EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis

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Introduction [H1]

When the panel of experts nominated by the European Association for the Study of the Liver (EASL) governing board began work to update the Clinical Practice Guidelines (CPGs) on ascites, spontaneous bacterial peritonitis (SBP), and hepatorenal syndrome (HRS) [1] , it became obvious that all other complications of decompensated cirrhosis had to be covered. Within this framework, a formal definition of decompensated cirrhosis was sought. The natural history of cirrhosis is characterised by a silent, asymptomatic course until increasing portal pressure and worsening liver function produce a clinical phenotype. In the asymptomatic phase of the disease, usually referred to as compensated cirrhosis, patients may have a good quality of life, and the disease may progress undetected for several years. Decompensation is marked by the development of overt clinical signs, the most frequent of which are ascites, bleeding, encephalopathy, and jaundice. Following the first appearance of any of these, the disease usually progresses more rapidly towards death or liver transplantation (LT). This phase of the disease has been designated "decompensated cirrhosis" [2]. Progression of the decompensated disease may be further accelerated by the development of other complications such as rebleeding, acute kidney injury (AKI), with or without the features of HRS, hepato-pulmonary syndrome (HPS), portopulmonary hypertension (PPHT), cirrhotic cardiomyopathy (CCM), and bacterial infections. Indeed, the development of bacterial infections as well as hepatocellular carcinoma may accelerate the course of the disease at any stage, but especially in decompensated cirrhosis [3]. Having defined the potential field of action, and having emphasised the importance of initiating aetiologic treatment for any degree of hepatic disease at the earliest possible stage, the panel decided to extend the work to all those complications of cirrhosis which have not yet been covered by EASL guidelines, namely: gastrointestinal (GI) bleeding, bacterial infections other than SBP, acute-on-chronic liver failure (ACLF), adrenal failure, HPS, PPHT and CCM. In doing so, we have had to deal

with the recommendations regularly proposed by very well recognised international expert groups who have worked in the field of GI bleeding or ascites and ascites-related complications for many years. Given their extreme importance in clinical practice, only specific aspects of their recommendations were further developed in an attempt to give a more integrated view of the pathophysiology and management of patients with decompensated cirrhosis. Thus, this document can no longer be considered an update of earlier guidelines, but rather the first CPG on the management of decompensated cirrhosis with the sole purpose of improving clinical practice.

Guidelines development process

A panel of hepatologists with a great interest on decompensated cirrhosis, approved by the EASL Governing Board, wrote and discussed this CPG between March 2017 and February 2018. The guidelines were independently peer reviewed, and all contributors to the CPG disclosed their conflicts of interest by means of a disclosure form provided by the EASL Office prior to work commencing. The EASL Ethics Committee reviewed the composition of the panel to eliminate the potential for real or perceived bias. The CPG panel conflict of interests are declared in this submission. These guidelines have been produced using evidence from PubMed and Cochrane database searches before 27 March 2018. Tables describing the rationale behind the grades of evidence and of recommendations are provided (Table 1a and Table 1b, respectively).

Pathophysiology of decompensated cirrhosis [H1]

The transition from compensated asymptomatic cirrhosis to decompensated cirrhosis occurs at a rate of about 5% to 7% per year [4]. Once decompensation has occurred,

cirrhosis becomes a systemic disease, with multi-organ/system dysfunction [5]. At this stage, patients become highly susceptible to bacterial infections because of complex cirrhosis-associated immune dysfunction, which involves both innate and acquired immunity [6]. In turn, patients with bacterial infections are burdened by severe morbidity, up to ACLF, and high mortality [6, 7]. Because of these events, decompensation represents a prognostic watershed, as the median survival drops from more than 12 years for compensated cirrhosis to about two years for decompensated cirrhosis [4]. For decades the clinical manifestations of decompensated cirrhosis have been seen as the consequence of a haemodynamic disturbance, the hyperdynamic circulatory syndrome, ascribable to peripheral arterial vasodilation that mainly occurs in the splanchnic circulatory area. The extent of such vasodilation is to endanger effective volaemia, ultimately leading to peripheral organ hypoperfusion, the kidney being most affected [8]. Indeed, reduced effective volaemia brings about the activation of vasoconstrictor and water and sodium retaining mechanisms, such as the renin-angiotensin-aldosterone (RAAS), sympathetic nervous system and arginine-vasopressin secretion. This explains some of the cardinal features of decompensated cirrhosis, such as renal retention of sodium and water leading to ascites formation and HRS. Other manifestations attributable to haemodynamic abnormalities include HPS, increased susceptibility to shock, and a reduced cardiovascular responsiveness to physiological and pharmacological vasoconstrictor stimuli. Subsequent studies have highlighted that a cardiac dysfunction, due to CCM [9], is also involved in the pathogenesis of effective hypovolaemia [10]. This occurs particularly in the most advanced stages of decompensation, when such an abnormality prevents cardiac output from increasing enough to comply with the needs of systemic circulation. Although the molecular mechanisms responsible for arterial vasodilation, consisting of an enhanced endothelial production of vasodilating substances, such as nitric oxide, carbon monoxide, prostacyclin and endocannabinoids have been

convincingly demonstrated [11], the primary causes of such abnormalities remained somewhat obscure until it became clear that patients with advanced cirrhosis present a state of chronic inflammation, as witnessed by increased circulating levels of pro-inflammatory cytokines and chemokines [12]. This is likely caused by the systemic spread of bacteria and bacterial products, called pathogen associated molecular patterns (PAMPs), as a result of an abnormal bacterial translocation (BT). Changes in the microbiome and increased intestinal permeability account for this phenomenon. A similar role is likely played by other molecules, called danger associated molecular patterns (DAMPs), released by the diseased liver because of local inflammation and cell apoptosis and necrosis. Both PAMPs and DAMPs bind with innate recognition receptors of immune cells that, once activated, produce and release pro-inflammatory molecules, along with reactive oxygen and nitrogen species. This cascade of events contributes to the development of circulatory dysfunction and, along with it, directly favours the development of multi-organ dysfunction and failure (Fig. 1) [5]. Current strategies for prophylaxis and treatment of decompensation and organ failure in cirrhosis rely on measures aimed to prevent or improve the outcome of each complication, that is renal sodium retention leading to ascites formation, ammonia production in hepatic encephalopathy, effective hypovolaemia after large-volume paracentesis (LVP) or during HRS, renal dysfunction induced by SBP, and intestinal dysbiosis or bacterial overgrowth in patients predisposed to develop infections. All these strategies will be discussed in these CPGs. However, the improved knowledge of the pathophysiological background of decompensated cirrhosis now offers the opportunity for more comprehensive therapeutic and prophylactic approaches to disease management. Indeed, besides treating the underlying aetiologic factor(s), whenever possible, mechanistic approaches to counteract key pathophysiologic mechanisms may prevent or delay disease progression and the incidence of complications

and multi-organ dysfunction, thus improving patient survival and quality of life, as well as reducing the economic burden of the disease.

Management of decompensated cirrhosis [H1]

Ideally, the strategy of management of patients with decompensated cirrhosis should be based on preventing cirrhosis progression (*i.e.* further decompensation) rather than treating complications as they occur. The ultimate treatment for decompensated cirrhosis would be one that targets primarily the pathological alterations within the liver with the aim of restoring the integrity of liver architecture by suppressing inflammation, causing fibrosis regression, regularising the portal and arterial circulation, and normalising cell number and function. Unfortunately, such a treatment does not exist at present. Several antifibrotic or anti-inflammatory drugs have shown promise in experimental models of chronic liver diseases, but no treatment has yet been translated into clinical practice [13]. Meanwhile, the overall management of decompensated cirrhosis can be addressed using two approaches. The first approach is the suppression of the aetiological factor(s) that has caused liver inflammation and cirrhosis development, whereas the second approach is based on targeting key factors of pathogenesis of cirrhosis decompensation and progression.

Effects of suppression of aetiological factor on outcome of decompensated cirrhosis [H1]

Removal of the aetiological factor(s) causing liver injury is an important cornerstone in the management of cirrhosis. This approach is clearly effective in preventing decompensation and improving outcome in patients with compensated cirrhosis. However, results in patients with decompensated cirrhosis are less efficacious and probably depend, among other factors, on the actual status of liver disease at the time of removing the aetiological

factor of liver injury. For example, although in some patients with decompensated alcoholic cirrhosis suppression of alcohol consumption is associated with progressive "re-compensation" of cirrhosis and excellent long-term outcome, in other patients alcoholic cirrhosis progresses despite stopping alcohol intake [14, 15]. Likewise, in patients with cirrhosis due to hepatitis B virus (HBV) infection, treatment with antiviral agents is associated with improved outcome in some, but not all patients [16]. Moreover, treatment of patients with decompensated cirrhosis due to hepatitis C virus infection with direct antiviral agents is associated with beneficial effects in liver function and portal hypertension and likely improves outcome, but these effects are unfortunately not generalisable to all patients treated [17, 18]. The beneficial effects of removing responsible factors in other aetiologies of decompensated cirrhosis are less clear, perhaps with the exception of autoimmune hepatitis.

Effects of targeting key pathogenic events in prevention of cirrhosis progression [H1]

Several strategies have been evaluated to prevent disease progression in patients with decompensated cirrhosis, including i) targeting microbiome abnormalities and BT, to improve gut-liver axis; ii) improving the disturbed circulatory function; iii) treating the inflammatory state; and iv) targeting portal hypertension.

Administration of rifaximin has been shown to reduce the risk of development of several complications of cirrhosis besides hepatic encephalopathy in retrospective studies and small case series [19]. Nonetheless, data from prospective randomised double-blind studies are lacking. In patients with decompensated cirrhosis, treatment with norfloxacin reduces the risk of SBP and HRS [20, 21], but its use is hampered by the possibility of increased risk of infection by resistant bacteria. The potential effectiveness of improving circulatory and kidney function by long-term administration of albumin to patients with

decompensated cirrhosis has been explored in two recent randomised controlled trials (RCTs), both published in abstract form, with contradictory findings [22, 23]. The discrepant findings may be related to different doses of albumin used and/or heterogeneity in the study population. Further studies are needed to find out whether long-term albumin administration is efficacious in decompensated cirrhosis. Interestingly, treatment with statins, through their pleotropic effects, has been shown to reduce portal hypertension and improve survival in patients with advanced cirrhosis [24, 25]. These remarkable effects require validation in future studies. Another potential terapeutical strategy in the prevention of decompensation may be anticoagulation. Indeed, in a small RCT, a 12-month course of enoxaparin was safe and effective in preventing portal vein thrombosis (PVT) in patients with cirrhosis and a Child-Pugh scores of 7–10. In addition, enoxaparin appeared to delay the occurrence of hepatic decompensation and to improve survival suggesting that both PVT and decompensation may be related to a worsening of portal hypertension and the consequent progressive damage of the intestinal mucosal barrier [26]. From the same perspective, two other strategies should be considered. In 2010, it was shown that pentoxifylline treatment significantly reduced the risk of liver-related complications compared to placebo in an RCT of patients with advanced cirrhosis. The prevention of these complications, which included bacterial infections, renal failure, and hepatic encephalopathy was probably related to the fact that pentoxifylline prevents intestinal BT and the consequent development of systemic inflammation [27]. Finally, some investigations have shown that treatment with propranolol is not only effective in reducing portal hypertension and the consequent the risk of variceal bleeding but also in decreasing the risk of other complications of cirrhosis related to portal hypertension, such as ascites, HRS, SBP, and hepatic encephalopathy [28]. These effects occur specifically in patients who respond to propranolol treatment by markedly decreasing portal pressure, emphasising the strong relationship between pressure and complications of cirrhosis.

Nevertheless, in these studies most of patients had compensated cirrhosis. Therefore, studies should be performed in the group of patients with decompensated cirrhosis with the objective of assessing these beneficial effects in cirrhosis progression.

Recommendations [Note to the typesetter: the Recommendation boxes should be typeset according to the approved mock-up for typeset Recommendation boxes]

- **In patients with decompensated cirrhosis, the aetiological factor, should be removed, particularly alcohol consumption and hepatitis B or C virus infection as this strategy is associated with decreased risk of decompensation and increased survival (grade of evidence II-2, 1)**

- **Strategies based on targeting abnormalities in gut-liver axis by antibiotic administration (*i.e.* rifaximin), improving the disturbed systemic circulatory function (*i.e.* long-term albumin administration), decreasing the inflammatory state (*i.e.* statins), and reducing portal hypertension (*i.e.* beta-blockers) have shown potential benefit to decrease cirrhosis progression in patients with decompensated cirrhosis. However, further clinical research is needed with these strategies to confirm their safety and potential benefits as therapeutic approaches with the aim of preventing cirrhosis progression in decompensated patients.**

Management of specific complications of decompensated cirrhosis [H1]

Ascites [H1]

Ascites is the most common cause of decompensation in cirrhosis, as 5% to 10% of patients with compensated cirrhosis per year develop this complication [29]. The mainstay of ascites formation is renal sodium retention due to the activation of sodium retaining

systems, such as the renin-angiotensin-aldosterone system RAAS and sympathetic nervous system. The resulting positive fluid balance ultimately leads to extracellular fluid volume expansion. Reduced effective volaemia secondary to splanchnic arterial vasodilation is a main determinant of these alterations [8], but renal function abnormalities induced by systemic inflammation also play a role, especially in the most advanced stages of cirrhosis [5]. Portal hypertension also contributes [30] by acting as a compartmentalising factor of the expanded extracellular fluid volume.

The occurrence of ascites impairs patient working and social life, often leads to hospitalisation, requires chronic treatment and is a direct cause of further complications, such as SBP, restrictive ventilatory dysfunction, or abdominal hernias. The appearance of ascites heralds a poor prognosis, as the five-year survival drops from about 80% in compensated patients to about 30% in patients with decompensated cirrhosis and ascites [4].

Uncomplicated ascites [H2]

Evaluation of patients with ascites [H3]

Cirrhosis is the main cause of ascites in the Western world, being responsible for about 80% of cases. Malignancy, heart failure, tuberculosis, pancreatic disease, or other rarer diseases account for the remaining cases. Initial patient evaluation should include history, physical examination, abdominal ultrasound, and laboratory assessment of liver and renal functions, serum and urine electrolytes, as well as an analysis of the ascitic fluid.

Diagnosis of ascites [H3]

Ascites can be graded from 1 to 3 according to the amount of fluid in the abdominal cavity [31](Table 2). The ascites that recurs at least on three occasions within a 12-month period

despite dietary sodium restriction and adequate diuretic dosage is defined as recidivant [32].

Diagnostic paracentesis is indicated in all patients with new onset of grade 2 or 3 ascites and in those admitted to the hospital for any complication of cirrhosis [31, 32]. Manual or automated neutrophil count , total protein and albumin concentration, and culture should be always assessed. A neutrophil count above 250 cells/µl denotes SBP [33]. A total protein concentration <1.5 g/dl is generally considered a risk factor for SBP, although there are conflicting data [33,34]. Ascitic fluid culture requires the bedside inoculation of at least 10 ml into blood culture bottles to enhance its sensitivity [35]. The calculation of serum-ascites albumin gradient (SAAG) may be useful when the cause of ascites is not immediately evident, as SAAG ≥1.1 g/dl indicates that portal hypertension is involved in ascites formation with an accuracy of about 97% [36]. Other tests, such as amylase, cytology, or culture for mycobacteria should be guided by clinical presentation. Ascitic cholesterol determination followed by cytology and carcinoembryonic antigen (CEA) determination in samples where cholesterol concentration exceeds 45 mg/dl appears to be a cost-effective method for the differential diagnosis between malignancy-related and non-malignant ascites [37].

Recommendations [Note to the typesetter: the Recommendation boxes should be typeset according to the approved mock-up for typeset Recommendation boxes]

- **A diagnostic paracentesis is recommended in all patients with new onset grade 2 or 3 ascites, or in those hospitalised for worsening of ascites or any complication of cirrhosis (II-2; 1).**

- **Neutrophil count and culture of ascitic fluid culture (bedside inoculation blood culture bottles with 10 ml fluid each) should be performed to exclude**

bacterial peritonitis. A neutrophil count above 250 cells/µl is required to diagnose SBP (II-2; 1).

- **Ascitic total protein concentration should be performed to identify patients at higher risk of developing SBP (II-2; 1).**

- **The SAAG should be calculated when the cause of ascites is not immediately evident, and/or when conditions other than cirrhosis are suspected (II-2;1).**

- **Cytology should be performed to differentiate malignancy-related from non-malignant ascites (II-2;2).**

Prognosis of patients with ascites [H3]

The development of ascites in patients with cirrhosis is associated with a poor prognosis, as their one and two-year mortality is about 40 and 50%, respectively [1]. Thus, patients with ascites should generally be considered for referral for LT. Hyponatraemia, low arterial pressure, glomerular filtration rate (GFR) and low renal sodium excretion are independent predictors of mortality in cirrhosis with ascites [38]. As these parameters are not included in the Child-Pugh score, and only serum creatinine (SCr), which overestimates GFR in cirrhosis [39], is included in the model for end-stage liver disease (MELD) score, the most commonly used prognostic scores can underestimate the mortality risk in patients with ascites. Modifications of the MELD score, such as the MELD-Na and MELD-Ascites scores have only partially overcome this limitation [40]. Thus, patients with ascites may not receive adequate priority in transplant lists, and improved methods to assess prognosis in these patients are needed. A prognostic score able to identify patients with low MELD score (<18) at high risk of 12-month adverse outcome has recently been proposed, but it still has limited application [41].

Recommendation [Note to the typesetter: the Recommendation boxes should be typeset according to the approved mock-up for typeset Recommendation boxes]

- **Since the development of grade 2 or 3 ascites in patients with cirrhosis is associated with reduced survival, LT should be considered as a potential treatment option (II-2;1).**

Management of uncomplicated ascites [H3]

Ascites is uncomplicated when it is not infected, refractory or associated with HRS [31,32].

Grade 1 or mild ascites [H4]

No data on the evolution of grade 1 ascites are available, nor it is known whether its treatment modifies its natural history.

Grade 2 or moderate ascites [H4]

Patients who develop grade 2 ascites do not require hospitalisation, unless other complications are present. They have a positive sodium balance, which can be corrected by reducing the dietary sodium intake and increasing renal sodium excretion with diuretics. Although upright posture favours renal sodium reabsorption [42] and attenuates the response to diuretics [43], there is no evidence that a prolonged maintenance of the supine position eases the treatment of ascites.

Sodium restriction [H5]

The prophylactic use of salt restriction in patients who never had ascites is not supported by evidence. Dietary sodium restriction can lead to the resolution of ascites in about 10% of patients [44], especially in those with the first episode of ascites. A clear advantage from the use of low-sodium diets associated with diuretics has not emerged from clinical trials

comparing different dietary regimens [44, 45]. Extreme sodium restriction favours the development of diuretic-induced hyponatraemia and renal failure [46]. Moreover, even moderate sodium restriction, when not prescribed with an adequate educational programme, is often associated with reduced calorie intake [47], and may impair nutritional status. The current opinion is that dietary sodium should only be moderately restricted (80–120 mmol/day), mainly to avoid excess salt intake.

Recommendations [Note to the typesetter: the Recommendation boxes should be typeset according to the approved mock-up for typeset Recommendation boxes]

- **A moderate restriction of sodium intake (80–120 mmol/day, corresponding to 4.6–6.9 g of salt) is recommended in patients with moderate, uncomplicated ascites (I;1). This is generally equivalent to a no added salt diet with avoidance of pre-prepared meals. Adequate nutritional education of patients on how to manage dietary sodium is also recommended. (II-2;1).**

- **Diets with a very low sodium content (<40 mmol/day) should be avoided, as they favour diuretic-induced complications and can endanger a patient's nutritional status (II-2;1).**

- **Prolonged bed rest cannot be recommended because there is insufficient evidence that it is beneficial in the treatment of ascites (III;1).**

Diuretics [H5]

Neither diuretics nor LVP are associated with a survival benefit because they act downstream of the pathophysiological cascade, being symptomatic therapies. The negative fluid balance induced by diuretics should not lead to a body weight loss exceeding 0.5 Kg/day in patients without peripheral oedema and 1 Kg/day in the presence of peripheral oedema to avoid plasma volume contraction, ultimately leading to renal

failure and hyponatraemia [48]. Since secondary hyperaldosteronism plays a pivotal role in the renal sodium retention in patients with cirrhosis, [49,50] anti-mineralocorticoid drugs (spironolactone, canrenone or K-canrenoate) represent a mainstay in the medical treatment of ascites [50]. Four hundred mg/day represents the maximal dosage usually recommended [31, 32]. The mechanism of action of anti-mineralocorticoids explains their slow effect. In fact, the activated aldosterone pathway, which involves interaction with a cytosolic receptor and, then, a nuclear receptor, needs to be exhausted before their natriuretic effect arises. Therefore, the dosage of these drugs should not be increased earlier than 72 h. Amiloride, a diuretic acting in the collecting duct, is less effective than anti-mineralocorticoids, and should only be used in patients who develop severe side effects with aldosterone antagonists [51].

Proximal tubular sodium reabsorption promotes renal sodium retention through various mechanisms, such as increased angiotensin II production, sympatho-adrenergic hyperactivity and reduced renal perfusion [49]. As proximal tubular sodium reabsorption can become relatively prevalent in patients with long-standing ascites [52,53], loop diuretics are indicated in this setting. However, they should be combined with but not substituted for anti-mineralocorticoids. Indeed, despite their potent activity, the natriuretic effect of loop diuretics can be completely blunted by unopposed hyperaldosteronism [54]. Whether diuretic treatment should be initiated with anti-mineralocorticoids alone or should also include a loop diuretic has long been debated. Two studies have addressed this matter providing apparently conflicting results because of differences in patient populations [55, 56]. In both studies, the effects of a diuretic regimen initially consisting of spironolactone or K-canrenoate alone at stepwise increasing dosages (from 100/200 to 400 mg/day), with furosemide added in non-responder patients, were compared with those of the combination of anti-mineralocorticoids with furosemide (from 40 to 160 mg/day) from the beginning of treatment. In one study [56], the response rate, the rapidity of ascites

mobilisation and the incidence of diuretic-induced complications were similar in both regimens. However, as the sequential treatment required less dose adjustments, it appeared to be more suitable for treating ascites on an outpatient basis. In the other study [55], the combined regimen achieved the resolution of ascites in a shorter time, with a lower incidence of side effects, mainly hyperkalemia. Such divergent results likely arose from differences in the patient populations. In one study [56], patients with ascites at the first appearance and well preserved renal function prevailed, while, in the other [55], most patients had recurrent ascites and many showed a substantial reduction of GFR. Thus, patients with ascites at the first appearance can confidently be treated with anti-mineralocorticoids alone, as they will likely develop a satisfactory response with few side effects. Patients with long-standing, recurrent ascites should receive the combination therapy, which likely shortens the time to achieve natriuresis and lowers the incidence of hyperkalemia [1]. In a randomised double-blind cross-over trial torasemide induced greater cumulative 24 h diuresis than furosemide, suggesting that torasemide might be more advantageous in patients exhibiting a weak response to furosemide [57]

Following mobilisation of ascites, diuretics should be tapered to the lowest dosages able to maintain patients with minimal or no ascites, to minimise side effects. Whenever possible, an aetiologic treatment of the underlying cirrhosis should be instituted, as this eases the control of ascites in many cases.

Complications of diuretic therapy [H5]

The haemodynamic status of patients with cirrhosis and ascites [8] makes them highly susceptible to rapid reductions in extracellular fluid volume, which mostly occur with loop diuretics. Thus, renal failure is frequent in this setting [48], as is hepatic encephalopathy, also favoured by increased renal ammonia production. Loop diuretics can also lead to potassium and magnesium depletion. Hyponatraemia is another common diuretic-induced

side effect in cirrhosis. It mostly, but not exclusively, occurs with loop diuretics, as they inhibit Na-K-Cl transporter and, therefore, solute-free water generation. Plasma volume contraction can also enhance arginine-vasopressin release. Thus, hyponatraemia can also ensue with anti-mineralocorticoid administration, albeit infrequently. Most experts agree on at least temporarily withdrawing diuretics when serum sodium concentration decreases below 120–125 mmol/L. Hyperkalemia, especially in patients with reduced renal perfusion, and painful gynecomastia are the most common side effects induced by anti-mineralocorticoids.

