolization of portosystemic shunts, ideally MELD<12
Enhance nitrogen scavenging	Glycerol and sodium phenylbutyrate (used in urea cycle disorders) Sodium benzoate (used in urea cycle disorders) L-Ornithine L-Aspartate (urea cycle substrate and activator of glutamine synthetase in peripheral organs) Ornithine phenylacetate
Ammonia lowering and prevent ammonia-induced neurotoxity	Acetyl L-carnitine (reduce blood/brain ammonia, enhance cellular/mitochondrial energy production)
Toxin binding	Albumin infusion Albumin dialysis
Direct vigilance modulators	Golexanolone (early-stage clinical trials) Caffeine (limited data)