Muscle cramps can impair quality of life in patients receiving diuretics. Albumin infusion can relieve cramps [58], as well as baclofen (10 mg/day, with a weekly increase of 10 mg/day up to 30 mg/day), which was safely used in a recent RCT [59]. One RCT investigated the use of quinidine at the dose of 400 mg/day for four weeks in patients with cirrhosis with painful muscle cramps. Although more effective than placebo, quinidine was associated with diarrhoea in about one-third of cases requiring treatment withdrawal [60]. Because of the frequency of diuretic-induced side effects, especially during the first month of treatment [55], serial measurements of SCr, sodium, and potassium are warranted. The assessment of urine sodium excretion can be limited to non-responders, to unveil excessive sodium intake.

Recommendations [Note to the typesetter: the Recommendation boxes should be typeset according to the approved mock-up for typeset Recommendation boxes]

- **Patients with the first episode of grade 2 (moderate) ascites should receive an anti-mineralocorticoid drug alone, starting at 100 mg/day with stepwise increases every 72 h (in 100 mg steps) to a maximum of 400 mg/day if there is no response to lower doses (I;1).**

- **In patients who do not respond to anti-mineralocorticoids, as defined by a body weight reduction of less than 2 kg/week, or in patients who develop hyperkalemia, furosemide should be added at an increasing stepwise dose from 40 mg/day to a maximum of 160 mg/day (in 40 mg steps) (I;1).**

- **Patients with long-standing or recurrent ascites should be treated with a combination of an anti-mineralocorticoid drug and furosemide, the dose of which should be increased sequentially according to the response, as explained (I;1).**

- **Torasemide can be given in patients exhibiting a weak response to furosemide (I;2).**

- **During diuretic therapy a maximum weight loss of 0.5 kg/day in patients without oedema and 1 kg/day in patients with oedema is recommended (II-2;1).**

- **Once ascites has largely resolved, the dose of diuretics should be reduced to the lowest effective dose (III;1).**

- **During the first weeks of treatment patients should undergo frequent clinical and biochemical monitoring particularly on first presentation (I;1).**

- **In patients presenting with GI haemorrhage, renal impairment, hepatic encephalopathy, hyponatraemia, or alterations in serum potassium concentration, these abnormalities should be corrected before starting diuretic therapy (III;1) In these patients, cautious initiation of diuretic therapy and frequent clinical and biochemical assessments should be performed (III;1). Diuretic therapy is generally not recommended in patients with persistent overt hepatic encephalopathy (III;1).**

- **Diuretics should be discontinued if severe hyponatraemia (serum sodium concentration <125 mmol/L), AKI, worsening hepatic encephalopathy, or incapacitating muscle cramps develop (III;1).**

- **Furosemide should be stopped if severe hypokalemia occurs (<3 mmol/L). Anti-mineralocorticoids should be stopped if severe hyperkalemia occurs (>6 mmol/L) (III;1).**

- **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 (I;1).**

Grade 3 or large ascites [H4]

The treatment of choice for the management of patients with grade 3 ascites is represented by LVP. Paracentesis should be performed under strict sterile conditions using disposable sterile materials. The procedure is associated with a very low risk of local complications, particularly bleeding [61,62] even in patients with international normalized ratio (INR) >1.5 and platelet count <50,000/µl, minor bleeding from puncture site occurred in two out of 142 paracentesis [61]. Thus, there are no data supporting the prophylactic use of fresh frozen plasma of pooled platelets, even though these are employed in many centres when prothrombin activity is below 40% and platelet count <40,000/µl. LVP should be avoided in the presence of disseminated intravascular coagulation. Other contraindications to LVP are reported (Table 3).

The removal of large volumes of ascitic fluid is potentially associated with a further reduction of effective blood volume, a condition known as post-paracentesis circulatory dysfunction (PPCD) [63]. The clinical manifestations of PPCD are renal failure, dilutional hyponatraemia, hepatic encephalopathy and decreased survival [63]. Plasma volume expansion should be performed at the completion of LVP to prevent this complication.

Artificial plasma expanders, such as dextran-70 (8 g/L of ascites removed) [64] or polygeline (150 ml/L) [64], saline solution (170 ml/L) [65], only show a similar efficacy to 20% albumin (8 g/L) [64] when less than 5 L of ascites are removed. However, polygeline is no longer used in many countries because of the potential risk of transmission of prions and dextran carries the risk of severe allergic reaction and renal failure. A meta-analysis of randomised trials showed that albumin is superior to any other plasma expander or vasoconstrictor not only in preventing PPCD, but also its clinical consequences, such as hyponatraemia and mortality [66]. Moreover, albumin infusion after LVP appears to be more cost-effective than a cheaper plasma volume expander, such as polygeline, because of the lower number of liver-related complications and hospital costs for a 30-day period [67]. LVP combined with infusion of albumin in patients with grade 3 ascites is more effective and safer than diuretics [68,69]. However, LVP does not modify the underlying pathophysiological abnormalities leading to ascites formation. Thus, patients treated with LVP require diuretic therapy to prevent the re-accumulation of ascites [70].

Recommendations [Note to the typesetter: the Recommendation boxes should be typeset according to the approved mock-up for typeset Recommendation boxes]

- **LVP is the first-line therapy in patients with large ascites (grade 3 ascites), which should be completely removed in a single session (I;1).**
- **LVP should be followed with plasma volume expansion to prevent PPCD (I;1).**
- **In patients undergoing LVP of greater than 5 L of ascites, plasma volume expansion should be performed by infusing albumin (8 g/L of ascites removed), as it is more effective than other plasma expanders, which are not recommended for this setting (I;1).**
- **In patients undergoing LVP of less than 5 L of ascites, the risk of developing PPCD is low. However, it is generally agreed that these patients should still**

be treated with albumin because of concerns about use of alternative plasma
expanders (III;1).

- After LVP, patients should receive the minimum dose of diuretics necessary
  to prevent re-accumulation of ascites (I;1).

- When needed, LVP should also be performed in patients with AKI or SBP (III;
  1).

Drugs contraindicated in patients with ascites [H3]

As non-steroidal anti-inflammatory drugs inhibit renal prostaglandin synthesis, they should
not be used in patients with cirrhosis and ascites, where an increased vasodilating
prostaglandin synthesis counteracts the renal vasoconstrictor effects of angiotensin II.
Indeed, their administration can lead to acute renal failure, hyponatraemia, and diuretic
resistance [71]. It would appear that selective inhibitors of cyclooxygenase-2 do not impair
renal function and response to diuretics in patients with ascites [72]. However, it is not
known whether these drugs can be safely used in clinical practice when analgesia is
needed. Patients with ascites are also particularly sensitive to the renal vasoconstrictor
effect of endogenous adenosine, and dipyridamole can induce a marked reduction in renal
perfusion [73].

The maintenance of an adequate arterial pressure in cirrhosis with ascites is assured by
the activation of endogenous vasoconstrictor systems. Thus, angiotensin-converting
enzyme inhibitors [74], angiotensin II receptor antagonists, and α1-adrenergic blockers
[75] should be avoided, as they can induce arterial hypotension and renal function
impairment. Aminoglycosides should be avoided in the treatment of bacterial infections,
except in specific cases (discussed later), because they are associated with high incidence
of nephrotoxicity [76]. Although cirrhosis with ascites and preserved renal function does
not appear to be a risk factor for renal failure induced by contrast media [77], this cannot

be excluded in patients with impaired renal function. In these cases, preventive measures such as plasma volume expansion with saline may be employed [78].

Recommendations [Note to the typesetter: the Recommendation boxes should be typeset according to the approved mock-up for typeset Recommendation boxes]

- **Non-steroidal anti-inflammatory drugs should not be used in patients with ascites because of the high risk of developing further sodium retention, hyponatraemia, and AKI (II-2; 1).**
- **Angiotensin-converting-enyzme inhibitors, angiotensin II antagonists, or α1-adrenergic receptor blockers should not generally be used in patients with ascites because of increased risk of renal impairment (II-2;1).**
- **The use of aminoglycosides is discouraged, as they are associated with an increased risk of AKI. Their use should be reserved for patients with severe bacterial infections that cannot be treated with other antibiotics (II-2;1).**
- **In patients with ascites and preserved renal function, the use of contrast media does not appear to be associated with an increased risk of renal impairment (II-2). There are insufficient data in patients with renal failure. Nevertheless, a cautious use of contrast media and the use of preventive measures for renal impairment are recommended (III;1).**

Refractory ascites [H2]

Evaluation of patients with refractory ascites [H3]

According to the criteria of the International Ascites Club, refractory ascites is defined as "ascites that cannot be mobilised or the early recurrence of which (*i.e.*, after LVP) cannot be satisfactorily prevented by medical therapy" [31,32]. The diagnostic criteria of refractory ascites are shown in Table 4. Refractoriness of ascites is associated with a poor

prognosis, with a median survival of about six months [79]. Therefore, if a patient with refractory ascites has not yet been considered for LT, he/she should be immediately referred to a liver transplant center. The potential underestimation of the mortality risk by commonly used prognostic scores, as discussed earlier also applies to patients with refractory ascites [80].

Recommendations [Note to the typesetter: the Recommendation boxes should be typeset according to the approved mock-up for typeset Recommendation boxes]

- **The diagnosis of refractory ascites relies on the assessment of the response of ascites to diuretic therapy and salt restriction. Such an evaluation should be done in stable patients without associated complications, such as bleeding or infection, after ascertaining patient compliance to treatment has been ascertained (III; 1).**
- **Patients with refractory ascites should be evaluated for LT (III;1).**

Management of refractory ascites [H3]

Large-volume paracentesis [H4]

There is general agreement that LVP is an effective and safe treatment of refractory ascites [31, 35], which should be associated with albumin administration to prevent PPCD.

Diuretics in patients with refractory ascites [H4]

Once refractoriness of ascites has been ascertained, diuretics should be discontinued. Only when renal sodium excretion on diuretics exceeds 30 mmol/day, maintenance of diuretic therapy can be considered, when tolerated [31].

Non-selective beta-blockers in patients with refractory ascites [H4]

The controversial issue on the use of non-selective beta-blockers (NSBBs) in patients with ascites and, particularly, in those with refractory ascites will be developed in the section dedicated to GI bleeding.

Transjugular intrahepatic portosystemic shunts [H4]

Transjugular intrahepatic portosystemic shunts (TIPS) decompresses the portal system by shunting an intrahepatic portal branch into a hepatic vein. Its insertion accentuates short-term peripheral arterial vasodilation. However, within 4-6 weeks its result is an improvement in effective volaemia and renal function, ultimately leading to an increase in renal sodium excretion [81-85] TIPS-induced natriuresis can be delayed by advanced age and reduced pre-TIPS GFR [84], and prevented by intrinsic kidney disease [86]. TIPS may also exert beneficial effects on nitrogen balance and nutrition [87] and quality of life [88]. A major complication after TIPS insertion using bare stent grafts is the development of hepatic encephalopathy, which can occur in up to 50% of patients [89, 90]. The incidence of this complication can be significantly reduced to about 18% with the use of polytetrafluoroethylene (PTFE)-covered stent grafts of 8 mm [91], a result confirmed by a recent randomised trial comparing 8 mm and 10 mm stent grafts [92]. Notably, this favourable effect is better than with larger stent grafts underdilated to 8 mm. Indeed, it has been shown that underdilated 10 mm stent grafts passively expand to almost the full diameter within 1–6 weeks [93]. It must be underlined that the indication for TIPS insertion in these studies was the prevention or treatment of recurrent bleeding, which may restrict the relevance of these results in patients with refractory ascites. Dysfunction of TIPS with bare stent grafts because of stent thrombosis and stenosis can develop in up to 80% of cases [89]. This complication has been significantly reduced with the use of PTFE-covered stents [94].

Controlled studies and meta-analysis [H5]

The clinical effects of TIPS with bare stents in patients with refractory or recurrent ascites have been assessed in six prospective RCTs [95-100], whose main features are reported (Table 5). Based on these RCTs, seven meta-analyses were performed [101-107]. The final messages can be summarised as follow: i) TIPS controlled ascites better than LVP, and ii) TIPS is followed by a greater incidence of hepatic encephalopathy. However, discrepant results were obtained with respect to survival. A better survival with LVP, mainly because of a detrimental effect of TIPS in Child-Pugh class C patients, was reported by one study [96], while no difference was reported by two [95, 100]. A better survival with TIPS was reported in another two studies [97, 99], while, in the remaining one [98], although a survival advantage was not found, TIPS was independently associated with transplant-free survival at multivariate analysis. In four meta-analyses [101, 104-106], the five studies available at that time were included [95, 96, 98-100], and no survival advantage with TIPS emerged. However, a trend towards reduced mortality with TIPS was seen [104] after the exclusion of an outlier trial [96]. The latter was also excluded in the only meta-analysis on individual patient data, and an increased transplant-free survival was found [107]. Finally, the two meta-analyses that included all six trials [102,103] provided contrasting results, as an improved transplant-free survival was found in one [107], while a survival advantage with TIPS was limited to patients with recurrent ascites in the other [102].

Fewer studies assessing the effects of TIPS with PTFE-covered stent grafts are available. Two retrospective studies [108,109] reported better control of ascites and one-year [108] or two-year [109] survival with covered stent grafts than bare stent grafts in patients with refractory ascites. A survival benefit of TIPS *vs.* serial paracentesis in patients with refractory ascites has been reported in a single-centre case-control propensity score

analysis [110]. In a recent RCT comparing covered TIPS *vs.* LVP in patients with recurrent ascites, a better one-year transplant-free survival was seen in patients treated with covered stents, without any significant increase in occurrence of hepatic encephalopathy [111]. Thus, currently available data suggest that TIPS improves survival compared to LVP in patients with recurrent ascites, but it does not in those with refractory ascites.

A careful selection of patients is also crucial to maximise the beneficial effects of TIPS, as TIPS can even be detrimental in patients with the most advanced stages of cirrhosis, such as those belonging to Child-Pugh class C [96]. The main exclusion criteria for TIPS insertion in the seven RCTs are reported in Table 5. A score system based on SCr, INR, serum bilirubin and aetiology of cirrhosis has been proposed to predict survival after TIPS insertion for refractory ascites [112]. Another simple predictor of survival suggested for patients receiving TIPS for refractory ascites consists of the combination of serum bilirubin concentration and platelet count [113]. Another factor that seems to influence mortality is the number of TIPS procedures performed in a centre, as the risk of inpatient mortality is lower in hospitals performing ≥20 TIPS per year [114].

Other treatments [H4]

Based on the exclusion criteria reported (Table 5), a substantial portion of patients with refractory ascites are not candidates for TIPS insertion. Thus, the search for alternative treatments is warranted.

Medical treatments [H5]

Therapies aimed at improving circulatory and renal function have been proposed. The α1-adrenergic agonist midodrine has been shown to improve systemic and renal haemodynamics in patients with cirrhosis and uncomplicated ascites [115]. In a small RCT comparing the addition of midodrine (7.5 mg t.i.d) to diuretic treatment with diuretic

treatment alone in patients with refractory or recurrent ascites for six months, only a transient beneficial effect on the control of ascites was seen at the third month [116]. The use of terlipressin, an analogue of vasopressin with a predominant vasoconstrictor effect in the splanchnic circulatory area in patients with refractory ascites has only been assessed in acute studies. In one [117], terlipressin administration (1 to 2 mg intravenous [i.v.], according to body weight) only increased renal sodium excretion when associated with exogenous atrial natriuretic factor. In another [118], 2 mg of terlipressin led to an increase in GFR, renal plasma flow and renal sodium excretion. However, in this study only eight patients with refractory ascites were included. Whether a prolonged treatment with terlipressin may lead to a clinically relevant improvement of renal function and sodium excretion in refractory ascites is not known.

The α2-adrenoceptor agonist clonidine, a sympatholytic drug, which suppresses RAAS activity and improves the response to diuretics in patients with cirrhosis and ascites was tested in a large prospective RCT. It was shown that clonidine administration on top of diuretics for three months led to an overall response to diuretics in 60% of cases, while no response was seen with diuretics alone. This effect was associated with significant reductions of RAAS and sympathetic nervous system activity. Interestingly, the favourable effects of clonidine were predicted by the variant genotype of G protein (GNB3 C825T) and adrenergic receptor (ADRA2C Del 322-325) polymorphisms, and the baseline norepinephrine level [119]. Small scale or pilot studies evaluated the effects of various combinations of midodrine with either clonidine [120], the antagonist of vasopressin V2-receptors tolvaptan [121], or octreotide and albumin [122] in patients with refractory and recurrent ascites. Some promising results were obtained, but they need to be confirmed by sufficiently powered RCTs. A recent RCT [123] compared the effects of the combined administration of midodrine (5 mg t.i.d) and rifaximin (550 mg b.i.d) on top of diuretics for 12 weeks with diuretics alone. After 12 weeks, 80% of patients in the active arm were

complete responders with a significant improvement in survival in the midodrine/rifaximin arm. Due to weakness in the study design, these results are not definitive, but they certainly warrant further investigation.

Alfapump® [H5]

The automated low-flow ascites pump (Alfapump®) system consists of a subcutaneously implanted battery-powered programmable pump. It is connected to catheters that transfer ascites from the peritoneal cavity to the bladder, from which it is eliminated with urine. The device has internal sensors that monitor pump function. In two multicentre safety and efficacy studies [124,125], Alfapump® ensured a significant reduction of the number and volume of paracentesis in patients with advanced cirrhosis and refractory ascites. However, adverse effects directly related to the device occurred in about one-third [124] to half [125] of cases. In a multicentre RCT in patients with refractory ascites, Alfapump® reduced the median number of paracentesis per month by 85% with respect to LVP, and significantly improved quality of life and nutritional parameters, as assessed by hand-grip strength and body mass index. Alfapump® had no effect on survival and was associated with a significantly higher incidence of serious adverse events (85.2 *vs.* 45.2%), mainly represented by AKI [126]. Thus, even though Alfapump® is effective in reducing the need for paracentesis in patients with refractory ascites, its frequent side effects require close monitoring of patients. Indeed, in addition to device-related adverse event, it should be noted that the evaluation of kidney and circulatory function in 10 patients with cirrhosis and refractory ascites carrying Alfapump® has shown a significant GFR decline within six months, which was associated with a marked increase in plasma renin activity and norepinephrine concentration [127]. This likely represented the pathophysiological background of 18 episodes of AKI experienced by seven patients.

Recommendations [Note to the typesetter: the Recommendation boxes should be typeset according to the approved mock-up for typeset Recommendation boxes]

- **Repeated LVP plus albumin (8 g/L of ascites removed) are recommended as first line treatment for refractory ascites (I;1).**

- **Diuretics should be discontinued in patients with refractory ascites who do not excrete >30 mmol/day of sodium under diuretic treatment (III; 1).**

- **Although controversial data exist on the use of NSBBs in refractory ascites, caution should be exercised in cases of severe or refractory ascites. High doses of NSBBs (*i.e.* >80 mg/d propranolol) should be avoided. (II-2;1).**

- **Patients with refractory or recurrent ascites (I;1), or those for whom paracentesis is ineffective (*e.g.* due to the presence of loculated ascites) should be evaluated for TIPS insertion (III;1).**

- **TIPS insertion is recommended in patients with recurrent ascites (I;1) as it improves survival (I;1) and in patients with refractory ascites as it improve the control of ascites (I;1).**

- **The use of small-diameter PTFE-covered stents in patients is recommended to reduce the risk of TIPS dysfunction and hepatic encephalopathy with a high risk of hepatic encephalopathy is recommended (I;1).**

- **Diuretics and salt restriction should be continued after TIPS insertion up to the resolution of ascites (II-2;1), as well as close clinical follow-up (III,1).**

- **Careful selection of patients for elective TIPS insertion is crucial, as is the experience of the centre performing this procedure. TIPS is not recommended in patients with serum bilirubin >3 mg/dl and a platelet count lower than 75 x 10^9/L, current hepatic encephalopathy grade ≥2 or chronic hepatic encephalopathy, concomitant active infection, progressive renal failure, severe systolic or diastolic dysfunction, or pulmonary hypertension (III;1).**

- **At present the addition of clonidine or midodrine to diuretic treatment cannot be recommended (III;1).**

- **Alfapump® implantation in patients with refractory ascites not amenable to TIPS insertion is suggested in experienced centres. However, close patient monitoring is warranted because of the high risk of adverse events including renal dysfunction and technical difficulties (I;2).**

Hepatic hydrotorax [H4]

Hepatic hydrotorax describes the accumulation of transudate in the pleural space of patients with decompensated cirrhosis in the absence of cardiac, pulmonary or pleural disease. Its formation is secondary to small diaphragmatic defects, more often located in the right side, through which ascites moves into the pleural space because of the negative intrathoracic pressure induced by inspiration. Hepatic hydrothorax can lead to respiratory failure and can be complicated by spontaneous bacterial infections (empyema). Its appearance is associated with poor prognosis, as the median survival of patients with hepatic hydrothorax ranges from 8–12 months [128,129] Notably, the most common prognostic scores, such as Child-Pugh and MELD, seem to underestimate such an adverse outcome [128].

Diagnosis of hepatic hydrothorax [H5]

Once pleural effusion has been ascertained, cardiopulmonary and primary pleural diseases should be excluded by standard clinical approaches. Diagnostic thoracentesis is required to rule out bacterial infection, whose diagnosis relies on the same criteria described for ascites. The protein content of pleural effusion in uncomplicated hepatic hydrothorax is low and the serum to pleural fluid albumin gradient is greater than 1.1 g/dl [128].

The presence and extent of diaphragmatic defects can be assessed indirectly, by radioisotope techniques, or directly by magnetic resonance imaging or colour-Doppler ultrasonography [130,131].

Treatment of hepatic hydrothorax [H5]

The first-line management relies on the treatment of ascites with diuretics and/or LVP as discussed earlier. However, it is not rare for pleural effusion to persist despite successful treatment of ascites (refractory hydrothorax). Therapeutic thoracentesis is required to relieve dyspnoea. Its efficacy in refractory hepatic hydrothorax is transient and repeated thoracentesis are required, which increase the risk of complications such as pneumothorax, pleural or soft tissue infection, and bleeding [132]. The frequent occurrence of these complications discourages the use of chronic pleural drainage, which can also be followed by renal dysfunction from fluid loss [133]

Whenever indicated and possible, LT represents the best option for patients with refractory hepatic hydrothorax, which does not seem to adversely affect the outcome of transplantation [134,135]. TIPS has been effectively employed as definitive treatment or bridge to transplantation in patients with refractory hepatic hydrotorax, whose general outcome seems to be related to the severity of the underlying cirrhosis [136, 137]. These results have been confirmed by a more recent meta-analysis [138].

Pleurodesis induced by various agents, such as talc, tetracycline, doxycycline, bleomycin and povidone-iodine, can be offered to patients who are not candidates for TIPS or LT. A recent meta-analysis showed that the pooled rate of complete response after pleurodesis was 72%. However, the pooled rate of complications related to this procedure was as high as 82% [139]. Finally, thoracoscopic repair with mersilene mesh appears to be effective in patients with well-defined diaphragmatic defects [140]. Advanced liver disease, as assessed by MELD score, and preoperative renal dysfunction appear to adversely affect

three-month survival. Unfortunately, clear cut-off values cannot be retrieved from that study.

Recommendations [Note to the typesetter: the Recommendation boxes should be typeset according to the approved mock-up for typeset Recommendation boxes]

- **Patients with hydrothorax should be evaluated for LT (III;1).**

- **Cardiopulmonary and primary pleural disease should be ruled out before diagnosing hepatic hydrothorax (III;1). Diagnostic thoracentesis should be performed especially when infection of the pleural effusion is suspected (III;1).**

- **Diuretics and thoracentesis are recommended as the first-line management of hepatic hydrothorax (III;1).**

- **Therapeutic thoracentesis is indicated in patients with dyspnoea (III;1). Chronic pleural should not be performed because of the frequent occurrence of complications (II-2;1).**

- **In selected patients, TIPS insertion for recurrent symptomatic hepatic hydrothorax is recommended (II-2;1).**

- **Pleurodesis can be suggested to patients with refractory hepatic hydrothorax not amenable to LT or TIPS insertion. However, the frequent occurrence of side effects related to this technique restricts its use to selected patients (I;2).**

- **Mesh repair of diaphragmatic defects is suggested for the management of hepatic hydrothorax in very selected patients. The best results can be achieved in patients with non-advanced cirrhosis without renal dysfunction (II-2;2).**

Hyponatremia [H1]

Defintion and pathophysiology [H2]

Hyponatremia is common in patients with advanced cirrhosis, and has been arbitrarily defined as serum sodium concentration lower than 130 mmol/L [141,142]. However, according to guidelines on hyponatremia in the general patient population [143], reductions below 135 mmol/L should also be considered. Hyponatremia has a poor prognostic significance, as it is associated with increased mortality [144, 145] and morbidity, particularly neurological complications [146,147], and reduced survival after liver transplantation [148]. Incorporating serum sodium concentration into MELD score, a new score (MELD-Na) was generated that provides more accurate survival prediction than MELD alone [149], especially in patients with ascites and hyponatremia with intermediate MELD score values [150]. Both hypovolemic and hypervolemic hyponatremia can occur in patients with cirrhosis. The second, most common, is characterized by an expansion of the extracellular fluid volume, with ascites and edema. It may occur spontaneously, or as a consequence of excessive hypotonic fluids (i.e., 5% dextrose), or secondary to complications of cirrhosis leading to an abrupt worsening of effective volemia. Non-osmotic hypersecretion of vasopressin and enhanced proximal nephron sodium reabsorption impairing free water generation, both due to effective hypovolemia, are its main drivers. As opposed to hypervolemic hyponatremia, hypovolemic hyponatremia is characterized by the frequent absence of ascites and edema. It is caused by a prolonged negative sodium balance with marked loss of extracellular fluid often due to excessive diuretic therapy.

Management of hyponatremia [H2]

It is generally considered that hyponatremia should be treated when serum sodium is lower than 130 mmol/L, although there is no good evidence as to what is the level of serum sodium in which treatment should be initiated. Hypovolemic hyponatremia requires plasma volume expansion with saline solution and the correction of the causative factor. It will not be considered further in these guidelines. The management of hypervolemic hyponatremia consists in attaining a negative water balance. Non-osmotic fluid restriction is helpful in preventing a further decrease in serum sodium levels, but it is seldom effective in improving natremia. Hypertonic sodium chloride administration to patients with decompensated cirrhosis may improve natremia but enhances volume overload and worsens the amount of ascites and edema. Therefore, it should be limited to severely symptomatic hyponatremia, as defined by life-threatening manifestations, cardio-respiratory distress, abnormal and deep somnolence, seizures and coma, which do not frequently occur in patients with cirrhosis. Furthermore, hypertonic sodium chloride administration can be considered in patients with severe hyponatremia who are expected to get a liver transplant within a few days. In these cases, hyponatremia must not be corrected completely and rapidly to avoid the risk of central pontine myelinolisis that is increased in advanced cirrhosis [143]. In practice, after an initial rapid correction aimed at attenuating clinical symptoms (5 mmol/L in the first hour), serum sodium concentration should not increase more than 8 mmol/L per day [143]. Albumin infusion appears to improve serum sodium concentration, but more information is needed [151].

3.1.2. Vaptans.

Vaptans are selective antagonists of the V2-receptors of arginine-vasopressin in the principal cells of the collecting ducts that enhance solute-free water excretion [152]. Indeed, these drugs are effective in improving serum sodium concentration in conditions associated with high vasopressin levels, such as the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and heart failure [152]. The effects of the administration of Vaptans to hyponatremic patients with cirrhosis

and ascites have been assessed in several studies. Namely, Tolvaptan, Satavaptan and Lixivaptan lead to an increased urine volume, a solute-free water excretion, and an improvement of hyponatremia in 45–82% of cases [153-155]. In another study, a short-term intravenous infusion of Conivaptan for 1 to 4 days in patients with end stage liver disease awaiting OLT was also effective in increasing serum sodium concentration [156]. However, the safety of vaptans has only been established for short-term treatments lasting from one week to one month. When one of them, namely, Satavaptan, was used in addition to diuretics for a long term, in spite of an improvement of both serum sodium concentration and control of ascites a higher all-cause mortality rate, mostly associated with known complications of cirrhosis, was reported as compared to standard medical treatment [157,158]. Moreover, a recent study casted doubts about the efficacy of Tolvaptan in patients with cirrhosis and severe hypervolemic hyponatremia (serum sodium ≤125 mEq/L) in a real-life setting [159]. At present, both Conivaptan and Tolvaptan have been approved in US by FDA while only Tolvaptan in Europe has been approved by EMA for the management of severe hypervolemic hyponatremia (<125 mmol/L). The unique indication given for Tolvaptan by EMA is SIADH, while FDA also included heart failure and liver cirrhosis. However, the occurrence of serious hepatic injury in three patients with autosomal dominant polycystic kidney disease treated with Tolvaptan in a double-blind placebo-controlled trial [160] led FDA to determine that this drug should not be used in patients with underlying liver disease.

Recommendations

- **The development of hyponatremia (serum sodium concentration <130 mmol/L) in patients with cirrhosis carries an ominous prognosis, as it is associated with increased mortality and morbidity. These patients should be evaluated for LT (II-2, 1).**

- The removal of the cause and administration of normal saline are recommended in the management of hypovolemic hyponatremia (III;1).

- Fluid restriction to 1000 ml/day seldom is recommended in the management of hypervolemic hyponatremia since it may prevent a further reduction in serum sodium levels (III;1).

- The use of hypertonic saline in the management of hypervolemic hyponatremia should be limited to the rare cases presenting with life threatening complications. It could also be considered in patients with severe hyponatremia who are expected to get LT within a few days. The correction of serum sodium concentration, once an attenuation of symptoms has been obtained, should be slow ($\leq$ 8 mmol/L per day) to avoid irreversible neurological sequelae, such as osmotic demyelinization (II-3;1).

- Albumin administration can be suggested in hypervolemic hyponatremia, but data are very limited to support its use (II-3;2).

- At present, the use of Vaptans should be limited to controlled clinical studies. (III;1)

Gastrointestinal bleeding [H1]

Pathophysiology [H2]

Variceal haemorrhage (VH) occurs because of the rupture of the variceal wall due to excessive wall tension. Variceal wall tension is an intrinsic property of the vessel wall that opposes the expansive force determined by variceal transmural pressure, which depends on portal pressure and vessel size. Tissue support surrounding the varix may counteract the increase in variceal pressure and size, protecting the wall from rupture [161]. Once variceal wall rupture occurs, the amount of bleeding is related to transmural pressure (which mainly depends on portal pressure), to the area of rupture in the vessel wall and to blood viscosity and/or alterations of haemostasis [161]. All these factors can be influenced

by therapy. Drug therapy and portal-systemic derivative procedures, reduce portal (and variceal) pressure. Endoscopic therapies and other physical methods, such as balloon tamponade or expandable prosthesis, act merely by both interrupting the blood flow into the varix and sealing the vascular wall. Portal pressure is a key factor determining both variceal rupture and the severity of the bleeding episode [161]. During acute bleeding, portal pressure may increase because of different factors such as over-transfusion or absorption of blood from the gut, which may have a role in failure to control bleeding and/or precipitating rebleeding. Portal pressure is usually assessed by the hepatic venous pressure gradient (HVPG).

Natural history of gastro-oesophageal varices and variceal haemorrhage [H2]

Variceal haemorrhage, causative of 70% of all upper GI bleeding events in patients with portal hypertension, remains one of the most severe and immediate life-threatening complications in patients with cirrhosis and constitutes the second most frequent decompensating event after ascites [162, 163]. Decompensated patients have 'clinically significant portal hypertension' (CSPH) per definition and, consequently, a high risk of having gastro-oesophageal varices. In fact, while only 42% of Child A patients have gastro-oesophageal varices, 72% of Child B/C patients do [164]. When decompensation develops, patients without varices on a previous endoscopy should have a repeat endoscopy performed given the risk of developing varices due to worsening of portal hypertension and liver dysfunction. In those without varices at screening, *"de novo"* varices develop at a rate of 7–8%/year [165, 166], which could be higher in patients decompensated due to worsening of portal hypertension and liver dysfunction. The progression rate from small to large varices runs up to 22% at one year and 51% at three years in patients with Child B/C cirrhosis, especially when alcoholic in origin and/or when

red wale marks are present at first endoscopy, compared to 2% and 16%, respectively, in compensated patients without those risk factors [165,166]. Prospective studies have consistently demonstrated that the risk of VH, estimated overall at 5–15% per year, is related to variceal size [166-170]. This risk is further amplified by the severity of liver dysfunction (Child B/C) and/or the presence of red wale marks on varices. Thus, not only medium/large varices (*i.e.* varices that do not collapse with insufflation at endoscopy), but also small varices with red signs or in Child C should be considered *'high-risk'* varices. Despite improvement in therapy, overall mortality with each episode of VH remains around 15% to 25% at six weeks. Such risk is much higher in patients who develop VH in addition to other decompensation (over 80% at five-years) than in those presenting with VH as an isolated decompensating event (20% at five-years) [170, 171]. Mortality risk is particularly high when VH is associated with AKI and/or concomitant bacterial infections [172]. Without secondary prophylaxis, rebleeding occurs in approximately 60% to 70% of patients, usually within one to two years of the index haemorrhagic event [173]. Although increasing efforts are performed to test non-invasively for the presence of gastro-oesophageal varices, these efforts largely remain restricted to compensated cirrhosis [167]. Given the high prevalence of 'high-risk varices' in decompensated cirrhosis, oesophago-gastroduodenoscopy (EGD) should be performed to detect the presence, size of varices and presence of red wale marks [168, 169].

Recommendations [Note to the typesetter: the Recommendation boxes should be typeset according to the approved mock-up for typeset Recommendation boxes]

- **Because they are deemed high risk, patients in whom decompensation develops should have EGD performed to screen for gastro-oesophageal varices, unless previously diagnosed and treated (II-2;1).**

- **If EGD is performed, the presence, size and presence of red wale marks should be reported (II-2;1).**

- **In patients without varices on screening EGD in whom the aetiological factor persists and/or the state of decompensation continues, screening EGD should be repeated every year. In the remaining patients the screening could be prolonged, but the exact interval is unclear and more data is required (III;2).**

Prevention and treatment of variceal haemorrhage [H2]

Considering the high-risk of death when VH occurs in patients with decompensated cirrhosis, implementation of strategies to adequately treat VH and to prevent (re)bleeding and death should be actively pursued in patients with decompensated cirrhosis. It should be noted that the current recommendations will concentrate on decompensated patients given the focus of these CPGs.

Primary and secondary prophylaxis of VH in decompensated patients [H3]

The Baveno VI [168] and American Association for the Study of Liver Diseases (AASLD) [169] guidelines primarily recommend NSBBs for primary prophylaxis of VH in patients with cirrhosis who have high-risk varices and also, combined with endoscopic band ligation (EBL), for secondary prophylaxis of VH. Both NSBBs and EBL have shown to be equally effective in preventing first bleeding in patients with high-risk varices. The choice between options depends on factors such as patient preference, contraindications or adverse events. Although numerically EBL induces less side effects, it has been associated with more severe and potentially life-threatening complications, resulting from bleeding EBL-ulcers. Moreover, EBL does not impact on portal hypertension. Thus, it does not reduce/prevent other complications and surveillance endoscopies are required to detect

variceal recurrence, supporting overall primary preference for NSBBs [174,175]. For prevention of rebleeding (secondary prophylaxis), combined therapy with NSBBs plus EBL is recommended because combination therapy significantly decreases the probability of rebleeding compared to monotherapy using either EBL or drug therapy. NSBBs are the cornerstone of combined therapy because a meta-analysis shows an improvement in survival with the addition of NSBBs (± nitrates) to EBL, while the addition of EBL to NSBBs (± nitrates) has no effect on mortality [176]. Recent RCTs indicate that guiding therapy according to the HVPG response to NSBBs can be valuable in this high-risk setting [91, 177]. HVPG-guided therapy may improve the outcomes achieved with current first-line therapy combining NSBBs and EBL [91], and may achieve a similar survival as covered TIPS, which is the most effective therapy in terms of preventing bleeding [177]. Accordingly, HVPG-guided therapy can be used when available. However, this approach has relevant drawbacks such as invasiveness and limited availability and, therefore, cannot be widely recommended. NSBBs, such as propranolol and nadolol, act on portal hypertension because non-selective beta-blockade reduces cardiac output and splanchnic blood flow while the unopposed effect of alpha-1 adrenergic receptors leads to splanchnic vasoconstriction, thus reducing portal pressure and its consequential complications. Nonetheless, haemodynamic response rates to NSBBs are modest: approximately 46% of cases according to meta-analyses [178, 179], endorsing the overall search for novel therapeutic options. Carvedilol, an NSBB with intrinsic anti-alpha-1 receptor activity, has been associated with a greater reduction in portal pressure than the traditional NSBBs and has therefore become a valuable alternative [180]. Its beneficial action on alpha-1 receptors reduces both porto-collateral and intrahepatic resistance, however, this is at the cost of more profound effects on systemic arterial pressure, particularly in decompensated patients. The problem with all the recommendations mentioned so far is that they are based on high quality RCTs that usually excluded patients with more advanced cirrhosis,

while major controversy has arisen in recent years regarding the use and safety of NSBBs in patients with advanced disease, particularly in those with refractory ascites and/or SBP. The discussion was initiated by the Clichy group [181], who reported poor survival and increased risk of PPCD among patients with refractory ascites on NSBB therapy. The mechanism underlying these findings was thought to relate to further induction of systemic arterial hypotension and exhaustion of cardiac reserve, in light of the progressive hyperdynamic circulation typically associated with end-stage disease. As a result, end-organ perfusion becomes critical and sets off a multitude of complications, like HRS. Therefore, "the window hypothesis" was proposed which suggested refractory ascites as a critical juncture where the protective effects of NSBBs may cease and a detrimental impact may begin [182]. However, this hypothesis was challenged by opposing reports suggesting protective effects with NSBBs even in decompensated patients [183-186]. Illustratively, a recent *post hoc* analysis of three RCTs where vaptans and NSBBs were co-administered to patients with ascites showed that NSBBs did not increase mortality [183]. On the contrary, during follow-up, 29% of initial NSBB users stopped taking NSBBs, inducing a marked rise in mortality and coinciding with variceal bleeding, bacterial infection and/or development of HRS [183]. Non-haemodynamic effects of NSBBs, like reduction of intestinal permeability, inflammation and BT, are considered to contribute to the beneficial effect, particularly in this advanced stage [187-189]. Whether NSBBs are detrimental in some patients with advanced cirrhosis should be clarified by future studies (ideally RCTs), as well as the optimal drug-schedule in such stages. Meanwhile some considerations could be made regarding dosing, type of NSBB and titration [168, 184, 185, 190]. Firstly, dosing of NSBBs was suggested as a potential determinant according to a Danish study in which low propranolol doses (<160 mg/day) were associated with reduced mortality after experiencing an SBP compared to higher doses [184, 190]. Secondly, not all NSBBs proved equal. Carvedilol, which exhibits additional vasodilatory anti-alfa-1-adrenergic

activity, might be deleterious in decompensated patients as it is more likely to cause a systemic haemodynamic depressive effect and may be best avoided or very closely monitored [185]. Thirdly, the concept of titration of NSBBs to a target heart rate of 50–55 bpm might be challenged in decompensated patients given that, in parallel to the progression of liver disease, the hyperdynamic state evolves similarly, which may lead to treatment of the most vulnerable patients paradoxically with higher, and potentially hazardous, doses. Therefore, the use of NSBBs should be based on a critical risk/benefit evaluation in patients with refractory ascites and signs of systemic circulatory dysfunction [168, 191]. Parameters such as severe hyponatraemia [191], low mean arterial pressure [38] or cardiac output [192], and increasing SCr [193] identify more vulnerable patients among those with decompensated cirrhosis, in whom a dose reduction or temporal discontinuation of NSBB treatment should be considered. The recent BAVENO VI consensus [168] proposed that in patients with refractory ascites and (i) systolic blood pressure <90 mmHg, or (ii) SCr >1.5 mg/dl, or (iii) hyponatraemia <130 mmol/L, the NSBB dose should be reduced or even temporarily discontinued. Abrupt interruption of beta-blockers for a mean of three to six days was recently found to be associated with neither an apparent increase in the risk of variceal bleeding nor with a haemodynamic rebound [194]. If upon rechallenge, NSBB intolerance occurs, EBL should be considered as an alternative in primary prophylaxis [168]. In the setting of refractory ascites and secondary prophylaxis, covered TIPS placement may be considered if the patient is an appropriate candidate [111,168].

Recommendations [Note to the typesetter: the Recommendation boxes should be typeset according to the approved mock-up for typeset Recommendation boxes]

- **Primary prophylaxis must be initiated upon detection of "high-risk varices" (*i.e.* small varices with red signs, medium or large varices irrespective of Child-Pugh classification or small varices in Child-Pugh C patients) because of increased risk of VH (I;1).**

- **Patients with small varices with red wale marks or Child-Pugh C should be treated with NSBBs (III;1).**

- **Patients with medium-large varices should be treated with either NSBBs or EBL (I;1). The choice of treatment can be based on local resources and expertise, patient preference, contraindications and adverse events (III;2). NSBBs could be preferred because in addition to lowering portal pressure, they also exert other potential beneficial effects (II-2;2).**

- **Although ascites is not a contraindication for NSBBs, caution should be exercised in cases of severe or refractory ascites (I;1). High doses of NSBB should be avoided (II-2;1). The use of carvedilol can not be recommended at present (I;2).**

- **In patients with progressive hypotension (systolic BP <90mmHg), or in patients who develop an acute inter-current conditions such as bleeding, sepsis, SBP or AKI, NSBBs should be discontinued (III,1). After recovery, reinstatement of NSBBs can be attempted (III,2). When NSBB intolerance or contraindications persist, patients bleeding risk should be managed by expeditious EBL (III,1).**

Recommendations [Note to the typesetter: the Recommendation boxes should be typeset according to the approved mock-up for typeset Recommendation boxes]

- **Combination therapy of NSBBs + EBL is recommended since it reduces the risk of rebleeding compared with monotherapy (I,1).**

- **Similar recommendations as for primary prophylaxis can be made with respect to NSBB usage in patients with ascites or developing an acute inter-current condition (III,2).**

- **If the patient continues to be intolerant to NSBB, covered TIPS placement is recommended provided that there are no absolute contraindication (cf. criteria in ascites section) (III,1).**

Variceal haemorrhage [H3]

Acute GI bleeding in cirrhosis, either because of gastro-oesophageal varices or non-variceal lesions, is a medical emergency with a high incidence of complications and high mortality and therefore requires intensive care (Fig. 2). Acute variceal haemorrhage (AVH) must be suspected in any cirrhotic patient presenting with upper acute GI bleeding and treatment should be started as soon as bleeding is clinically confirmed, regardless the lack of confirmation by upper endoscopy [195]. Initial therapy should be directed at restoring volaemia [196]. Vasoactive drug therapy [197,198] and antibiotic prophylaxis [195,196] should be initiated as soon as AVH is suspected. Goals of therapy in AVH include the control of bleeding, as well as the prevention of early recurrence and the prevention of six-week mortality, which is considered the main treatment outcome by consensus [168, 199]. Blood volume restitution should be initiated promptly to restore and maintain haemodynamic stability to ensure tissue perfusion and oxygen delivery. To facilitate resuscitation at least two catheters should be placed, large enough to allow rapid volume expansion, which can usually be done with crystalloids [196]. No benefit has been demonstrated with the use of colloids compared to crystalloids [200]. Red blood cells are

used to improve oxygen delivery to tissues in case of severe anaemia. A restrictive transfusion strategy is adequate in most patients with acute GI bleeding, with a haemoglobin threshold for transfusion of 7 g/dl and a target range after transfusion of 7 to 9 g/dl [201]. The threshold for transfusion may be higher in patients with massive haemorrhage or in those with underlying conditions that preclude an adequate physiological response to acute anaemia. Recommendations regarding management of coagulopathy and thrombocytopenia cannot be made based on currently available data [168, 169, 199].

As mentioned above vasoactive drug therapy should be initiated as soon as AVH is suspected. Starting vasoactive drugs before endoscopy decreases the incidence of active bleeding during endoscopy and facilitates endoscopic therapy, improving the control of bleeding, and potentially survival [197, 198]. Either terlipressin, somatostatin or octreotide are accepted drugs with proven efficacy [202]. All these drugs require i.v administration. The recommended dose of terlipressin is 2 mg/4 h during the first 48 h, followed by 1 mg/4 h thereafter. The recommended dose of somatostatin is a continuous infusion of 250 µg/h (that can be increased up to 500 µg/h) with an initial bolus of 250 µg. The recommended dose of octreotide is a continuous infusion of 50 µg/h with an initial bolus of 50 µg. A bolus of somatostatin or octreotide can be given again if bleeding is ongoing. Once AVH is confirmed, vasoactive drug therapy should be administered for five days to avoid early rebleeding [168,169]. Shorter administration of vasoactive drugs (48–72 h) can be considered in less severe episodes although more data are required [203]. Once blood volume restitution has been initiated and haemodynamic stability has been achieved, upper endoscopy should be performed, as soon as possible within the first 12 h after admission, to ascertain the cause of haemorrhage (up to 30% of cirrhotic patients bleed from non-variceal causes) and to provide endoscopic therapy if indicated [168,169]. Erythromycin should be considered before emergency endoscopy (250 mg i.v., 30–120

min before) to facilitate the procedure by improving visibility, in the absence of contraindications (QT prolongation) [204]. When AVH is confirmed by endoscopy, EBL should be performed within the same procedure. EBL is more effective than sclerotherapy to control bleeding, with fewer adverse effects, and may even improve survival [196]. Sclerotherapy can be used when ligation is not feasible. The combination of endoscopic therapy and vasoactive drugs is more effective than the isolated use of either of these options alone [205, 206], because it combines the local haemostatic effect on the varices induced by endoscopic treatment and the portal hypotensive effect achieved with drugs. This combination is currently considered the standard of care in AVH [168, 169]. Cyanoacrylate injection and EBL are accepted options for endoscopic therapy in patients bleeding from gastric (cardiofundal) varices as both therapies are equally effective [207]. However, EBL should only be performed on small gastric varices in which the complete vessel can be suctioned into the ligation device. Other endoscopic therapies, such as the endoscopic ultrasound–guided insertion of coils and/or cyanoacrylate, are available for fundal varices. Prevention of complications should run simultaneously to haemostatic therapies from admission of patients with cirrhosis and acute GI bleeding. The main complications, whatever the cause of bleeding, include bacterial infections (such as aspiration pneumonia or SBP), hepatic encephalopathy and deterioration of renal function. Bacterial infections are observed in more than 50% of patients and may already be present at the time of bleeding (20%) acting as a precipitating event [196]. Moreover, the presence of bacterial infection is an independent predictor of failure to control bleeding and death [208]. Antibiotic prophylaxis is recommended because it reduces the incidence of infections and improves control of bleeding and survival [199, 208]. Ceftriaxone (1 g/24 h) for up to seven days, is the first choice in patients with advanced cirrhosis, in those on quinolone prophylaxis and in hospital settings with high prevalence of quinolone-resistant bacterial infections [209, 210]. Oral quinolones (norfloxacin 400 mg b.i.d) can be used in

the remaining patients. These recommendations are however best evaluated and cross-checked from the perspective of local resistance patterns. Renal function should be preserved by the adequate replacement of fluids and electrolytes [211]. Nephrotoxic drugs (such as aminoglycosides and non-steroidal anti-inflammatory drugs [NSAIDs]) as well as LVP, beta-blockers, vasodilators and other hypotensive drugs should be avoided during the course of AVH. Oral non-absorbable disaccharides may be used to prevent the development of hepatic encephalopathy [169], although more studies are needed. When encephalopathy develops, lactulose or lactitol should be used [168, 169]. Proton pump inhibitors (PPIs) have not shown efficacy for the management of AVH. However, a short course therapy with PPI after EBL may reduce the size of post-banding ulcers [212]. Despite therapy with vasoactive drugs plus EBL and prophylactic antibiotics, up to 10–15% of patients with AVH have persistent bleeding or early rebleeding [195,199]. In such cases, TIPS should be considered as the rescue therapy of choice [168, 169]. When TIPS is not feasible or in case of modest rebleeding, a second endoscopic therapy may be attempted while vasoactive drugs can also be optimised, by doubling the dose of somatostatin and/or changing to terlipressin if not used previously. Balloon tamponade should be used in case of massive bleeding, as a temporary "bridge" until definitive treatment can be instituted and for a maximum of 24 h, preferably under intensive care facilities [168, 169]. Because of the high risk of aspiration pneumonia, tamponade should be preceded by prophylactic orotracheal intubation in comatose or encephalopathic patients. Removable, covered and self-expanding oesophageal stents are an alternative to balloon tamponade, and may have lower rates of serious adverse events [213]. RCTs suggest that in high-risk patients, early (preemptive) PTFE-coated TIPS placed within 72 h (ideally in less than 24 h) may result in better permanent control of bleeding and may improve survival [214,215]. However, these studies had relevant drawbacks such as the inclusion of a highly selected population because of strict exclusion criteria, while

observational studies have not confirmed the effect on survival [216,217]. The use of Child-Pugh class B plus active bleeding at endoscopy as a criterion to select high-risk patients has also been criticised [218]. It has also been suggested that a recalibrated MELD score may better identify patients at high risk than other scores [219]. At present, early TIPS should be considered in patients with Child-Pugh class C, with a score <14. However, future studies should clarify which criteria may be preferred to select high-risk patients before a wide implementation of early TIPS. Future studies should also clarify whether an adequate stratification of risk in patients with AVH can optimise therapy.

Recommendations [Note to the typesetter: the Recommendation boxes should be typeset according to the approved mock-up for typeset Recommendation boxes]

- **Acute GI bleeding, both due to gastro-oesophageal varices or to non-variceal lesions, carries a high incidence of complications and mortality in decompensated cirrhosis and therefore requires close monitoring (II-2;1).**

- **Volume replacement should be initiated promptly to restore and maintain haemodynamic stability (III;1). Either colloids and/or crystalloids should be used (III;1). Starch should not be used for volume replacement (I;1).**

- **A restrictive transfusion strategy is recommended in most patients with a haemoglobin threshold for transfusion of 7 g/dl and a target range of 7–9 g/dl (I;1).**

- **Antibiotic prophylaxis is recommended in cirrhotic patients with acute GI bleeding because it reduces the incidence of infections and improves control of bleeding and survival. Treatment should be initiated on presentation of bleeding and continued for up to seven days (I;1). Ceftriaxone (1 g/24 h) is the first choice in patients with decompensated cirrhosis, those already on**

quinolone prophylaxis, and in hospital settings with high prevalence of quinolone-resistant bacterial infections. Oral quinolones (norfloxacin 400 mg b.i.d) should be used in the remaining patients (I;1).

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Recommendations [Note to the typesetter: the Recommendation boxes should be typeset according to the approved mock-up for typeset Recommendation boxes]

- **Vasoactive drug therapy should be initiated as soon as acute variceal bleeding is suspected, and before endoscopy. Terlipressin, somatostatin or octreotide are accepted options. In patients with acute variceal bleeding drug therapy should be administered for three to five days (I;1).**

- **Gastroscopy should be performed within the first 12 h after admission once haemodynamic stability has been achieved, to ascertain the cause of haemorrhage and to provide endoscopic therapy (II-2;1).**

- **When acute variceal bleeding is confirmed by endoscopy, variceal ligation should be performed within the same procedure (I;1).**

- **In the absence of contraindications (QT prolongation) pre-endoscopy erythromycin (250 mg i.v., 30–120 min before) can be used to facilitate the procedure (I;2).**

- **The combination of vasoactive drugs and ligation is recommended as the first therapeutic option in acute variceal bleeding (I;1).**

- **Early pre-emptive covered TIPS (placed within 24-72 h) can be suggested in selected high-risk patients, such as those with Child class C with score <14 (I;2). However, the criteria for high-risk patients, particularly Child B with active bleeding, remains debatable and needs further study.**

Recommendations [Note to the typesetter: the Recommendation boxes should be typeset according to the approved mock-up for typeset Recommendation boxes]

- **Up to 10–15% of patients have persistent bleeding or early rebleeding despite treatment with vasoactive drugs plus variceal ligation, and prophylactic antibiotics. TIPS should be used as the rescue therapy of choice in such cases (I;1).**

- **Balloon tamponade should be used in case of uncontrolled bleeding, but with pre-requisite of expertise and as a temporary "bridge" until definitive treatment can be instituted and for a maximum of 24 h (III;1). Removable, covered and self-expanding oesophageal stents can be used as alternative to balloon tamponade (I; 2).**

- **In the context of bleeding, where encephalopathy is commonly encountered, prophylactic lactulose may be used to prevent encephalopathy, but further studies are needed (I; 2).**

- **Beta-blockers and vasodilators should be avoided during the acute bleeding episode (III, 1).**

Portal hypertension gastropathy and intestinopathy [H2]

Portal hypertension gastropathy (PHG) often presents in decompensated patients given that its natural history is significantly influenced by the severity of liver disease and portal hypertension. The presence of oesophageal varices and a Child-Pugh class B or C at enrollment were found to predict the incidence of PHG, which might range between 30 and 45% [220,221]. The incidence and severity of PHG may increase following endoscopic treatment for oesophageal varices [222]. Portal hypertension should be distinguished from gastric antral vascular ectasia (GAVE or watermelon stomach), which have different

underlying pathophysiologies and different therapeutic implications. The diagnosis of PHG is made by endoscopy and typically shows a snake-skin mosaic pattern (mild subtype), which may have superimposed red signs (severe PHG) and is most commonly located in the proximal stomach (fundus and body) whereas GAVE is characterised by the presence of red spots without a background mosaic pattern, typically located in the gastric antrum [170]. Similar endoscopical lesions, as documented in PHG, may be observed in other areas of the GI tract where they have been termed portal hypertensive duodenopathy, portal hypertensive enteropathy or portal hypertensive colopathy depending on the location of the lesions [223]. PHG and every form of enteropathy might be clinically important because they are sometimes responsible for insidious blood loss (chronic iron deficient anaemia) and in exceptional cases even overt acute bleeding. When PHG is found as an incidental asymptomatic finding without concomitant oesophageal or gastric varices, its relevance is unclear and endoscopic follow-up or prophylactic treatment is not recommended [168]. First-line therapy for chronic haemorrhage from PHG is an NSBB [168, 224, 225]. The same considerations regarding the use of NSBBs in decompensated patients should be made as for gastro-oesophageal varices, except that there is no alternative, endoscopic, standard intervention available for PHG. In addition, iron supplementation should be provided [168, 226]. In patients with medically refractory PHG and compensated cirrhosis, TIPS has shown to improve the endoscopic appearance and decrease the transfusion requirement [227]. In case of acute PHG bleeding, albeit rare, small and uncontrolled studies have suggested pharmacological intervention with somatostatin-analogues or terlipressin because of their portal hypotensive effects and reduction in gastric blood flow [226, 228]. In addition, similar measures are to be taken as for AVH (antibiotic prophylaxis, restrictive transfusion policy). For portal hypertension intestinopathy, there is no established standard of treatment and an approach analogous

to that for PHG is suggested. As for any given complication, LT should be considered as part of the management of decompensated patients.

Recommendations [Note to the typesetter: the Recommendation boxes should be typeset according to the approved mock-up for typeset Recommendation boxes]

- **NSBB and iron supplementation and/or blood transfusion, when indicated, are recommended as first-line therapy for chronic haemorrhage from PHG is an (I;1).**

- **In patients with transfusion-dependent PHG in whom NSBBs fail or are not tolerated, covered TIPS placement may be used provided the patient has no contraindication for TIPS (II-3;2).**

- **Acute PHG bleeding may be treated with somatostatin-analogues or terlipressin but substantiating data are limited (I;2).**

Gastric varices [H2]

The Sarin classification is most commonly used for risk stratification and management of gastric varices (Table 6) [229]. Gastric varices are present in about 20% of patients with cirrhosis. Gastro-oesophageal varices type 1, which are the most common (75% of gastric varices), are oesophageal varices extending below the cardia into the lesser curvature and, in the absence of specific studies, are commonly managed following guidelines for oesophageal varices [168]. Cardiofundal varices (gastro-oesophageal varices type 2 & isolated gastric varices type 1) bleed less frequently. However, haemorrhage from cardiofundal varices is often more severe, more difficult to control and shows a higher risk of recurrent bleeding and mortality (up to 45%) compared to oesophageal varices [229]. Cardiofundal varices are more frequent in patients with splanchnic venous thrombosis,

which should be investigated by imaging. The evidence to support recommendations for management of gastric VH is much less robust than that for oesophageal varices. Regarding primary prophylaxis of bleeding from gastric varices, a single randomised trial suggested that cyanoacrylate injection may be more effective than NSBBs in preventing first bleeding in patients with large cardiofundal varices, although survival was similar [230]. Therefore, the last BAVENO consensus concluded that further studies are needed to evaluate the risk/benefit ratio of using cyanoacrylate in this setting before a formal recommendation can be made and meanwhile propose NSBBs as the primary approach [168]. Acute gastric VH is medically treated like bleeding oesophageal varices. However, injection therapy with cyanoacrylate ('glue') may be the preferable option for endoscopic haemostasis [231]. Although equally effective as EBL in initial haemostasis, the rebleeding rate is significantly lower [232]. TIPS, with or without additional embolisation of collaterals, is equally effective in gastric and oesophageal VH for control of acute bleeding events and prevention of rebleeding [233]. In case of massive bleeding, balloon tamponade with the Linton-Nachlas tube may serve as a bridge to other treatments. Regarding secondary prophylaxis, in one RCT repeated cyanoacrylate injection was superior to NSBBs to prevent rebleeding from cardiofundal varices, [232] while the addition of NSBBs to cyanoacrylate did not improve the outcomes achieved with glue alone in another RCT [234]. Another trial comparing TIPS to glue injection showed that TIPS proved more effective in preventing rebleeding from gastric varices, with similar survival and frequency of complications [235]. The option of early TIPS should be strongly considered, particularly in cardiofundal varices given the high rebleeding rate, provided that patient is an appropriate candidate for such a procedure. Alternatively, balloon-occluded retrograde transvenous obliteration (BRTO) can be considered. This interventional radiological procedure enables treatment of fundal varices associated with a large gastro/splenorenal collaterals, which has the theoretical advantage over TIPS of not diverting portal blood

inflow from the liver. However, no randomised trials are available comparing BRTO with other therapies. Several variations of this technique are available, such as balloon-occluded antegrade transvenous obliteration (BATO) [236].

Recommendations [Note to the typesetter: the Recommendation boxes should be typeset according to the approved mock-up for typeset Recommendation boxes]

- **NSBBs are suggested for primary prevention of VH from gastro-oesophageal varices type 2 or isolated gastric varices type 1 (III;2).**

- **Primary prevention for gastro-oesophageal varices type 1 follow the recommendations of oesophageal varices (III;2).**

- **Acute gastric VH should be treated medically, like oesophageal VH (I;1). Cyanoacrylate is the recommended endoscopic haemostatic treatment for cardiofundal varices (gastro-oesophageal varices type 2 or isolated gastric varices type 1) (I;2).**

- **TIPS with potential embolisation efficiently controls bleeding and prevents rebleeding in fundal VH (gastro-oesophageal varices type 2 or isolated gastric varices type 1) and should be considered in appropriate candidates (II-2;1).**

- **Selective embolisation (BRTO/BATO) may also be used to treat bleeding from fundal varices associated with large gastro/splenorenal collaterals, although more data is required (III;2).**

Bacterial infections [H1]

The risk of bacterial infection in cirrhosis is caused by multiple factors that include liver dysfunction, portosystemic shunting, gut dysbiosis, increased BT, cirrhosis-associated

immune dysfunction [237-238], and genetic factors This immune defect facilitates BT, induced by increased intestinal permeability and gut bacterial overgrowth observed in cirrhosis [239]. Genetic immune defects can contribute to the high risk of bacterial infections in cirrhosis, particularly SBP. Cirrhotic patients carrying *NOD2* variants associated with impaired recognition of the bacterial product muramyl dipeptide have a higher risk of SBP and a reduced survival time [240].

Spontaneous bacterial peritonitis [H2]

Definition [H3]

Spontaneous bacterial peritonitis has been defined as a bacterial infection of ascitic fluid without any intra-abdominal surgically treatable source of infection. SBP is very common in patients with cirrhosis and ascites [241,242]. When first described, its mortality exceeded 90% but it has been reduced to approximately 20% with early diagnosis and treatment [243].

Diagnosis [H3]

The diagnosis of SBP is based on diagnostic paracentesis [33,244]. All patients with cirrhosis and ascites are at risk of SBP and the prevalence of SBP in outpatients is 1.5–3.5% and ~10% in hospitalised patients [245]. Half the episodes of SBP are present at the time of hospital admission while the rest are acquired during hospitalisation [33]. Patients with SBP may have one of the following [33]: i) local symptoms and/or signs of peritonitis: abdominal pain, abdominal tenderness, vomiting, diarrhoea, ileus; ii) signs of systemic inflammation: hyper or hypothermia, chills, altered white blood cell count, tachycardia, and/or tachypnoea; iii) worsening of liver function; iv) hepatic encephalopathy; v) shock; vi) renal failure; and, vii) GI bleeding. However, it is important to point out that SBP may be asymptomatic, particularly in outpatients [245]. In an observational study in 239 patients

with SBP, delayed diagnostic paracenteseis (>12 h after admission) was associated with a 2.7-fold increase in mortality [246]. Peritoneal infection causes an inflammatory reaction resulting in an increased number of neutrophils in ascitic fluid. Despite the use of sensitive methods, ascites culture is negative in as many as 60% of patients with clinical manifestations suggestive of SBP and increased ascites neutrophil count [33]. The gold standard for ascitic neutrophil count is manual microscopy, but it is labour intensive and associated with interobserver variability, time and costs. In most places this has been substituted with automated counts based on flow cytometry for counting and differentiating cells. This technique has been documented to have high linearity with manual microscopy and thus sensitivity and specificity close to 100% [247, 248]. The greatest sensitivity for the diagnosis of SBP is reached with a cut-off neutrophil count of $250/mm^3$, although the greatest specificity is reached with a cut-off of 500 neutrophils/mm^3 [33]. The use of reagent strips cannot be recommended for the rapid diagnosis of SBP [249]. Although the presence of bacterial DNA in plasma and/or ascites is associated with an impairment of circulatory function [250], there are not enough data to support its use in clinical practice [251]. Ascites culture is essential to guide antibiotic therapy. Patients with an ascitic fluid neutrophil count ≥250 cells/mm^3 and negative culture have culture-negative SBP [252]. Their clinical presentation is like that of patients with culture-positive SBP and should be treated in a similar manner. Some patients have 'bacterascites' in which cultures are positive but there is normal ascitic neutrophil count (<250/mm^3) [33]. In some patients bacterascites is the result of secondary bacterial colonisation of ascites from an extraperitoneal infection. These patients usually have general symptoms and signs of infection. In other patients, bacterascites is due to the spontaneous colonisation of ascites, and can either be clinically asymptomatic or lead to abdominal pain or fever. While in some patients, particularly in those who are asymptomatic, bacterascites represents a transient and spontaneously reversible colonisation of ascites, in other patients, mainly those who

are symptomatic, bacterascites may represent the first step in the development of SBP [33]. Spontaneous fungal peritonitis is a rare, less recognised and studied complication, occurring in <5% of cases, but observational data suggest a worse prognosis [253].

Spontaneous bacterial pleural empyema [H3]

Infection of a pre-existing hydrothorax, known as spontaneous bacterial pleural empyema, is uncommon. One study followed 3,390 patients with cirrhosis for four years and observed it in 2.4% of the overall population and 16% of patients with pre-existing hydrothorax, with associated mortality of 38% [254]. The diagnosis is based on pleural fluid analysis obtained by diagnostic thoracocentesis. In the largest observational study reported so far, the diagnosis of spontaneous bacterial empyema was established when the pleural fluid analysis showed a positive culture and more than 250 neutrophils/mm^3 or a negative culture and more than 500 neutrophils/mm^3, in the absence of lung infection [255]. Pleural fluid culture in blood culture bottles was positive in 75% of cases [255]. Spontaneous bacterial pleural empyema was associated with SBP in ~50% of cases [255].

Secondary bacterial peritonitis [H3]

A small proportion (~5%) of patients with cirrhosis may develop peritonitis due to perforation or inflammation of an intra-abdominal organ, a condition known as secondary bacterial peritonitis [256]. The differentiation of this condition from SBP is important. Secondary bacterial peritonitis should be suspected in patients who have localised abdominal symptoms or signs, presence of multiple organisms on ascitic culture, very high ascitic neutrophil count and/or high ascitic protein concentration, or in those patients with an inadequate response to therapy [256]. Patients with suspected secondary bacterial

peritonitis should undergo prompt computed tomography (CT) scanning and early consideration for surgery.

Recommendations [Note to the typesetter: the Recommendation boxes should be typeset according to the approved mock-up for typeset Recommendation boxes]

- **A diagnostic paracentesis should be carried out in all patients with cirrhosis and ascites without delay at hospital admission to rule out SBP. A diagnostic paracentesis should also be performed in patients with GI bleeding, shock, fever or other signs of systemic inflammation, GI symptoms, as well as in patients with worsening liver and/or renal function, and hepatic encephalopathy (II-2;1).**

- **The diagnosis of SBP is based on neutrophil count in ascitic fluid of >250/mm^3 (II-2;1). Neutrophil count is determined by microscopy, but can be substituted with a flow cytometry based automated count. The use of reagent strips has no clear evidence to support it in routine practice. (II-2; 1).**

- **Although ascitic fluid positivity is not a pre-requisite for the diagnosis of SBP, colture should be performed in order to guide antibiotic therapy (II-2;1).**

- **Blood cultures should be performed in all patients with suspected SBP before starting antibiotic treatment (II-2;1).**

- **Patients with bacterascites (neutrophil count less than 250/mm^3 but positive bacterial culture) exhibiting signs of systemic inflammation or infection should be treated with antibiotics (II-2;1). Otherwise, the patient should undergo a second paracentesis. If the culture results come back positive again, regardless of the neutrophil count, the patient should be treated. (III;1).**

- **The diagnosis of ppontaneous bacterial pleural empyema should be based on positive pleural fluid culture and increased neutrophil count of >250/mm³ or negative pleural fluid culture and a neutrophil count of >500/mm³ in the absence of pneumonia (II-2;1).**

- **Secondary bacterial peritonitis should be suspected in case of multiple organisms on ascitic culture, very high ascitic neutrophil count and/or high ascitic protein concentration, or in those patients with an inadequate response to therapy. Patients with suspected secondary bacterial peritonitis should undergo prompt CT scanning and early considerations for surgery (III, 1).**

Management of spontaneous bacterial peritonitis [H3]

Empirical antibiotic therapy [H4]

Empirical antibiotic therapy must be initiated immediately after the diagnosis of SBP [33]. Potentially nephrotoxic antibiotics (*i.e.*, aminoglycosides) should not be used as empirical therapy [76]. In the 1990s, cefotaxime, a third-generation cephalosporin, was extensively investigated in patients with SBP because at that time it covered most causative organisms and because of its high ascitic fluid concentrations during therapy [1,33]. Infection resolution was obtained in 77 to 98% of patients. A dose of 4 g/day is as effective as a dose of 8 g/day [257]. A five-day therapy is as effective as a 10-day treatment [258]. Alternatively, amoxicillin/clavulanic acid, first given i.v. then orally, has similar results with respect to SBP resolution and mortality as cefotaxime [259] and at a much lower cost. However, there is only one comparative study with a small sample size and results should be confirmed in larger trials. In addition, some concern exists regarding

amoxicillin/clavulanic acid as its use is associated with a high rate of drug induced liver injury (DILI) [260]. Administration of i.v. ciprofloxacin for seven days results in a similar SBP resolution rate and hospital survival as cefotaxime, but at a significantly higher cost [261]. However, switch therapy (*i.e.,* use of i.v. antibiotic initially, followed by oral step-down administration) with ciprofloxacin is more cost-effective than i.v. ceftazidime [262]. Oral ofloxacin has shown similar results as i.v. cefotaxime in uncomplicated SBP, without renal failure, hepatic encephalopathy, GI bleeding, ileus, or shock [263]. However, the spread of resistant bacteria in the healthcare environment during the last two decades has led to an alarming increase in the number of infections caused by multi-drug resistant organisms (MDROs) [264] that are defined by an acquired non-susceptibility to at least one agent in three or more antimicrobial categories [265]. Patients with advanced cirrhosis are highly susceptible to the development of infections caused by MDROs, because they require repeated hospitalisations, are often submitted to

invasive procedures and are frequently exposed to antibiotics, either as prophylaxis or as treatment. All these factors are well kown risk factors for the development of infections sustained by MDROs [266]. Bacterial resistance increases four fold the risk of mortality of SBP [267]. In particular, nosocomial SBP has been associated with multi-drug resistance and poor outcomes [266]. The landscape of bacterial resistance is continuously changing and challenging recommendations for antibiotics. Thus, it is crucial to separate community-acquired SBP from health care-associated and nosocomial SBP [6,266-268] and to consider both the severity of infection and the local resistance profile in order to decide the empirical antibiotic treatment of SBP. Piperacillin/tazobactam has been recommended as the primary approach for health care and nosocomial SBP in areas with low prevalence of infections sustained by MDROs. On the contrary meropenem alone or/and combined with glycopeptides or with daptomycin has been suggested as the primary approach for health care-associated SBP when severe, or in areas with high prevalence of MDROs, and for

nosocomial SBP in general [6, 266,268,269]. Regarding the severity of infection, it should be highlighted that, recently, the new criteria for the definition of sepsis, namely qSOFA and Sepsis-3 [270] have been validated in patients with cirrhosis and bacterial infections, proving that they are more accurate than those related to the systemic inflammatory response syndrome in predicting hospital mortality [271]. Accordingly, a new algorithm has been proposed for the application of qSOFA and Sepsis-3 in the management of cirrhotic patients (Fig. 3). Some more detailed recommendations on the empirical antibiotic treatment of SBP based on the severity and the environment of the infection as well as on local resistance profiles are provided (Fig. 4). A randomised trial with 32 nosocomial episodes of SBP, found meropenem plus daptomycin more effective (86.7%) than ceftazidime (25%) to manage SBP, defined as >25% decrease of neutrophil count at 48 h and to <250/mm^3 at day seven [243]. If ascitic fluid neutrophil count fails to decrease to less than 25% of the pretreatment value after two days of antibiotic treatment, there is a high likelihood of failure to respond to therapy [33]. This should raise the suspicion of an infection caused by bacteria resistant to antibiotic therapy, indicating the need for modification of antibiotic treatment according to *in vitro* sensitivity or on an empirical basis, or the presence of 'secondary peritonitis'. In this context, it should be highlighted that the progressive increase of the use of carbapenems because of the worldwide pandemic of extended spectrum beta-lactamases (ESBLs) producing *Enterobacteriaceae* has promoted the emergence of carbapenem-resistant *Enterobacteriaceae*. This implies a potential shift from MDR bacteria to extensively drug resistance (XDR) bacteria defined by a non-susceptibility to at least one agent in all but two or fewer antimicrobial categories or to pandrug resistance (PDR) bacteria defined by a non-susceptibility to all agents in all antimicrobial categories [265]. The shift requires an active surveillance in patients at risk, in order to identify patients who are colonised or infected by these clones and prevent their dissemination. The shift may also seriously affect the effectiveness of the broadest

spectrum empirical antibiotic treatment among those previously recommended for SBP and infections other than SBP. Carbapenemase-producing and carbapenem-resistant non-carbapenemase-producing *Enterobacteriaceae* can be treated with tigecycline or with the combination of tigecycline at high doses and a carbapenem in continuous infusion. Addition of i.v. colistin could be necessary in severe infections. Severe infections caused by *Pseudomonas aeuruginosa* resistant to carbapenems and quinolones usually require the combination of i.v. amikacin/tobramycin or colistin plus a carbapenem/ceftazidime (needed as synergic antibiotics despite antibiotic resistance). Vancomycin resistant *Enterococci* should be treated with linezolid, daptomycin or tigecycline. All this means reintroducing into clinical practice antibiotics known to be highly nephrotoxic in patients with cirrhosis. It follows that serum levels of aminoglycosides and vancomycin must be monitored closely in these patients, to decrease the risk of renal failure. The shift from MDR to XDR bacteria re-emphasises the interest of the pharmaceutical industry for the development of new antibiotics. Several new glycopeptides such as oritavancin, new oxazolidinones such as tedizolid phosphate, new cephalosporins, such as ceftaroline and ceftobiprole and razupenem, a new carbapemen, display extended activity against gram-positive bacteria including vancomycin-resistant *Enterococci.* In contrast, few newly developed antibiotics are active against gram-negative MDROs. Temocillin, a derivative of ticarcillin, is effective against organisms producing ESBLs. Among cephalosporin-betalactamase inhibitor combinations, ceftazidime/avibactam and ceftolozane/tazobactam represent further new alternatives to carbapenems for the treatment of patients with infections sustained by ESBL producing, carbapenem-resistant *Enterobacteriaceae* and *Pseudomonas aeruginosa*. However, there are currently no data regarding the clinical use of these drugs in cirrhosis [266].

Recommendations [Note to the typesetter: the Recommendation boxes should be typeset according to the approved mock-up for typeset Recommendation boxes]

- **Empirical i.v. antibiotics should be started immediately following the diagnosis of SBP (II-2;1).**

- **Environment (nosocomial *vs.* community acquired), local bacterial resistance profiles and severity of infection should guide empirical antibiotic treatment (I;1).**

- **Third-generation cephalosporins are recommended as first-line antibiotic treatment for community-acquired SBP in countries with low rates of bacterial resistance (I;1). In countries with high rates of bacterial resistance piperacillin/tazobactam or carbapenem should be considered. (II-2;1).**

- **Healthcare associated and nosocomial SBP is more likely to harbour resistance to antibiotics. Piperacillin/tazobactam should be given in areas with low prevalence of multi-drug resistance while carbapenem should be used in ares with high prevalence of ESBL producing *Enterobacteriaceae*. Caarbapenem should be combined with glycopeptides or daptomycin or linezolid in areas with high prevalence of methiciliin-resistant *Staphylococcus aureus* (I;1).**

- **Severe infections sustained by XDR bacteria may require the use of antibiotics known to be highly nephrotoxic in patients with cirrhosis, such as vancomycin or aminoglycosides. In these cases, patients' plasma level should be monitored in accordance with local policy thresholds. (III;1).**

- **De-escalation according to bacterial susceptibility based on positive cultures is recommended to minimise resistance selection pressure (II-2;1).**

- **The efficacy of antibiotic therapy should be checked with a second paracentesis at 48 h from starting treatment. Failure of first-line antibiotic therapy should be suspected if there is worsening of clinical signs and symptoms and/or increase or no marked reduction in leucocyte count (at least 25%) in 48 h. (II-2;1).**

- **The duration of treatment should be at least 5–7 days (III;1).**

- **Spontaneous bacterial empyema should be managed similarly to SBP (II-2;2).**

Intravenous albumin in patients with spontaneous bacterial peritonitis [H4]

SBP without septic shock may precipitate deterioration of circulatory function with severe liver failure, hepatic encephalopathy, and type 1 HRS and has approximately 20% hospital mortality despite infection resolution [272]. A randomised, controlled study in patients with SBP treated with cefotaxime showed that albumin (1.5 g/kg body weight at diagnosis, followed by 1 g/kg on day three) significantly decreased the incidence of type 1 HRS (from 30% to 10%) and reduced mortality from 29% to 10% compared with cefotaxime alone. Treatment with albumin was particularly effective in patients with baseline serum bilirubin ≥68 µmol/L (4 mg/dl) or SCr ≥88 µmol/L (1 mg/dl). It is unclear whether i.v. albumin is useful in patients with baseline bilirubin <68 µmol/L and creatinine <88 µmol/L, as the incidence of type 1 HRS in patients meeting these criteria was very low in the two treatment groups (7% without albumin and 0% with albumin) [272]. The application of the schedule of this therapeutic option should be implemented in clinical practice [273]. Non-randomised studies in patients with SBP also show that the incidence of renal failure and death are very low in patients with moderate liver failure and without renal dysfunction at diagnosis of SBP, so albumin is probably not necessary. [274].

Recommendations [Note to the typesetter: the Recommendation boxes should be typeset according to the approved mock-up for typeset Recommendation boxes]

- **The administration of albumin (1.5 g/kg at diagnosis and 1 g/kg on day 3) is recommended in patients with SBP (I;1).**

Prophylaxis of SBP [H3]

Since most episodes of SBP are thought to result from the translocation of enteric gram-negative bacteria, the ideal prophylactic agent should be safe, affordable and effective at decreasing the amounts of these organisms from the gut while preserving the protective anaerobic flora (selective intestinal decontamination) [267]. Given the high cost and inevitable risk of developing resistant organisms, the use of prophylactic antibiotics must be strictly restricted to patients at high risk of SBP [267]. Three high-risk patient populations have been identified: i) patients with acute GI haemorrhage; ii) patients with low total protein content in ascitic fluid and no prior history of SBP (primary prophylaxis), and iii) patients with a previous history of SBP (secondary prophylaxis) [275].

Primary prophylaxis in patients with low total protein content in ascitic fluid without prior history of SBP [H4]

Cirrhotic patients with low ascitic fluid protein concentration (<10 g/l) and/or high serum bilirubin levels are at high risk of developing a first episode of SBP [267]. Several studies have evaluated prophylaxis with norfloxacin in patients without prior history of SBP [267]. Fernandez *et al.* randomised 68 patients with cirrhosis and low ascites protein levels (<15 g/l) with advanced liver failure (Child-Pugh score ≥9 points with serum bilirubin level ≥3 mg/dl) or impaired renal function (SCr level ≥1.2 mg/dl, blood urea nitrogen level ≥25 mg/dl, or serum sodium level ≤130 mEq/L) to receive norfloxacin (400 mg/day for 12 months) or placebo [276]. Norfloxacin significantly improved the three-month probability of

survival (94% *vs.* 62%; *p* = 0.03) but at one year the difference in survival was not significant (60% *vs.* 48%; *p* = 0.05). Norfloxacin administration significantly reduced the one-year probability of developing SBP (7% *vs.* 61%) and HRS (28% *vs.* 41%). In a double-blind placebo-controlled trial, 100 patients with ascitic fluid total protein level <15 g/l were randomised to ciprofloxacin (500 mg/day for 12 months) or placebo [277]. The probability of survival at one year was higher in patients receiving ciprofloxacin (86% *vs.* 66%; *p* <0.04). Meta-analyses of all the trials together or including only pure primary prophylaxis support a significant preventive effect against SBP (RR 0.2; 95% CI 0.07–0.52; *p* = 0.001) [278,279]. The survival benefit is most pronounced at three months (94% *vs.* 62%, *p* = 0.003) and seems to decrease over time and may be lost after 12 months follow-up (RR 0.65; 95% CI; 0.41-1.02) [280].

Recommendations [Note to the typesetter: the Recommendation boxes should be typeset according to the approved mock-up for typeset Recommendation boxes]

- **Primary prophylaxsis with norfloxacin (400 mg/day) in patients with Child-Pugh score ≥9 and serum bilirubin level ≥3 mg/dl, with either impaired renal function or hyponatraemia, and ascitic fluid protein lower than 15 g/L is recommended (I;1).**
- **Norfloxacin prophylaxis should be stopped in patients with long-lasting improvement of their clinical condition and disappearance of ascites (III;1).**

Patients with prior SBP [H3]

In patients who survive an episode of SBP, the cumulative recurrence rate at one year is approximately 70% [33]. Probability of survival at one year after an episode of SBP is 30–50% and falls to 25–30% at two years. Therefore, patients recovering from an episode of

SBP should be considered for LT. There is only one randomised, double-blind, placebo-controlled trial of norfloxacin (400 mg/day orally) in patients who had a previous episode of SBP [281]. Treatment with norfloxacin reduced the probability of recurrence of SBP from 68% to 20%. In an open-label, randomised study comparing norfloxacin 400 mg/day to rufloxacin 400 mg/week in the prevention of SBP recurrence, the one-year probability of SBP recurrence was 26% and 36%, respectively ($p = 0.16$) [282]. Norfloxacin was more effective in the prevention of SBP recurrence due to *Enterobacteriaceae* (0% *vs.* 22%, $p = 0.01$). The use of intermittent ciprofloxacin has been associated with a higher rate of quinolone-resistant organisms and should be avoided [282,283]. It is uncertain whether prophylaxis should be continued without interruption until LT or death in all patients with prior SBP, or if treatment could be discontinued in patients showing an improvement of liver disease. Many patients receive rifaximin to prevent recurrent episodes of hepatic encephalopathy [284]. There are no data to guide new indications for primary or secondary prophylaxis of SBP among patients already on rifaximin. However, rifaximin may also be effective against recurrent SBP [285].

Recommendations [Note to the typesetter: the Recommendation boxes should be typeset according to the approved mock-up for typeset Recommendation boxes]

- **The administration of prophylactic Norfloxacin (400 mg/day, orally) is recommended in patients who recover from an episode of SBP (I;1).**
- **At present, Rifaximin can not be recommended as an alternative to Norfloxacin for secondary prophylaxis of SBP (I;2)**
- **Patients who recover from SBP have a poor long-term survival and should be considered for LT (II-2, 1).**

- **Since it has been suggested that PPI may increase the risk for the development of SBP, its use should be restricted to those with a clear indication. (II-2, 1).**

Concomitant medications [H3]

Very frequently PPIs are used in patients with cirrhosis, which may increase the risk of SBP. Indications for long-term use should be carefully assessed and PPIs discontinued when possible [286, 287]. NSBBs may be detrimental in end-stage liver disease with haemodynamic derangement, patients should be monitored closely and doses adjusted or drug discontinued if contraindications occur [168,190,288]. Probiotics have been assessed as combination therapy with norfloxacin in one randomised trial in a mixed group of patients on primary and secondary prevention of SBP. No additional benefits were demonstrated [289].

Infections other than SBP [H2]

Prevalence, diagnosis and impact on prognosis [H3]

Non-SBP infections are frequent in patients with cirrhosis and present or develop during hospitalisation in 25–30% of patients. The most frequent infections other than SBP are: urinary tract, pneumonia, skin and soft tissue infections, and bacteraemia [242,290]. They constitute a heterogeneous group regarding clinical course and prognosis. Non-SBP infections increase the odds ratio for death by 3.75 and are associated with a 30% one-month and 63% 12-month mortality [291]. Endocarditis, secondary peritonitis, pneumonia and bacteraemia have worse prognoses. The combination of data on liver and renal

dysfunction and the type of infection enables the identification of patients with poor prognosis [290]. In particular, non-SBP infections, as well as SBP, are known as common precipitating factors for ACLF [3]. An early diagnosis of all these infections and of SBP is a crucial step in the management of patients with cirrhosis. Since the presentation and the initial course of any bacterial infection may be subtle and not very specific, clinical suspicion is important. Indeed, all inpatients with cirrhosis should be considered as potentially infected until proven otherwise. Therefore, a complete work-up should be carried out at admission and at any time during the hospital stay when clinical deterioration occurs [6]. In addition, close microbiological surveillance is needed in patients who are at risk of developing infections caused by methicillin resistant organisms. C reactive protein and procalcitonin can be used for detecting infection and to define the severity of the infection [6], while their use in the stewardship of antibiotic treatment deserves further investigation [292]. To optimise the empirical antibiotic treatment, it is quite important to distinguish among community acquired, health care associated and nosocomial infections. Mortality for nosocomial infections is higher (25–48%) than for community-acquired infection (7–21%) since they are more commonly sustained by MDR bacteria [6,266,268]. Like in SBP, there is an increasing challenge of resistant bacteria among non-SBP infections. Among 312 patients with cirrhosis and blood stream infections gram-negative bacteria, gram-positive bacteria and *Candida* were the cause of blood stream infections episodes in 53%, 47% and 7% of the cases, and 31% of the infections were caused by MDR bacteria [293].

Management of infections other than SBP [H3]

In a randomised trial 94 patients with cirrhosis and infections (most prevalent were urinary tract infections [46%], SBP [22%], and pneumonia [19%]) were randomised to a broad-spectrum antibiotic regimen or a standard regimen. In-hospital mortality was significantly

higher in the standard than in the broad-spectrum group (25% *vs.* 6%; $p = 0.01$) [294]. Some more specific suggestions on the empirical antibiotic treatment of infections other than SBP based on the type, the severity and the environment of the infection as well as on local resistance profiles are given (Fig. 5-7). In patients who fail to respond to a broad-spectrum antibiotic treatment a fungal infection, including fungal SBP [295] should be suspected and investigated [296].

Finally, in two randomised trials, concomitant albumin may protect against deterioration in renal and circulatory function [297,298]. However, albumin did not improve survival and thus it cannot be recommended. The issue of the management of infections sustained by XDR bacteria has been previously developed.

Recommendations [Note to the typesetter: the Recommendation boxes should be typeset according to the approved mock-up for typeset Recommendation boxes]

- **Infections other than SBP are frequent and associated with increased mortality. Hospitalised patients with cirrhosis should be assessed and monitored closely for the presence of infections to enable early diagnosis and appropriate treatment (II-1;1).**

- **Empirical antibiotic therapy should be commenced promptly at suspicion of infection (II-1;1).**

- **The choice of empirical antibiotic therapy should be based on several factors including: environment (nosocomial *vs.* health care associated or community acquired), local resistance profiles, severity and type of infection. (I;1).**

- **In the context of high bacterial resistance to antibiotics, carbapenem alone or in combination with other antibiotics proved to be superior to third-**

generation cephalosporins in healthcare associated infections other than SBP, and therefore, should be preferred. (I;1).

- **Severe infections sustained by XDR bacteria can require the use of antibiotics known to be highly nephrotoxic in patients with cirrhosis such as vancomycin or aminoglycosides. In these cases, patients' plasma level should be monitored in accordance with local policy thresholds. (III;1).**

- **Routine use of albumin is not recommended in infections other than SBP (I; 1).**

Prophylaxis of infections other than SBP [H3]

There is preliminary evidence that in patients with Child-Pugh class C, norfloxacin administration can reduce the risk of infections and can decrease six-month mortality. However, more data are needed before a recommendation can be made [21].

Renal impairment [H1]

Definition and diagnosis [H2]

Renal impairment in patients with cirrhosis was defined more than 30 years ago by an SCr value ≥1.5 mg/dl because this value was considered an index of GFR ≤40 ml/min [32]. The use of SCr in the evaluation of renal function in patients with cirrhosis, has several well-known limitations. However, the diagnosis of renal dysfunction in liver disease is still based on it [32, 299]. The diagnosis should be based on different diagnostic categories including chronic kidney disease (CKD) and acute renal failure (ARF). When only based on reduction of GFR, the diagnosis of CKD in patients with cirrhosis is still challenging, because all the SCr-based equations that have been proposed overestimate GFR in patients with cirrhosis [300-304]. It can be reasonably assumed that patients with

decompensated cirrhosis frequently have CKD caused by certain comorbidities (*i.e.* diabetes, arterial hypertension) and/or specific causes (*i.e.* IgA nephropathy, virus-induced glomerulopathy) [305], however the prevalence of CKD in this population is still unknown. ARF is a common complication in patients with decompensated cirrhosis [306]. Historically, the diagnosis was based on an increase in SCr of 50% from baseline to a final value >1.5 mg/dl (133 µmol/L) [1, 32, 307]. Recently, the term ARF was replaced by AKI [308-310], irrespectively of its different types. AKI is now defined, as proposed by the Kidney Disease Improving Global Outcomes (KDIGO) group [310], as either an absolute increase in SCr of more than or equal to 0.3 mg/dl (≥26.4 µmol/L) in less than 48 h, or by a percentage increase in SCr of more or equal to 50% (1.5-fold from baseline) in less than seven days. A new staging system was also introduced, mainly based on the percentage increase of SCr from baseline (Table 7), either at the time of the first fulfillment of the KDIGO criteria (initial stage) or at the peak value of SCr during hospitalisation in case of progressive AKI (peak stage) [310]. Based on the staging system and according to the results of several prospective studies [311-317], a new algorithm for the management of AKI in patients with cirrhosis has been proposed [318] (Fig. 8). Recent studies have suggested that in patients with cirrhosis, in AKI stage 1, SCr <1.5 mg/dl is associated with a worse outcome than an SCr ≥1.5 mg/dl [313, 314, 317]. Thus, in contrast with the KDIGO staging system, it has been proposed to distinguish between a stage 1A (SCr <1.5 mg/dl) and a stage 1B (SCr ≥1.5 mg/dl) within AKI stage 1 [313,314,317]. It should be highlighted that the KDIGO criteria also include criteria based on urinary output in the diagnosis of AKI (Fig. 9) [310]. These criteria were not considered by the recent International Club of Ascites (ICA) consensus because (a) these patients are frequently oliguric with avid sodium retention, despite a relatively normal GFR, (b) they may have an increased urine output because of diuretics, and (c) on a regular ward, urine collection is often inaccurate and always untimely [318]. However, these criteria may also be applied

whenever a patient with cirrhosis requires a bladder catheter. The definition of baseline SCr used in the KDIGO criteria is crucial since it has been observed that about 25–30% of episodes of AKI occur before hospitalisation, representing the so-called "community-acquired AKI". Ideally, "community-acquired AKI" should be diagnosed at the time of hospital admission, requiring, according to the KDIGO criteria, an SCr value dated within the last week before admission. This point is so crucial for the application of the KDIGO criteria that it has been suggested that an SCr value be calculated when not available the seven days prior to admission. The baseline SCr can be calculated by inversely applying the formulas that are used to calculate the estimated GFR, considering normal values of GFR of 75 ml/min [319]. Whilst an imputed SCr is accepted in the general population, it can not be used in patients with cirrhosis [320]. Indeed, all SCr-based formulas overestimate the true GFR in these patients leading to an overestimation of the baseline SCr and thus underestimating the prevalence of AKI on admission [320]. Therefore, it has been proposed that not only the value obtained in the last seven days, but also that within the last three months be considered as a baseline value of SCr in patients with cirrhosis (Table 7). In addition, an SCr value obtained within the last three months is the reference to define acute kidney disease (AKD), a third category of renal impairment, along with AKI and CKD, which has been recently proposed in KDIGO recommendations. AKD is clearly a distinct category with different outcome, whether or not it is associated with AKI. AKD is defined by a GFR <60 ml/min/1.73 m^2 for less than three months, or a decrease in GFR ≥35% for less than three months, or an increase in SCr <50% within the last three months (Table 8). However, no data exist about the prognostic impact of AKD, with or without AKI, in patients with cirrhosis. Thus, waiting for these data, it seems even more justified to make the diagnosis of AKI in patients with cirrhosis on an increase in SCr ≥50% during the last three months. This assumption may also facilitate the diagnosis of AKI overlapping CKD.

Recommendations [Note to the typesetter: the Recommendation boxes should be typeset according to the approved mock-up for typeset Recommendation boxes]

- **In patients with liver diseases, even a mild increase in SCr should be considered since it may underlie a marked decrease of GFR (II-2;1)**

- **The first step to be addressed in the diagnostic process is to establish if the patient has a CKD, AKD or AKI as well as an overlap between these diagnostic categories. (II-2;1).**

- **The diagnosis of CKD should be based on a GFR <60 ml/min/1.73 m^2 estimated by SCr-based formulas, with or without, signs of renal parenchymal damage (proteinuria/haeamturia/ultrasongraphy abnormalities) for at least three months (II-2;1).**

- **The diagnostic process should be completed by staging CKD, which relies on GFR levels, and by investigating its cause. It should be highlighted that any SCr based formula overestimates GFR in patients with cirrhosis. (II-2, 1).**

- **In patients with cirrhosis the diagnosis of AKI should be based on adapted KDIGO criteria, thus, either on an increase in SCr of >0.3 mg/dl from baseline within 48 h, or an increase of ≥50% from baseline within three months (II-2,1).**

- **The staging of AKI should be based on an adapted KDIGO staging system, thus distinguishing within AKI stage 1, between AKI stage 1A and AKI stage 1B according to a value of SCr < 1.5 or ≥ 1.5 mg/dl, respectively (II-2, 1).**

Precipitating factors [H3]

Infections, diuretic-induced excessive diuresis, GI bleeding, therapeutic paracentesis without adequate volume expansion, nephrotoxic drugs, and NSAIDs are the other common precipitating factors of AKI in patients with cirrhosis [20, 242, 306]. The nephrotoxicity of contrast agents is still debated in patients with cirrhosis [321] but contrast imaging should be performed cautiously, particularly in decompensated cirrhosis or in patients with known CKD. Finally, the increase in intra-abdominal pressure associated with tense ascites may lead to AKI, by increasing renal venous pressure [322-324].

Management [H3]

The cause of AKI should be investigated as soon as possible, to prevent AKI progression. However, even in the absence of a definitive recognised cause of AKI, the management should be immediately started according to the initial stage (Fig. 2). Irrespective of the stage, diuretics should be discontinued. Similarly, even if there are controversial data, beta-blockers should be stopped [168]. Other precipitating factors of AKI should be identified and treated, including screening and treatment of infection, volume expansion when appropriate, and discontinuation of all nephrotoxic drugs, such as vasodilators or NSAIDs [318]. Volume replacement should be used in accordance with the cause and the severity of fluid loss. Patients with diarrhoea or excessive diuresis should be treated with crystalloids, whilst patients with acute GI bleeding should be given packed red blood cells to maintain haemoglobin level between 7–9 g/dl [325]. In patients with AKI and tense ascites, therapeutic paracentesis should be associated with albumin infusion since it improves renal function [326]. In case of no obvious cause and AKI stage >1A, 20% albumin solution at the dose of 1 g of albumin/Kg of body weight (with a maximum of 100 g of albumin) for two consecutive days should be given [307]. All other therapeutic options,

especially renal replacement therapy (RRT) and kidney transplantation will be discussed in the section dedicated to the management of HRS-AKI.

Recommendations [Note to the typesetter: the Recommendation boxes should be typeset according to the approved mock-up for typeset Recommendation boxes]

- **When a diagnosis of AKI is made, its cause should be investigated as soon as possible to prevent AKI progression. Even in absence of an obvious cause, the management should be immediately started. Maximal attention in the screening and treatment of infections should be carried out (II-2,1).**

- **Diuretics and/or beta-blockers as well as other drugs that could be associated with the occurrence of AKI such as vasodilators, NSAIDs and nephrotoxic drugs should be immediately stopped. (II-2,1).**

- **Volume replacement should be used in accordance with the cause and severity of fluid losses (II-2,1).**

- **In case of no obvious cause of AKI, AKI stage >1A or infection-induced AKI, 20% albumin solution should be used at the dose of 1 g of albumin/Kg of body weight (with a maximum of 100 g of albumin) for two consecutive days (III,1).**

- **In patients with AKI and tense ascites, therapeutic paracentesis should be associated with albumin infusion even when a low volume of ascetic fluid is removed. (III,1).**

Types of AKI [H3]

All types of AKI can occur in patients with cirrhosis, namely pre-renal AKI, HRS-AKI, intrarenal or intrinsic AKI, and post-renal AKI. The most common cause of AKI in

hospitalised patients with decompensated cirrhosis is pre-renal, accounting for approximately 68% of the cases [306,327,328]. Intrarenal-AKI is mainly represented by acute tubular necrosis (ATN) [306]. Finally, post-renal AKI is uncommon in decompensated cirrhosis [328]. Considering that most cases of pre-renal AKI are resolved by volume expansion and that post-renal AKI is uncommon, the key point is to differentiate HRS-AKI from ATN. As described in the section "Hepatorenal syndrome", the concept that HRS is only a functional injury has been challenged during the last decade and, thus, the definition of HRS probably has to be revised. In addition, as kidney biopsy is rarely performed in the setting of AKI in clinical practice, the distinction between HRS-AKI and ATN is difficult. Recently, novel biomarkers have emerged in this setting and urinary neutrophil gelatinase-associated lipocalin (NGAL) is the most promising. Indeed, several studies have shown that urinary NGAL, a marker of tubular damage, could help to determine the type of AKI [329-335]. However, cut-off values differ greatly according to series, there are overlaps between the different types of AKI and it should be highlighted that no study has confirmed the diagnosis by reference kidney biopsy. Diagnosis based on a combination of multiple biomarkers may be interesting but needs further evaluation [329,330,332-334].

Recommendations [Note to the typesetter: the Recommendation boxes should be typeset according to the approved mock-up for typeset Recommendation boxes]

- **All types of AKI can occur in patients with cirrhosis, namely pre-renal, HRS, intrinsic, particularly ATN, and post-renal. Therefore, it is important to differentiate among them. (II-2, 1)**

- **The diagnosis of HRS-AKI is based on revised ICA criteria. As kidney biopsy is rarely performed in the setting of AKI, biomarkers should be implemented**

In clinical practice among the different biomarkers to date, urinary NGAL can be used to distinguish between ATN and HRS. (II-2; 1)

Prognosis [H3]

In patients with decompensated cirrhosis, AKI has a negative impact on hospital survival according to either the initial stage [314], or the peak stage [313,317]. Even transient episodes of AKI are associated with a negative impact on mid-term survival [315]. Nevertheless, a more comprehensive prognostic classification also considering extra-renal organ failures is much more accurate than the KDIGO criteria for the prognosis in these patients. Finally, looking to the data in the general population, it should be highlighted that the risk for developing CKD is higher in patients with severe or repeated episodes of AKI [336]. Since patients with decompensated cirrhosis are prone to develop frequent episodes of AKI, it can be speculated that they are at higher risk of developing CKD.

Hepatorenal syndrome [H2]

Definition, diagnosis and classification [H3]

For a long time, HRS has been defined as "a functional renal failure caused by intrarenal vasoconstriction which occurs in patients with end-stage liver disease as well as in patients with acute liver failure or alcoholic hepatitis" [32,307]. Several data challenge this definition of HRS as well as the classification in type 1 and type 2. Firstly, as described below, pathogenesis of HRS includes both haemodynamic and inflammatory changes. Secondly, the absence of renal parenchymal damage, defining the functional nature, has never been proven by renal biopsies [337,338]. The absence of significant proteinuria and/or haematuria do not rule out renal lesions, particularly tubular and interstitial lesions [307]. In addition, studies assessing novel kidney biomarkers have shown that tubular

damage can occur in patients with HRS-AKI when HRS is diagnosed according to the traditional criteria [328-330,332]. Finally, it should be noted that HRS-AKI can occur in patients with underlying CKD. Type 1 and type 2 were historically defined based on time frame SCr increase [32,307]. In the recent revised classification, type 1 HRS now corresponds to HRS-AKI [318]. Consequently, type 2 HRS should now include renal impairment which fulfills the criteria of HRS but not of AKI, namely non-AKI-HRS (NAKI), and only HRS-CKD as previously proposed [339].

Pathophysiology [H3]

According to the new theory that has been developed on the pathophysiology of decompensated cirrhosis [5], the view on HRS has been changed in recent years, moving from the idea that it was only related to renal hypoperfusion due to macrocirculatory dysfunction (*i.e.* splanchnic arterial vasodilation and reduction of cardiac output) [192,338]. The new theory is that the increased circulating levels of pro-inflammatory cytokines and chemokines [340,341] may exercise a direct relevant role in the development of HRS. Such cytokines have been associated with renal impairment in patients and in animal models of cirrhosis with infection [342-345]. Moving from the concept that AKI and HRS-AKI are often precipitated by bacterial infection, the new hypothesis on the pathogenesis of sepsis-induced AKI should also be considered [346-348]. This theory proposes that a synergic interplay of inflammation and microvascular dysfunction is responsible for the amplification of the signal that PAMPs and DAMPs exert on proximal epithelial tubular cells. The recognition of this signal and its subsequent spread to all the other proximal tubular epithelial cells cause a mitochondria-mediated metabolic downregulation and reprioritisation of cell functions to favour survival processes above all else [349]. The sacrificed functions include the absorption on the lumen side of sodium and chloride. The consequent increases of sodium chloride delivery to the macula densa triggers further intrarenal activation of the RAAS and thus lowers GFR. Finally, severe cholestasis may

further impair renal function by worsening inflammation and/or macrocirculatory dysfunction, or by promoting bile salt-related direct tubular damage [350,351]. All these findings suggest that the pathophysiology of AKI, and particular of HRS-AKI, in patients with decompensated cirrhosis seems more complex than previously hypothesised, supporting the concept that AKI-HRS is not purely functional in nature.

Management [H3]

The non-specific management of AKI as been previously described. Thus, in this section, drug therapy, TIPS, RRT, LT and simultaneous liver and kidney transplantation (SLK) will be considered.

Drug therapy [H4]

Once the diagnosis of HRS-AKI has been made, patients should promptly receive vasoconstrictive drugs, in association with albumin. The rational for using vasoconstrictors is to counteract the splanchnic arterial vasodilation, improving renal perfusion [352]. Terlipressin, a vasopressin analogue, is the most commonly used. The efficacy of terlipressin plus albumin in the treatment of HRS has been proven in many studies [353-360]. In the most recent studies, rates of response (complete or partial response) to this treatment range from 64 to 76%, with a complete response, from 46 to 56% [358-360]. These response rates must now be evaluated according to the new definitions of responses in HRS-AKI recently proposed by the ICA (Table 7). In two meta-analyses terlipressin plus albumin was proven to improve not only renal function but also short-term survival in patients with HRS [361,362]. Terlipressin was initially proposed to be administered by i.v. boluses at a starting dose of 0.5-1 mg every 4–6 h, progressively increased to a maximum of 2 mg every 4–6 h in case of a reduction of baseline SCr <25% [353-358]. Adding albumin to terlipressin is more effective than terlipressin alone [354]. One possible explanation is that albumin, by increasing volaemia, may counteract the

decrease in cardiac output associated with HRS [192] but also by terlipressin [363]. In addition, antioxidant and anti-inflammatory properties of albumin may have a beneficial effect [364]. The dose of albumin in HRS treatment has not been well established. Studies have suggested adapting the dose according to the level of central venous pressure (CVP), but there is evidence that CVP is inaccurate to manage volume expansion and to assess cardiac output in patients with cirrhosis. In contrast, CVP may be helpful to prevent circulatory overload. Albumin has been used intravenously at the mean dose of 20-40 g/day. Treatment should be maintained until a complete response (SCr below 1.5 mg/dl) or for a maximum of 14 days either in case of partial response (decrease of SCr ≥50 with a final value still higher than 1.5 mg/dl) or in case of non-response. More recently, continuous i.v. infusion of terlipressin at an initial dose of 2 mg/day was proposed [359, 365], demonstrating a similar rate of response but lower adverse effects than the administration of the drug by i.v. boluses [360]. Indeed, terlipressin, when administered by continuous i.v. infusion, has a more stable lowering effect on portal pressure, even when used at lower doses than those provided by i.v. boluses [360]. The most common side effects of terlipressin are diarrhoea, abdominal pain, circulatory overload and cardiovascular ischaemic complications which have been reported in up to 45–46% of patients when the drug was delivered by i.v. boluses [360]. The rate of discontinuation because of side effects, mainly cardiovascular, is around 20% [360]. Accordingly, a careful clinical screening including electrocardiogram is recommended in all patients before starting treatment. Patients can be treated on a regular ward but the decision to transfer to a higher level of care should be case based. Recurrent HRS in responders, after the end of the treatment, has been reported in up to 20% of cases. Re-treatment is usually effective, however, in some cases, continuous recurrence occurs, thus a long-term treatment with terlipressin plus albumin and a long-term hospitalisation are required [366]. The possibility of treating some of these patients outside the hospital has recently been

proposed [367] but even if promising, further studies are needed. Other vasoconstrictive drugs include i.v. noradrenaline and oral midodrine plus subcutaneous or i.v. octretide, both in combination with albumin. Noradrenaline, given by continuous i.v. infusion at the dose of 0.5-3 mg/h, has been proven to be as effective as terlipressin regarding the increase in mean arterial pressure, the reversal of renal impairment and one-month survival [368-371]. However, the number of patients treated with noradrenaline remains too small to definitively confirm its efficacy. In addition, in contrast to terlipressin, the use of noradrenaline always requires a central venous line and, in most countries, the transfer of the patient to an intensive care unit (ICU). The combination midodrine plus octreotide, used in countries where terlipressin is not yet available [372], has been shown to be much less effective than terlipressin in the treatment of type 1 HRS in a recent RCT [359]. Vasoconstrictors, in particular terlipressin, in association with albumin, have also been proposed in the treatment of type 2 HRS. The treatment has been proven to be effective in most cases but, unfortunately, recurrence after the withdrawal of treatment is the norm. In addition, there are controversial data about the impact of this treatment on outcomes, especially in candidates for LT [373,374]. This may be, at least in part, due to the suboptimal definition of type 2 HRS, as previously discussed. The most relevant factors that may impair the response to vasoconstrictors are: a) the baseline value of SCr, b) the degree of inflammation and c) the degree of cholestasis [375-377]. The finding that the higher baseline values of SCr, the lower rate of response to terlipressin plus albumin [375], probably reflects the presence of renal parenchymal damage [337] and represents one of the main reasons behind the adoption of the KDIGO criteria for the definition of AKI in patients with cirrhosis, and the introduction of the new algorithm for its management. Regarding inflammation, it has been recently shown that, for the same value of baseline SCr, the rate of response is related to the number of extra-renal organ failures [376].

Recommendations [Note to the typesetter: the Recommendation boxes should be typeset according to the approved mock-up for typeset Recommendation boxes]

- **Vasoconstrictors and albumin are recommended in all patients meeting the current definition of AKI-HRS stage >1A, should be expeditiously treated with vasoconstrictors and albumin (III;1).**

- **Terlipressin plus albumin should be considered as the first-line therapeutic option for the treatment of HRS-AKI. Telipressin can be used by i.v. boluses at the initial dose of 1 mg every 4–6 h. However, giving terlipressin by continuous i.v. infusion at initial dose of 2 mg/day makes it possible to reduce the global daily dose of the drug and, thus, the rate of its adverse effects. In case of non-response (decrease in SCr <25% from the peak value), after two days, the dose of terlipressin should be increased in a stepwise manner to a maximum of 12 mg/day (I;1).**

- **Albumin solution (20%) should be used at the dose 20–40 g/day. Ideally, apart from routinely monitoring patients with HRS-AKI, the serial measurement of CVP or other measures of assessing central blood volume, can help to prevent circulatory overload by optimising the fluid balance and helping to titrate the dose of albumin (II-2;1).**

- **Noradrenaline can be an alternative to terlipressin. However, limited information is available (I;2).**

- **In contrast to terlipressin, the use of noradrenaline always requires a central venous line and, in several countries, the transfer of the patient to an ICU. Midodrine plus octreotide can be an option only when terlipressin or noradrenaline are unavailable, but its efficacy is much lower than that of terlipressin (I;1).**

- **According to the new definition of HRS-AKI, complete response to the treatment should be defined by a final SCr within 0.3 mg/dl (26.5 µmol/l) from the baseline value, while partial response should be defined by the regression of AKI stage to a final SCr ≥0.3 mg/dl (26.5 µmol/l) from the baseline value (III;1).**

- **Adverse events related to terlipressin or noradrenaline include ischaemic and cardiovascular events. Thus, a careful clinical screening including electrocardiogram is recommended before starting the treatment. Patients can be treated on a regular ward, but the decision to transfer to higher dependency care should be case based. For the duration of treatment, it is important to closely monitor the patients. According to the type and severity of side effects, treatment should be modified or discontinued (I;1).**

- **In cases of recurrence of HRS-AKI upon treatment cessation, a repeat course of therapy should be given (I;1).**

- **Terlipressin plus albumin is also effective in the treatment of HRS outside the criteria of AKI (HRS-NAKI), formerly known as HRS type II. Unfortunately, recurrence after the withdrawal of the treatment is the norm, and controversial data exists on the impact of the treatment on long-term clinical outcome, particularly from the perspective of LT. As such, vasoconstrictors and albumin are not recommended in this clinical scenario. (I;1).**

Transjugular intrahepatic portosystemic shunts [H4]

The use of TIPS may improve renal function in patients with type 1 HRS [378,379]. However, the applicability of TIPS in this clinical setting is usually very limited because, in most patients, TIPS is contraindicated because of severe degree of liver failure. TIPS has been studied in patients with type 2 HRS [380] and in the management of refractory

ascites, frequently associated with type 2 HRS. In these patients, TIPS has been shown to improve renal function [95,379].

Renal replacement therapy [H4]

Renal replacement therapy should be considered in the management of AKI, whatever the type. As far as HRS-AKI, it should be considered in non-responders to vasoconstrictors. RRT should also be considered in patients with end-stage kidney disease. The indications for RRT are the same in patients with cirrhosis as in the general population including: severe and/or refractory electrolyte or acid-base imbalance, severe or refractory volume overload, and/or symptomatic azotaemia. However, published data on RRT in patients with cirrhosis are scant, with controversial effects on survival [381,382]. It has been stated that indications for RRT depend on the perspective of LT. It has been stated that RRT may be considered in patients who are candidates for LT, while, in contrast, the decision to initiate RRT in non-candidates should be individualised to avoid futility [20]. However, it has recently been observed that critically ill liver cirrhotic patients requiring RRT have very high mortality independent of LT options. Thus, RRT and treatment at the ICU should not be limited to LT candidates but should be based on the individual severity of illness [383]. Therefore, repeated risk stratification is necessary during the course of treatment, assisted by prognostic scores in addition to clinical judgment and patients' wishes [383]. The ideal timing for RRT initiation has not been defined in patients with cirrhosis. However, data on AKI in patients with acute liver failure as well as in critically ill patients without liver disease suggest that early RRT improves survival [384-386]. Both haemodialysis or continuous renal replacement therapy (CRRT), have been used in patients with cirrhosis. Despite the available evidence [387], CRRT is probably better tolerated, providing greater cardiovascular stability and allowing a slower correction of severe or refractory hyponatraemia than haemodialysis.

In two controlled studies, both the so-called artificial liver support systems, either the molecular adsorbents recirculating system (MARS®) or Prometheus®, showed promising beneficial effects in patients with type 1 HRS, but should be further investigated [388,389].

Liver transplantation and simultaneous liver-kidney transplantation [H4]

The best therapeutic option in patients with HRS is LT [390]. However, several studies have shown that SCr after LT is higher in patients transplanted with HRS, compared to those without HRS at the time of LT. In addition, the presence of HRS at the time of LT has a negative impact on survival after LT [391]. The treatment of type 2 HRS before LT has given conflicting results on the clinical outcome after LT [373,374] and thus, requires further investigation. SLK can be indicated in patients with cirrhosis and CKD in the following conditions: a) estimated GFR (using MDRD6 equation) ≤40 ml/min or measured GFR using iothalamate clearance ≤30 ml/min, b) proteinuria ≥2 g a day, c) kidney biopsy showing >30% global glomerulosclerosis or >30% interstitial fibrosis, or d) inherited metabolic disease. SLK is also indicated in patients with cirrhosis and sustained AKI irrespective of its type, including HRS-AKI when refractory to drug therapy, in the following conditions: a) AKI on RRT for ≥4 weeks or b) estimated GFR ≤35 ml/min or measured GFR ≤25 ml/min ≥4 weeks [392]. Beyond these two conditions, in a candidate with high priority for LT due to a high MELD score, the option of SLK may be considered in the presence of risk factors for underlying undiagnosed CKD (diabetes, hypertension, abnormal renal imaging and proteinuria >2 g/day) [392]. The development of new biomarkers of kidney fibrosis, a common and irreversible feature of CKD, is also promising in this context [393].

Regarding the priority allocation of patients with HRS-AKI to the waiting list, some rules should be applied in case of response to drug therapy. In fact, by lowering SCr and

increasing serum sodium concentration, the treatment can significantly lower the MELD and MELD-Na score, potentially delaying LT. Considering that the survival rate in responders at three months is almost 50%, a specific policy of priority allocation is needed for these patients. This can be made either by continuing to consider the baseline MELD and/or MELD-Na score [394] rather than those during or after the end of the treatment, or by providing an exception to the MELD score [395].

Recommendations [Note to the typesetter: the Recommendation boxes should be typeset according to the approved mock-up for typeset Recommendation boxes]

- **There is insufficient data to advocate TIPS in HRS-AKI but it could be suggested in selected patients with HRS-NAKI (II-2;2).**

- **LT is the best therapeutic option for patients with HRS regardless of the response to drug therapy (I;1).**

- **The decision to initiate RRT should be based on the individual severity of illness (I;2).**

- **The indication for liver-kidney transplantation remains controversial. This procedure should be considered in patients with significant CKD or with sustained AKI including HRS-AKI with no response to drug therapy. (II-2;1).**

Prevention of hepatorenal symdrome [H3]

The prevention of HRS-AKI, as for other causes of AKI, is based on the use of albumin in patients who develop SBP [272] and the prevention of SBP using norfloxacin [276], as discussed before. In addition, the use of pentoxyfilline may decrease the incidence of renal failure in patients with cirrhosis [27] and of type 1 HRS as well as mortality in patients with severe alcoholic hepatitis [396]. However, recent papers do not confirm these results

[397,398] and further studies are needed.

Recommendations [Note to the typesetter: the Recommendation boxes should be typeset according to the approved mock-up for typeset Recommendation boxes]

- **HRS-AKI should be prevented in patients with SBP by albumin (1.5 g/kg at diagnosis and 1 g/kg on day three) (I;1).**
- **HRS-AKI could be prevented by prophylaxis of SBP with norfloxacin (400 mg/day) (I;1).**

Acute-on-chronic liver failure [H1]

Definitions and pathophysiology [H2]

Since the CANONIC study, the first major international observational study characterising the syndrome of ACLF [3], a large number of publications have described the association of this syndrome with different clinical, diagnostic and therapeutic approaches. ACLF occurs in 30% of admitted patients [3,399] and in 25% of outpatients [400], and is a major cause of death in cirrhosis, with an approximately 50% mortality rate [400]. Even though there is an ongoing debate regarding the definition of ACLF [401-405], the concept of the development of ACLF is similar across different continents and health systems. There is agreement that ACLF is not just decompensation of liver cirrhosis, but a distinct syndrome [406]. The reason is that ACLF is defined by a multi-organ failure and has a higher short-term mortality than a "simple decompensation" of cirrhosis [3,401,406]. The risk of developing ACLF is higher in outpatients with advanced liver disease according to the presence of ascites, low mean arterial pressure or anaemia and with a high MELD score [400]. ACLF develops on the background of acute decompensation (AD) of cirrhosis, but a

remarkable number of patients (~40%) admitted to hospital developed ACLF on the first episode of AD of their liver disease [3]. Thus, the presence of AD is an important clinical feature for the diagnosis of ACLF [3,401,406]. The EASL-CLIF Consortium has proposed and validated a prognostic score (CLIF-C AD score) for patients with AD who do not develop ACLF [407] The CLIF-C AD score (Table 9) was proved to be more accurate for predicting outcome in these patients than the MELD or MELD-Na score [407]. Once developed, ACLF is characterised by hepatic and extrahepatic organ dysfunction and/or failure, highly activated systemic inflammation, and a high 28-day mortality [3,408]. The overwhelming and devasting inflammatory response is a key pathogenic mechanism in the development of ACLF, probably explaining why ACLF frequently happens in younger patients [3,401,406,409]. The trigger of ACLF and this inflammatory response could not be identified in 40–50% of the patients in CANONIC study [3], which might be associated with genetic predisposition, severe portal hypertension or other factors predisposing the patients to development of AD and ACLF [410]. However, identification of the precipitating events of AD are of great importance to prevent and manage ACLF [411,412].

Precipitating events [H2]

The precipitating events vary between different populations, geographic areas and aetiologies. While in Western countries (Europe, North and Latin America) bacterial infection, followed by active alcohol intake or binge are major precipitating events [3,413,414], in Eastern countries (Asia, Pacific region) the exacerbation of hepatitis B, followed by alcohol or bacterial infections are the major causes of AD and ACLF development [415-417]. But there are a number of other insults, which might induce ACLF, such as superimposed infection with hepatotropic viruses (especially HAV, HEV), DILI, GI bleeding, circulatory dysfunction upon different situation (*e.g.* surgery, LVP without albumin). Therefore, in general the precipitating factors might be differentiated into three

major categories, hepatotoxic injury (active alcohol intake or binge, DILI), immunological insults (flairs of viral or autoimmune hepatitis, bacterial, fungal and viral infections, common cold, subclinical infections, *etc.*) and haemodynamic derangement following procedures (haemorrhage, surgery, LVP).

Bacterial infections [H3]

Overall, the major precipitating factor for ACLF is bacterial infections accounting for 30–57% of cases [410-411]. The importance of bacterial infections for the development of organ failures and ACLF was also underlined by the studies of North American Consortium for End-stage Liver Disease (NACSELD), who have defined ACLF by the development of two organ failures in presence of bacterial infections [413]. By contrast, bacterial infections were not considered to be precipitating events for ACLF according to the definition of Asian Pacific Association for the Study of the Liver (APASL) [402]. However, nowadays there is evidence that bacterial infections are mainly involved in the development of organ failures and thereby of ACLF in Asia as well [416,417]. In Western countries bacterial infections are the precipitating events in one-third of patients admitted with ACLF and in two-thirds of patients developing ACLF during follow-up [3,410,413,414]. Based on these data, preventive and early therapeutic interventions for the treatment of infections are of major importance to prevent the development of ACLF. The role of bacterial infections as triggers of AD and development of organ failures has already been discussed.

Active alcohol intake or binge [H3]

Alcoholic liver disease was the most prevalent in patients with AD and ACLF in the CANONIC study, as well as in recent reports from India [416-418]. Interestingly, active alcoholism and alcohol binge were not only a major trigger in these patients, but led to a

more severe syndrome than other triggers in alcoholic cirrhosis patients without heavy active alcoholism [3]. The role and mechanisms of active alcoholism need further investigation, especially regarding prevention and treatment.

Reactivation and superimposed viral hepatitis [H3]

Reactivation of HBV in patients with cirrhosis is the main precipitating event in the non-Caucasian Asian population [414,416], occurring mostly in genotypes B and D, and hepatitis B e antigen positive patients. Interestingly, superimposed HAV and HEV can also trigger ACLF in 14–18% [415,417]. According to the Western experience, these are unusual causes [3,414]. However, the role of HEV might have been overlooked, and might gain more importance now because of advances in diagnostics and increases in awareness [3,419]. A timely recognition and treatment of the precipitating event might prevent ACLF and improve outcome in these patients.

Clinical and diagnostic features of ACLF [H2]

As discussed previously, organ failures in the presence of AD of cirrhosis are the basis for the diagnosis of ACLF. However, in the CANONIC study the presence and grading of ACLF was based on mortality and the independent association of organ dysfunction/failure with mortality, which was chosen to be ≥15% at 28 days [3]. Organ failures were defined based on a sequential organ failure assessment (SOFA) score, which was adapted to patients with cirrhosis, the CLIF SOFA score (Table 10). However, two organs received special attention, the kidney and the brain [3]. In fact, it has been observed that even mild renal or brain dysfunction in the presence of another organ failure, is associated with a significant short-term mortality and therefore defines the presence of ACLF. Thus, patients

with renal failure, defined as creatinine ≥2 mg/dl, were classified as ACLF grade Ia while patients with a non-renal and non-cerebral organ failure combined either with mild renal dysfunction (creatinine between 1.5 and 1.9 mg/dl) and/or grade I and II hepatic encephalopathy, as well as those with cerebral failure combined with mild renal dysfunction were classified as ACLF grade Ib (Table 11) [3] Thereafter, patients with two organ failures are classified as grade II ACLF, and have a 28-day mortality rate of 32%. Patients with three or more organ failures are classified as grade III ACLF and have an average 28-day mortality of 78% (Table 10). According to this EASL-CLIF definition of ACLF, approximately one-quarter of patients admitted to the hospital for AD of cirrhosis had ACLF at admission or develop it during the hospitalisation. After having simplified the CLIF SOFA score into the CLIF Organ Failure score (Table 12), the EASL-CLIF Consortium formulated a new score, the CLIF-C ACLF score, which enables the prediction of mortality in patients with ACLF [420]. The CLIF-C ACLF score (Table 13) has been validated by different independent series of patients [418,421,422]. Other scores were recently proposed by the APASL ACLF Research Consortium and by the NACSELD, but they were not compared specifically with the CLIF-C-ACLF score [423,424].

Recommendations [Note to the typesetter: the Recommendation boxes should be typeset according to the approved mock-up for typeset Recommendation boxes]

- **The diagnosis of ACLF should be made in a patient with cirrhosis and AD (defined as the acute development or worsening of ascites, overt encephalopathy, GI-haemorrhage, non-obstructive jaundice and/or bacterial infections), when organ failure(s) involving high short-term mortality develop. (II-2;1).**

- **The diagnosis and the grading of ACLF should be based on the assessment of organ function as defined by the CLIF-C Organ Failure score (II-2,1).**

- **Potential precipitating factor(s), either hepatic (*i.e.* heavy alcohol intake, viral hepatitis, DILI, autoimmune hepatitis) and/or extrahepatic (*i.e.* infections haemodynamic derangements following haemorrhage, surgery) should be investigated. However, in a significant proportion of patients, a precipitant factor may not be identified (II-2,1).**

Management of ACLF [H2]

General management [H3]

Unfortunately, there is no specific effective treatment for ACLF [425]. Therefore, treatment is currently based on organ support and management of associated complications. The cause of liver injury can be specifically treated only in certain situations such as in ACLF secondary to HBV infection, as described later. Patients with ACLF should ideally be admitted to intensive care or intermediate care units, yet this decision should be individualised based on certain factors, particularly patients' age and associated comorbidities. Moreover, patients suitable for LT should be referred to a transplant centre early in the course of ACLF. Late referral may make transplantation impossible due to the rapid evolution of ACLF in most patients [426]. In patients in whom ACLF is associated with precipitating factors, such as bacterial infections, GI bleeding, or drug toxicity, early identification and management of these conditions is crucial to patient survival. Nonetheless, it should be emphasised that this early treatment of triggering factors may not prevent the progression of ACLF in all patients. Meanwhile, as already stated, in approximately half of patients with ACLF a precipitating factor cannot be identified [3]. Organ support is very important in the management of patients with ACLF [425].

Haemodynamic function should be monitored and vasopressor therapy administered in case of marked arterial hypotension. Hepatic encephalopathy should be treated early with standard therapy. Special care should be taken to preserve airway patency to prevent aspiration pneumonia. In patients with coagulation failure, either because of impairment of coagulation factors or low platelet count, substitutive therapy should be given only if there is clinically significant bleeding. If there is respiratory failure, patients should be given oxygen therapy and ventilation, if required. Finally, if there is kidney failure its cause should be identified and managed accordingly. Volume expansion should be given to patients with fluid loss or in the setting of SBP. Excessive volume expansion should be avoided. Patients meeting the criteria of AKI-HRS should be treated with terlipressin and albumin or norepinephrine, if terlipressin is not available. Patients with suspected ATN should be treated with RRT if they meet criteria for this treatment [392].

Specific therapies [H3]

Liver support systems [H4]

Extracorporeal liver support systems, particularly albumin dialysis (MARS system) and fractionated plasma separation and adsorption (Prometheus system) have been evaluated as therapies for ACLF. These systems remove albumin-bound substances and other substances that accumulate in the context of ACLF and may have deleterious effects on the function of different organs. Both methods have been evaluated in large RCTs in patients with ACLF and no significant effects on survival could be demonstrated [388,389]. It should be emphasised however, that the definition of ACLF in both trials was different than the current definition of ACLF based on the CANONIC study [3]. Moreover, a sub-analysis of the Prometheus study showed a beneficial effect on survival in patients with MELD score higher than 30 [389]. This finding deserves further investigation. Nonetheless,

based on the results of available RCTs, extracorporeal liver support systems do not improve survival of patients with ACLF and should not be recommended in this indication.

Antiviral therapy for chronic hepatitis B [H4]

Reactivation of hepatitis B is a very common cause of ACLF in certain areas of the world, particularly in southwest Asia [415]. A number of non-randomised studies and an RCT have shown that treatment with lamivudine, tenofovir or entecavir is associated with inhibition of HBV replication, improvement of liver function, and higher survival in patients with ACLF secondary to hepatitis B infection [427-430]. The only RCT included 24 patients, 14 treated with tenofovir and 13 treated with placebo, and showed significant differences in three-month survival (57% *vs.* 15%, respectively) [427]. Therefore, it seems evident that the presence of HBV infection should be investigated in all patients with ACLF and antiviral therapy should be started as soon as possible.

<u>*Other therapies [H4]*</u>

A number of therapies have been assessed in patients with ACLF, including dexamethasone, plasma exchange, chinese herbs, caspase inhibitors, mesenchymal stem cells transplantation, and administration of granulocyte-colony stimulating factor (G-CSF) [431-433]. In most cases, the information is still very preliminary and no recommendations can be made regarding their potential use in clinical practice. However, a note on G-CSF seems pertinent because this approach has been assessed in an RCT [433]. The rationale behind this treatment seems to be the mobilisation of stem cells from the bone marrow and their engraftment within the liver, although other beneficial effects may also occur. The only RCT evaluating this therapy included 47 patients with ACLF, as defined by the APASL criteria, 23 treated with G-CSF (12 doses of 5 µg/kg subcutaneously) and 24 treated with placebo in a double-blind manner. The main findings were an improvement in

60-day survival in the G-CSF group *vs.* the placebo group (66% *vs.* 26%, respectively; *p* = 0.001) along with a reduction in Child-Pugh, SOFA, and MELD scores and a decrease in the occurrence of HRS, hepatic encephalopathy and sepsis in G-CSF treated patients. Although these results are promising, additional studies in a larger number of patients are needed.

Liver transplantation [H4]

Liver transplantation is theoretically the definitive treatment for ACLF because it allows the cure of ACLF syndrome as well as the underlying liver disease [426]. However, some important issues regarding LT for ACLF deserve a comment, particularly the accessibility of patients to LT, evaluation of candidate subjects, the outcomes of LT on survival, and futility. The accessibility of patients with ALCF to LT is probably decreased compared to that of patients with other indications for LT, because patients with ACLF have a high mortality rate after diagnosis of the condition. Early referral to transplant centres is therefore crucial. Then, because ACLF is a rapidly evolving syndrome, candidate patients need to be submitted to a "fast-track" clinical evaluation of organ function and potential comorbidities that could contraindicate LT. Data on outcome of patients with ACLF treated with liver LT are scarce but nonetheless, patient survival at three-months after LT is about 80%, much higher than what would be anticipated if patients were not transplanted [426,434,435]. Almost all patients with ACLF-3 developed complications after LT, especially pulmonary, renal and infectious, compared to patients with no ACLF, or ACLF-1 and -2. This emphasises the need for special management when transplanting patients with ACLF-3, with repeated systematic screening for infection and careful monitoring of renal and respiratory parameters [435]. Another point is that some patients with ACLF are potentially too sick for LT. In the context of scarcity of donor livers, the potential benefit of LT for patients with ACLF must be balanced with the rationing. Thus, more data is needed

to determine medical futility in patients with ALCF [426,435]. However, if LT is contraindicated or not available for patients with organ failures ≥4 or CLIF-C ACLFs >64 at days 3-7 after diagnosis of ACLF-3, the intensive organ support should be discontinued owing to futility [426].

Recommendations [Note to the typesetter: the Recommendation boxes should be typeset according to the approved mock-up for typeset Recommendation boxes]

- **At present, there is no specific therapy for ACLF aside from antiviral therapy in patients with ACLF due to reactivation of HBV infection. Treatment of ACLF should be based on organ support and management of precipitants (see point below) and associated complications. Patients should be treated in intermediate care or intensive care settings. Organ function, particularly, liver, kidney, brain, lung, coagulation, and circulation should be monitored frequently and carefully throughout hospitalisation, as ACLF is a dynamic condition. However, monitoring and management should be individualised according to specific circumstances, mainly patients' age and comorbidities (III, 1).**
- **Early identification and treatment of precipitating factors of ACLF, particularly bacterial infections, are recommended. However, in some patients ACLF progresses despite treatment of precipitating factors (III;1).**
- **Administration of nucleoside analogues (tenofovir, entecavir, lamivudine) should be instituted as early as possible in patients with ACLF due to HBV infection (I;1).**

- **Early referral of patients with ACLF to liver transplant centres for immediate evaluation is recommended (II-3;1).**

- **Withdrawal of ongoing intensive care support can be suggested in patients, who are not candidates for LT, with four or more organ failures after one week of adequate intensive treatment (II-2, 2)**

- **Despite promising results, the administration of G-CSF can not be recommended at present (1;2).**

Relative adrenal insufficiency [H1]

Definition and pathophysiology [H2]

Relative adrenal insufficiency (RAI) is a condition of inadequate cortisol response to stress in the setting of critical illness [436], also named as "Critical Illness Related Corticosteroid Insufficiency" (CIRCI) [437]. RAI has also been described in patients with cirrhosis and, although it is mainly present in critically ill patients with sepsis or septic shock (68.9%), it also affects non-critically ill cirrhotic patients (41.8%), including those with compensated cirrhosis [438-443]. The pathophysiology of RAI in cirrhosis is not well defined. Suppression of the hypothalamic-pituitary-adrenal axis activity In addition to reduced effective volaemia, which may impair adrenal perfusion, and both impaired cholesterol synthesis and enhanced pro-inflammatory cytokine production likely contribute to impair adrenal steroidogenesis [444,445]. Adrenal dysfunction blunts the vascular effect of angiotensin II, norepinephrine and vasopressin, leading to further sympathetic nervous system activity [446]. These effects would worsen the cardio-circulatory dysfunction of advanced cirrhosis, and favour gut bacterial overgrowth, and hence BT, by impairing intestinal motility [446]. This explains why RAI in decompensated cirrhosis is associated

with a higher probability of severe sepsis and type-1 HRS, and higher short-term mortality [438,447].

Diagnosis [H2]

The diagnosis of RAI is influenced by the method employed, as the measurement of serum total cortisol, either at baseline or after stimulation by the standard dose- or low dose-short Synacthen tests can be utilised [448]. The consensus statements from the American College of Critical Care Medicine recommend referring to a delta total serum cortisol <250 nmol/L (9 µg/dl) after adrenocorticotrophic hormone administration or a random total cortisol <276 nmol/L (10 µg/dl) in critically ill patients [437]. There is no reason for not employing these indications in patients with cirrhosis. However, the diagnosis of RAI based on serum total cortisol concentration, which is measured by standard assays, may be flawed by the reduced serum levels of cortisol binding globulin (CBG) and albumin frequently seen in patients with cirrhosis. This may lead to an overestimation of RAI, as more than 90% of circulating cortisol is bound to these proteins [449]. The assessment of serum-free cortisol concentration would overcome this limitation. Serum-free cortisol levels <50 nmol/L at baseline, or <86 nmol/L (9 µg/dl) after adrenocorticotrophic hormone suggest the presence of RAI in critically ill patients [450]. By comparing RAI diagnosis in clinically stable patients with cirrhosis based on either total or free plasma cortisol, a clear discrepancy emerged, as the prevalence of RAI was 58% using total cortisol criteria and 12% using free cortisol with a peak plasma level <33 nmol/ after stimulation [451]. Unfortunately, the methods for determining free cortisol are complex and expensive, so they are not used in routine clinical practice. The surrogate methods that have been proposed for the calculation of plasma free cortisol [452,453] do not seem to be fully reliable in patients with cirrhosis [451]. For these reasons, salivary cortisol has received attention, as it correlates with free cortisol levels irrespective of the

concentration of binding proteins [454,455]. Baseline salivary cortisol <1.8 ng/ml (<0.18 µg/dl) or an increment <3 ng/ml (0.3 µg/dl) [454] following a standard-dose short Synacthen test are suggestive of RAI. However, even the evaluation of salivary cortisol is not without shortcomings [455].

Recommendations [Note to the typesetter: the Recommendation boxes should be typeset according to the approved mock-up for typeset Recommendation boxes]

- **Diagnosis of RAI should be based on a delta serum total cortisol after 250 µg corticotropin injection of <248 nmol/L (9 µg/dl) or a random total cortisol of <276 nmol/L (<10 µg/dl) (II-2,1). As serum free cortisol concentration can be influenced by the reduced serum levels of CBG and albumin frequently seen in patients with cirrhosis, salivary cortisol determination can be preferred (II-2;2).**

Treatment of relative adrenal insufficiency [H2]

It is not known whether cortisol supplementation in clinically stable cirrhosis with RAI is of any value. Two studies have evaluated the effects of treating RAI in critically ill patients with cirrhosis. In one study 17 patients with cirrhosis and sepsis, in whom RAI was diagnosed, received i.v. hydrocortisone (50 mg/6h), and were compared with 50 consecutive patients with cirrhosis and septic shock who had previously been admitted to the same ICU but did not receive steroids. A higher rate of shock resolution, survival in the ICU and hospital survival were seen in the patients treated with hydrocortisone [456]. In the second study, 57 patients with cirrhosis, septic shock and RAI were randomised to receive either i.v. 50 mg of hydrocortisone or normal saline every 6 h until haemodynamic stability was achieved, followed by steroid tapering over eight days. Lower vasopressor

doses and higher rates of shock reversal were seen in patients who received hydrocortisone. However, 28-day mortality did not differ between the two groups. Moreover, shock relapse and GI bleeding occurred more often in the hydrocortisone group [457].

Recommendations [Note to the typesetter: the Recommendation boxes should be typeset according to the approved mock-up for typeset Recommendation boxes]

- **At present, hydrocortisone treatment (at a dose of 50 mg/6h) of RAI cannot be recommended (I-2).**

Cardiopulmonary complications [H1]

Cirrhotic cardiomyopathy [H2]

Definition and pathophysiology [H2]

Cirrhotic cardiomyopathy (CCM) refers to chronic cardiac dysfunction in a patient with established cirrhosis, characterised by a blunted contractile response to stress (pharmacological/surgical or inflammatory) and an altered diastolic relaxation, often associated with electrophysiological abnormalities such as prolongation of the QTc interval. These phenomena occur in the absence of any other cardiac disease [458]. Systemic inflammation is thought to be key in inducing myocardial dysfunction associated with impaired diastolic relaxation and decreased left ventricular ejection fraction, however, there are few controlled studies [193,459-460]. Shear stress generated by portal hypertension exhibiting mechanical forces on myocardial fibres, may also play a part [461]. CCM is largely subclinical but its presence does influence prognosis in advanced disease [462], and it certainly impacts on the course of interventions such as TIPS and LT [463].

Diagnosis: [H2]

Characterisation of Systolic dysfunction in cirrhotic cardiomyopathy [H3]

Systolic dysfunction refers to impaired left ventricle contractile responses to stress on echo, translating to a resting left ventricular ejection fraction (LVEF) <55%. For most patients with cirrhosis, the resting systolic function is normal or even increased, due to the hyperdynamic circulation and reduced afterload to maintain cardiac output. To investigate systolic dysfunction in cirrhosis, it is necessary to induce circulatory stress either pharmacologically or through exercise. Systolic dysfunction then manifests as a lack of an appropriate left ventricular contractile response to the applied stress. As disease advances, the progressive reduction in peripheral vascular resistance unmasks systolic dysfunction. Early studies used exercise stress testing to demonstrate a lack of increment in cardiac output or LVEF [464,465] and this was even shown when noradrenaline levels were increased, suggesting loss of sympathetic responsiveness [466]. More recent studies used pharmacological stress echo to show a blunted response [467]. However, other studies using cardiac MRI, have shown normal chronotropic and inotropic responses suggesting the techniques used may give rise to variability [468].

Myocardial strain imaging for assessing systolic dysfunction: [H3]

Myocardial strain imaging is a more recent echocardiographic technique evaluating the degree of shortening of myocardial muscle fibres ('strain') influencing cardiac wall motion. The measurement of left ventricular global longitudinal systolic strain (GLS) is believed to be a sensitive marker of left ventricular systolic function and facilitates the assessment of systolic dysfunction at rest [469,470], as well as having prognostic importance in heart failure [471]. Studies of strain imaging in cirrhosis have demonstrated variable results; some showing impaired systolic strain in patients compared with healthy controls, albeit with no correlation to Child-Pugh score [472,473]. Others demonstrate systolic strain within

normal range and not influenced by the presence of ascites [474,475]. However, interestingly, when patients undergo LT, the systolic strain improves [472].

Characterisation of Diastolic dysfunction in Cirrhotic cardiomyopathy [H3]

Numerous echocardiographic criteria along with transmitral Doppler evaluation have been used to characterise diastolic dysfunction including, early diastolic/atrial filling ratio (E/A), early diastolic filling/mitral annular velocity (E/e') and tricuspid systolic jet velocity. Such measurements are influenced by the pre- and afterload changes of portal hypertension. The latest American Society of Echocardiography (ASE) and European Association of Cardiovascular Imaging guidelines for the evaluation of diastolic dysfunction recommend the following criteria based on a normal LVEF (often the case in cirrhosis) [476]:

i.   Average E/e'>14

ii. Septal e' velocity <7 cm/s OR Lateral e' velocity <10 cm/s

iii. Tricuspid velocity >2.8 m/s

iv. Left atrial volume index (LAVI) >34 ml/m^2

Diastolic dysfunction translates to impaired relaxation of the left ventricle, abnormal filling of the left atrium, and a higher left atrial volume. Indeed, increased LAVI has been associated with greater risk of heart failure in ischaemic cardiac disease [477]. Based on these guidelines, diastolic dysfunction is classified as: grade I if one of the three principle criteria (1,3 and 4 above) are met; and grade II if two or more of the criteria are met.

However, there is heterogeneity in descriptions of the prevalence of diastolic dysfunction in cirrhosis, in part reflecting the different echo techniques and/or diagnostic criteria applied, and the influence of vasoactive agents such as beta-blockers and terlipressin.

Several studies using an E/A ratio of ≤1 criteria have demonstrated left atrial enlargement in patients with ascites and advanced disease [465, 478]. Therapeutic paracentesis improves E/A ratio and importantly, in all studies, there is no relation to aetiology [479]. In

patients treated with TIPS there was no relation to aetiology, but diastolic dysfunction does show a positive correlation with higher MELD scores [463, 480]. A further study using E/e' ratio to define diastolic dysfunction in patients with ascites and elevated plasma renin, demonstrated that an increased E/e' was an independent predictor of development of HRS type 1 and one-year mortality [481]. By contrast, other studies fail to show a clear relationship with disease severity or survival [461, 473, 482], albeit in two studies echo criteria are not specified [461, 473]. Studies using the LAVI criteria suggest a closer association between left atrial enlargement and Child-Pugh C disease [483].

Newer techniques such as cardiac MRI with 'T1 mapping' and Late Gadolinium enhancement are being deployed to assess whether fibrosis or oedema modulates myocardial function in conditions such as amyloid and Fabry disease [484]. Literature on using such techniques in liver disease are very limited. A recent study in patients with chronic hepatitis C showed no significant differences in echo parameters to controls, but demonstrated lower post-contrast myocardial T1 time and higher partition coefficients, indicative of diffuse myocardial fibrosis [485].

Natural history: [H2]

Impact of disease related physiological stress: sepsis, decompensation and/or GI bleeding [H3]

There are limited studies of cardiac assessment during acute cirrhosis decompensation and associated haemodynamic instability. In a seminal study of acute cirrhosis decompensation with SBP, a subgroup with HRS were shown to have lower cardiac outputs at diagnosis and this correlated inversely with high inflammatory indices [193]. A follow-on study by the same group identified that patients with HRS had cardiac outputs that were further reduced at follow-up, compared to patients who do not develop HRS after SBP, and these patients had higher plasma noradrenaline and renin [486]. Other studies

recapitulate this with a demonstration of reduced kidney blood flow and importantly, suggest those with low cardiac index, also have increased mortality [192,486].

In relation to systemic inflammation and sepsis, one study showed lipopolysaccharide binding protein (LBP) levels (a surrogate for BT and lipopolysaccharide) in patients with ascites to be associated with significant diastolic dysfunction and left atrial enlargement. The E/e' ratio in these patients correlated with LBP levels. This data supports findings from experimental studies, which have shown a role for inflammation, signalling through the inflammasome and macrophage activation, as key pathological processes related to myocardial dysfunction [487-489].

Acute GI bleeding in cirrhosis is understandably associated with significant haemodynamic disturbances and has not been studied systematically in relation to cardiac function. Data assessing chronotropic function suggest the QTc interval is increased in cirrhotic patients during an acute bleeding episode compared to non-cirrhotic patients, and that this is associated with higher MELD scores and independently predicts survival [490]. This contrasts with a more recent study that fails to demonstrate a clear link between QTc prolongation and mortality [491]. Possible reasons for this heterogeneity in outcomes are the variable nature of vasoactive agents and their respective doses required for the control of bleeding in these studies. For example, one study showed terlirpessin decreased cardiac output by 17% and the reduction in wall motion after terlipressin correlated with the Child-Pugh score [492].

Impact of interventions on cirrhotic cardiomyopathy: [H3]

TIPS: [H4]

Cardiac reserve is a major clinical consideration for elective TIPS placement and a 2D echo to assess LVEF is standard practice. Despite this, some patients do have cardiac decompensation post TIPS insertion. Several studies show an association between

presence of diastolic dysfunction at the time of TIPS and poor survival [463, 480]. By contrast, others have not shown any difference in survival between patients with and without diastolic dysfunction at the time of TIPS [493]. However, uniformly, studies suggest an increase in left ventricular and atrial volume over time, implying that such patients may be at greater risk of future heart failure, based on literature for ischaemic heart disease and dilated cardiomyopathy [477, 494].

Liver transplantation: [H4]

Just as data on the effects of cirrhosis complications on cardiac function are variable, data on the impact of the physiological stress of LT on patients with pre-existing cardiac dysfunction is heterogenous, largely because of the different echo criteria and thresholds applied.

One study in 173 transplant recipients assessed systolic (resting ejection fraction <55%) and diastolic (E/A ratio <1 or a deceleration time >200 msec) dysfunction and reported it occurring in 2% and 43% of patients, respectively. Whilst patients with diastolic dysfunction were older, interestingly, outcomes were not influenced by the presence of diastolic dysfunction [495]. By contrast, another study used echo and brain natriuretic peptide (BNP) levels to grade severity of cardiac dysfunction. Those patients with higher BNP levels (>391) on day one tended to have higher mortality and longer dialysis requirements post transplantation. Of these, a subset with BNP levels >567 had ejection fractions <50%, and some of these died of cardiogenic shock within 72 h post-transplant. Autopsy in these patients showed diffuse myocardial fibrosis. In the main, BNP levels tended to decrease towards normal values over a week [496].

A further study performed a detailed echo assessment, including myocardial strain assessment with speckle tracking, in patients undergoing LT compared to non-transplanted patients over a median follow-up of 18 months. Whilst patients pre-transplant

had increased left ventricular mass and diastolic dysfunction, following transplantation, there was a significant improvement in systolic strain and reduced left ventricular mass. Conversely, cirrhosis patients who were not transplanted had an increase in left ventricular mass, albeit systolic strain did not change significantly [472]. This implies that some of the pathophysiological changes in CCM, such as increased left ventricular mass and size, are reversible with resolution of the disease. However, studies with comprehensive characterisation of cardiac function post transplantation are limited.

Prognosis for cirrhotic cardiomyopathy [H2]

Data relating cardiac dysfunction (especially diastolic dysfunction) with survival is variable. Some prospective studies, despite detailed evaluation of patients, including those with ascites and using speckle tracking, show no relation between cardiac dysfunction and survival, even among more decompensated patients [474, 497]. Many of the patients in these studies have evidence of diastolic dysfunction and some with even advanced grade II diastolic dysfunction albeit the GLS values in these studies are within the normal range. Conversely, other studies suggest an association between presence of diastolic dysfunction and higher two-year mortality, with diastolic dysfunction ranging from 38–67%, especially in patients with severe ascites [462, 498]. Indeed, in one such study, a multivariate analysis showed left ventricular diastolic dysfunction was an independent predictor of mortality [462]. Another study followed 80 patients to assess one-year mortality, finding 46% had diastolic dysfunction on echo criteria and about half of these had grade II dysfunction, in whom mean arterial blood pressure was lower and MELD score higher than grade I patients. The presence of diastolic dysfunction was associated with a higher degree of ascites and plasma renin levels and 38% of these patients developed criteria for HRS type I. Survival was 95% in those without diastolic dysfunction,

compared to 79% in those with grade I dysfunction and 39% with grade II diastolic dysfunction. E/e' ratio was an independent predictor of survival [481].

Recommendations [Note to the typesetter: the Recommendation boxes should be typeset according to the approved mock-up for typeset Recommendation boxes]

- **Evaluation of cirrhosis patients with echocardiography should be performed with dynamic stress testing either pharmacologically, or through exercise, given that systolic dysfunction may be masked by the hyperdynamic circulation and reduced afterload. Failure to increment cardiac output after physiological/pharmacological stress (and in the absence of influence of beta-blockade) indicates systolic dysfunction (II-1;1).**

- **Myocardial strain imaging and assessment of GLS may serve as a sensitive marker of left ventricular systolic function and facilitate its assessment at rest and in decompensated patients. (II-2;2) Cardiac MRI may also identify structural changes. However, with all these techniques, there is the need for more controlled studies and correlation with clinical endpoints (III;2).**

- **Diastolic dysfunction may occur as an early sign of cardiomyopathy in the setting of normal systolic function, and should be diagnosed using the recent ASE guidelines, namely: Average E/e'>14; Tricuspid velocity >2.8 m/s and LAVI >34 ml/m^2 (II-1;1).**

- **In patients with AD of cirrhosis, reduced cardiac output (as a manifestation of CCM) is of prognostic significance as it is associated with the development of AKI (specifically hepatorenal dysfunction) after infections such as SBP (II-1;1).**

- **Prolongation of the QTc interval is common in cirrhosis and can be evaluated since it may indicate a poor outcome. Agents that can prolong the QT interval should be used cautiously (II-2;2).**

- **Detailed functional cardiac characterisation should be part of the assessment for TIPS insertion (II-2;2) or LT (II-1;1].**

- **Standardized criteria and protocols for the assessment of systolic and diastolic function in cirrhosis are needed (II-2;2).**

Hepato-pulmonary syndrome [H1]

Definitions and Clinical manifestations [H2]

The association of chronic liver disease with respiratory symptoms and hypoxia is well recognised. Four main pulmonary complications may occur in patients with chronic liver disease: pneumonia, hepatic hydrotorax, HPS, PPHT. HPS is defined as a disorder in pulmonary oxygenation, caused by intrapulmonary vasodilatation and, less commonly, by pleural and pulmonary arteriovenous communications occurring in the clinical setting of portal hypertension [499,500]. It is most commonly diagnosed in patients with cirrhosis [499,500] and portal hypertension [501] but, it has also been described in patients with pre-hepatic portal hypertension [502], with venous obstruction but without cirrhosis, and even in patients with acute or chronic hepatitis [501] (Table 14). A severe impairment of liver function and a specific aetiology of liver disease are not needed for the development of HPS [499], based on the profiles of the patients studied. In terms of prevalence, HPS has been reported in 10% of patients with chronic viral hepatitis in 15–23% of those with cirrhosis and in 28% of those with Budd-Chiari syndrome [503-505]. However, the prevalence of HPS reported in patients with cirrhosis undergoing LT evaluation ranges from 5–32% [505-509], while intrapulmonary vascular dilatation (IPVD) can be detected by

echocardiography in 50–60% of cirrhosis patients undergoing LT evaluation. No relationship seems to exist between HPS and CCM [505]. The clinical manifestations of HPS in patients with chronic liver disease primarily involve dyspnoea and platypnoea [499,503,507]. Dyspnoea is the most common respiratory complaint in patients with HPS, but it is unspecific. Its onset is insidious, usually occurring on exertion. Platypnoea, which is a shortness of breath exacerbated by sitting up and improved by lying supine, is a less sensitive but a more specific finding in these patients. Hypoxemia with exertion or at rest is common and it is exacerbated in the upright position (orthodeoxia). There are no signs or hallmarks of HPS on physical examination. However, tachypnoea and polypnoea, digital clubbing and/or cyanosis in patients with the hallmarks of chronic liver disease suggest the presence of HPS [499,503,507].

Pathophysiology [H2]

The pathophysiology of HPS is characterised by an IPVD occurring within the pulmonary arterial circulation. This vascular abnormality consists of diffuse or localised abnormal dilated pulmonary capillaries and, less commonly, pleural and pulmonary arteriovenous communications [510], which result in impaired oxygenation of venous blood as it passes through the pulmonary circulation. IPVD impairs ventilatory/perfusion (V/Q) ratio and may result in anatomic and functional shunt leading to hypoxaemia (Fig. 10). In patients with advanced liver cirrhosis this leads to a subtle increase in intrapulmonary blood shunting, which is more pronounced in patients with HPS. The consequent increase of shunting and V/Q mismatch in the upright position is the cause of the orthodeoxia [511]. The pathogenesis of IPVD is probably multifactorial (Fig. 11). The release of nitric oxide, which is a potent vasodilator, plays a critical role in the development of HPS. The increased release of nitric oxide in the pulmonary circulation is related to an increased expression and activity of two isoforms of nitric oxide synthase (NOS), the endothelial NOS (eNOS)

and the inducible NOS (iNOS) [512-517]. Meanwhile, BT and the BT-related endotoxaemia and pro-inflammatory response also contribute to the accumulation of macrophages in the pulmonary microvasculature [518]. Endothelial activation of the fractalkine (CX3CL1), a chemokine, in the lung may favour the adherence of monocytes in the pulmonary microcirculation [519]. Monocytes express iNOS and produce heme oxygenase-1, leading to increased carbon monoxide production, further enhancing vasodilatation [520]. CX3CL1 and vascular endothelial growth factor (VEGF) A, produced by circulating monocytes, also contribute to angiogenesis, recently recognised as a further pathogenetic factor of pulmonary IPVD in experimental HPS [521-523]. A downregulation of miRNA-199 a-5p has recently been described as a contributory mechanism of pulmonary microvascular endothelial cell proliferation and thus pathogenesis of HPS [524]. Polymorphisms in genes involved in the regulation of angiogenesis have also been associated with the risk of HPS in patients with cirrhosis [525] (Fig.11). Finally, it has recently been observed that rosuvastatin, by down-regulating protein expression of nuclear factor kappa B and VEGF-1,2 and Rho-associated A kinase, may improve the intrapulmonary angiogenesis and the alveolar-arterial oxygen pressure gradient in common bile duct ligation rats [526].

Diagnosis [H2]

In patients with portal hypertension and the clinical suspicion of HPS partial pressure of oxygen (PaO_2) in arterial blood gas (ABG) should be assessed. A PaO_2 lower than 80 mmHg and or an alveolar-arterial oxygen gradient ($P[A-a]O_2$) ≥15 mmHg while breathing ambient air at sea level should lead to further investigations (Table 14). For adults ≥65 years a $P[A-a]O_2$ ≥20 mmHg cut-off is used [527]. However, it should be highlighted that although these criteria are well established, enabling one to unify the diagnostic methods and thus to better understand the disease, they are based on a consensus of experts. Pulse oximetry indirectly measures oxygen saturation (SpO_2), it is

non-invasive and may be useful in the diagnosis of HPS in adults since an SpO_2 <96% was found to be highly sensitive (100%) and specific (88%) for detecting HPS in patients with a PaO_2 <70 mmHg, limiting ABG testing to only 14% of patients [528]. The validity of this non-invasive approach was not confirmed, recently, in paediatric patients with HPS [529]. Serial SpO_2 measurements may be useful to monitor impaired oxygenation over time in patients with HPS. The ABG is essential for the staging of the severity of HPS. HPS can be categorised as mild (PaO_2 ≥80 mmHg), moderate (PaO_2 60–79 mmHg), severe (PaO_2 50–59 mmHg), and very severe (PaO_2 <50 mmHg) [499,501,502,504]. Recently, it has been observed that HPS is associated with elevated von Willenbrand factor antigen (vWF-Ag) levels. Thus, vWF-Ag has been proposed as a potentially useful screening tool for early detection of HPS, but further studies are needed to validate it [530]. The chest X ray is usually non-specific, nevertheless, it can be used to effectively rule out other concomitant pulmonary diseases since only a mild interstitial pattern in the lower part of the lungs may be found, because of pulmonary vasodilatation [499,501,502,504]. A decrease in the single-breath diffusing capacity for carbon monoxide is the only alteration of the routine pulmonary function test that is frequently and consistently abnormal in patients with HPS. However, it is not specific and it may not normalise after LT [499,501,502,504]. All the other respiratory function tests are unspecific, showing normal or reduced forced vital capacity or maximum forced expiratory volume during the first second (FEV1). Thus, they can only be used to rule out other concomitant pulmonary diseases. Thoracic CT scans have also been proposed as a complementary technique to rule out another underlying pulmonary pathology [499,500], although there is little information regarding their specific role in the diagnosis of HPS. It has been suggested that thoracic CT scans can be useful to measure the calibre of the peripheral arteries and the bronchial/arterial relationship [531,532]. Furthermore, CT

scanning makes it possible to define the vascular pattern of HPS in a similar manner to arteriography by detecting pleural and pulmonary arteriovenous communications. Contrast-enhanced transthoracic echocardiography with saline (shaken to produce microbubbles >10 µm in diameter) is the most useful method to detect pulmonary vascular dilatation. After the administration of agitated saline in a peripheral vein, microbubble opacification of the left atrium within three to six cardiac cycles after right-atrial opacification indicates microbubble passage through an abnormally dilated vascular bed, since microbubbles do not pass through normal capillaries [533]. The injection of technetium-99 m–labeled macro-aggregated albumin (MAA) in the peripheral vein for lung scanning (MAA scan) is a potential alternative diagnostic procedure although it is more invasive and less sensitive. Particles, with a 20–50 µm size, escape through the abnormal pulmonary capillaries and stay in downstream capillary beds supplied by systemic arteries, such as the brain, kidneys, and spleen. Quantitative imaging of the MAA scan in the brain and lung enables calculation of the degree of shunting [534-535]. The measurement of shunting with MAA scans may be useful as a complementary diagnostic tool in patients with HPS in two clinical situations. Firstly, in patients with a severe hypoxaemia and a coexistent HPS and intrinsic lung disease since a shunting >6% at MAA scan proves the major contribution of HPS to hypoxaemia. Secondly, in patients with HPS and very severe hypoxaemia (PaO_2 <50 mmHg), since the presence of shunting >20% is associated with a poor outcome after LT [536]. Despite the potential role of lung perfusion scintigraphy for prognostic use in patients with cirrhosis and IPVD, its diagnostic accuracy for HPS remains to be established [537]. Finally, neither constrast ecocardiography nor MAA scan can differentiate discrete arteriovenous communications from diffuse precapillary and capillary dilatations or intracardiac shunt. The former distinction can be made by means of pulmonary angiography. The latter distinction can be made by means of transoesophageal contrast-enhanced echocardiography that directly reveals the intra-atrial septum.

Pulmonary angiography should not be performed in all patients with suspected HPS, but only in: a) patients with the severe hypoxaemia (PaO$_2$<60 mmHg) poorly responsive to administration of 100% oxygen, and b) patients strongly suspected (by means of a CT chest scan) of having arteriovenous communications that would be amenable to embolisation.

Recommendations [Note to the typesetter: the Recommendation boxes should be typeset according to the approved mock-up for typeset Recommendation boxes]

- **In presence of tachypnoea and polypnoea, digital clubbing and/or cyanosis in a patient with the hallmarks of chronic liver disease HPS should be suspected and investigated (II-2,1).**

- **Pulse oximetry is the screening tool for HPS in adult patients, but not in paediatric patients. For patients with SpO$_2$ <96%, ABG analysis should be performed. A PaO$_2$ lower than 80 mmHg and or an alveolar-arterial oxygen gradient (P[A-a]O$_2$) ≥15 mmHg while breathing ambient air, should lead to further investigations. For adults ≥65 years a P[A-a]O$_2$ ≥ 20 mmHg cut-off should be used (II-2,1).**

- **The use of contrast (microbubble) echocardiography to characterise HPS is recommended (II-2;1).**

- **Trans-oesophageal contrast-enhanced echocardiography can be performed to exclude definitively intra-cardiac shunts, albeit this technique is not devoid of risks (II-2;2).**

- **An MAA scan should be performed as a complementary tool to quantify the degree of shunting in patients with severe hypoxaemia and coexistent intrinsic lung disease, or to assess the prognosis in patients with HPS and very severe hypoxaemia (PaO$_2$ <50 mmHg) (II-2;1).**

- **Neither contrast echocardiography nor MAA scan can definitively differentiate discrete arteriovenous communications from diffuse precapillary and capillary dilatations or cardiac shunts. Pulmonary angiography should be performed only in patients with the severe hypoxaemia (PaO$_2$ <60 mmHg), poorly responsive to administration of 100% oxygen, and in whom there is a strong suspicion of arteriovenous communications that are amenable to embolisation. (II-2;1)**

Natural history [H2]

The natural history of IPVD as well as of HPS is still unclear. Most patients with IPVD maintain a normal gas exchange over time, and it is not clear the reason why a subset of patients with IPVD develops HPS [538]. A diagnosis of HPS is associated with a poor outcome in terms of both survival and quality of life [506,508,509]. Regarding survival, it should be highlighted that in patients undergoing evaluation for LT, the mortality rate was almost double in patients with HPS compared to patients with cirrhosis without HPS, independent of other potential predictors of mortality such as age, MELD score and comorbidities [506]. In patients with cirrhosis and HPS, who were not evaluated for LT, the five-year survival rate was 23% while it was 63% in patients with cirrhosis without HPS who were matched for the aetiology and severity of cirrhosis according to the Child-Pugh classification, age, and MELD score [504]. Survival was significantly worse among patients with HPS and a PaO$_2$ of less than 50 mmHg at the time of diagnosis [507,508].

Management [H2]

Medical treatment [H3]

Spontaneous resolution of HPS is uncommon. There is no established medical therapy currently available for HPS. Several drugs have been applied for the treatment of HPS with conflicting results. However, no large randomised trial has been conducted, probably because of the low number of patients. Data from several uncontrolled clinical studies and anecdotal evidence indicate that treatment with beta-blockers, cyclooxygenase inhibitors, systemic glucocorticoids and cyclophosphamide, almitrine bismesylate, inhaled nitric oxide, nitric oxide inhibitors, and antimicrobial agents has been uniformly unsuccessful [506]. Pentoxifylline has also been tried in the treatment of HPS in adults and children in two small pilot studies with contradictory results in terms of improvements in oxygenation and frequent GI side effects [539,540]. Administration of garlic was found to be associated with an improvement in the PaO_2 in a small randomised study [541]. However, a case of moderate hepatotoxicity associated with short-term, high-dose garlicin therapy in an LT recipient with persistent HPS was recently reported [542]. The use of TIPS has been proposed to reduce portal pressure in patients with HPS. However, data are insufficient even when a systemic analysis review is considered [543]. In addition, there is some concern that TIPS can enhance pulmonary vasodilation by exacerbating the hyperkinetic circulation. Thus, no recommendation for the use TIPS to treat HPS can be given [499,506]. Finally, coil embolisation (embolotherapy) has been shown to improve arterial oxygenation temporarily in the context of angiographic arteriovenous communications [532,544]. Endothelin-1 receptor antagonist or angiogenesis inhibitors have not been tested up to now in patients with HPS. Thus, long-term oxygen therapy remains the most frequently recommended therapy for symptoms in patients with severe hypoxaemia. However, some aspects of this treatment such as efficacy, costs, and compliance, remain to be evaluated.

Recommendations [Note to the typesetter: the Recommendation boxes should be typeset according to the approved mock-up for typeset Recommendation boxes]

- **Long-term oxygen therapy is recommended in patients with HPS and severe hypoxaemia. Nevertheless, there is no available data concerning effectiveness, tolerance, cost-effectiveness, compliance and effects on survival rates of this therapy. (II-2;1)**

- **No recommendation can be proposed regarding the use of drugs or the placement of TIPS for the treatment of HPS. (I;1)**

Liver transplantation [H3]

The most common and the only successful treatment for HPS is LT. LT results in a complete reversal or in a significant improvement of HPS in more than 85% of patients with severe hypoxaemia [545]. In a prospective clinical study performed in the pre-MELD era, a pre-LT severe hypoxaemia, in particular when it was associated with a large shunting at MAA scan, was found to be a very strong predictor of mortality after LT [536]. In 2007, five years after the introduction of MELD in US, the United Network for Organ Sharing (UNOS) recommended assigning an MELD score of 22 for the initial application of patients with severe HPS (PaO_2 <60 mmHg), with further increases every three months, to balance pre- and post-LT outcomes between HPS and non-HPS candidates [546]. In the largest retrospective study comparing the results of LT between the pre-MELD era and the MELD era in patients with HPS, the five-year survival rate after LT was found to improve from 67% during the pre-MELD era to 88% in the MELD era [547]. Other data showed that in post-MELD era, there was no association between pre-LT oxygenation and waitlist survival in patients with HPS. These findings reflect not only the results of the introduction of HPS as an MELD exception, but also of an improved perioperative management in patients with HPS. The regular assessment of the severity of hypoxaemia

may facilitate LT prior to the occurrence of very severe hypoxaemia. In fact, hypoxaemia can worsen in patients with HPS who are on the active transplantation list, with a median decrease in pO_2 of 5.2 mmHg per year [509], and it has been recently confirmed that a pre-LT room-air PaO_2 ≤44.0 mmHg is still associated with increased post-LT mortality [548]. Thus, it has been suggested that an ABG analysis should be carried out every six months, but no study has clarified which is the best method for carrying out it (ABG analysis *vs.* pulse oximetry) nor how frequently it should be performed. Despite the increased survival rate in patients with HPS after LT in the MELD era, it has recently been observed that HPS MELD exception patients had lower overall mortality compared to others awaiting LT, suggesting that the appropriateness of the HPS MELD exception policy should be reassessed [549]. There are very few and small studies on the impact of HPS on anaesthetic procedures, as well as in the post-LT management in the ICU. Nevertheless, it seems that inhaled nitric oxide, methylene blue, extracorporeal membrane oxygenation and non-invasive ventilation may improve oxygenation immediately post-LT [550-552].

Recommendations [Note to the typesetter: the Recommendation boxes should be typeset according to the approved mock-up for typeset Recommendation boxes]

- **Patients with HPS and PaO_2 <60mmHg should be evaluated for LT since it is the only treatment for HPS that has been proven to be effective up to now. (II-2;1)**
- **Since a severe hypoxaemia (PaO_2 <45–50 mmHg) is associated with increased post-LT mortality, an ABG analysis should be carried out every six months in order to facilitate prioritisation to LT. (II-2;1)**

Portopulmonary hypertension [H2]

Definition and diagnosis [H3]

A diagnosis of PPHT should be considered in a patient with established portal hypertension in the absence of other causes of pulmonary artery or venous hypertension. namely: chronic thromboembolism, chronic lung disease/hypoxia; chronic left heart disease.

Patients may be asymptomatic but often present with exertional dyspnoea and they may have clinical signs of right heart failure when moderate to severe disease develops [553]. Classification of severity is based on mean pulmonary arterial pressure (mPAP) and assumes there is high pulmonary vascular resistance (PVR). PPHT is graded as mild (mPAP ≥25 and <35 mmHg); moderate (mPAP ≥35 and <45 mmHg), and severe (mPAP ≥45 mmHg) [499]. The diagnosis also requires there to be normal pulmonary occlusion pressures, to exclude elevation of pulmonary pressure resulting from elevated left ventricular filling pressure. Transthoracic Doppler echocardiography (TDE) is the main screening tool for evaluating the presence of PPHT when screening high-risk patients, such as those being considered for TIPS or LT [554-556]. As a screening test, some studies suggest a pulmonary artery systolic pressure of >30 mmHg on TDE has a negative predictive value of 100%, but a positive predictive value of only 59% [555]. However, when assessing patients for LT, the threshold for right heart catheterisation is less clear, with a right ventricular systolic pressure >50 mmHg and/or significant right ventricular hypertrophy seen as the trigger for this investigation to rule out significant PPHT [556].

Pathophysiology [H3]

In patients with portal hypertension, PPHT is thought to arise from limited blood flow in the pulmonary arterial circulation because of vasoconstriction. Numerous factors are thought to be responsible for this including: Changes in endogenous vaso-regulators; increased endothelin 1 and reduced prostacyclin synthase from pulmonary endothelial cells;

proliferation of smooth muscle cells/endothelial activation and platelet aggregation.

Natural history and prognosis [H3]

From studies in patients evaluated for LT, the incidence is thought to be between 3–10% based on haemodynamic criteria. Furthermore, female sex and pre-existing autoimmune liver disease are thought to be independent risk factors [557]. Genetic variation in oestradiol levels may increase the predisposition to pulmonary artery vasoconstriction. Indeed, women are at three times greater risk than men [558]. There is also an association between patients who have moderate to severe PPHT and the presence of large portosystemic shunts [559]. However, there is no clear association between the severity of liver disease or portal hypertension and the development of severe PPHT [557,560]. Studies quote survival rates at one year of between 35–46% without specific treatment [561,562]. Mortality is often associated with other complications of liver disease such as hepatocellular cancer, sepsis and GI bleeding and right ventricular failure. Increased rates of mortality are related to higher right atrial pressure and lower cardiac index [560,563]. In a multicentre registry study, patients with PPHT were shown to have worse outcomes than patients with idiopathic pulmonary hypertension, with a five-year survival of 40% *vs.* 64% [564]. However, a retrospective French study challenges this, whilst reporting increased mortality in those with a lower cardiac index, likely reflecting failed compensation to increased right ventricular dysfunction, and patients with more advanced liver disease [565].

Medical treatment [H3]

The evidence base for pharmacological therapies in PPHT is limited with most data extrapolated from studies in pulmonary arterial hypertension not related to liver disease

[566,567]. Drugs to promote acute vasodilatation during right heart catheterisation assessment, theoretically may be deleterious as they run the risk of further reducing cardiac index. There is a lack of data to clarify this [568]. Conversely, whilst patients with advanced portal hypertension may be on treatment with beta-blockers, withdrawing beta-blocker therapy may help to increase cardiac output and thereby help exertional dyspnoea, in patients with advanced PPHT [569].

Endothelin receptor antagonists [H4]

Bosentan has been shown to improve pulmonary artery haemodynamics and exercise tolerance in patients with PPHT, independently of liver disease severity [570-573]. One retrospective study reports survival rates of up to 89% at three years [574]. Others have shown improvements in cardiac index up to 39%, albeit in a small number of patients, but an increase in aminotransferases, which responded to dose reduction or discontinuation [572]. The FDA places a caution on this class of drug in patients with advanced liver dysfunction. There is limited data on the use of other members in this family of agent, including ambrisentan and macitentan, for PPHT [575,576].

Phosphodiesterase subtype-5 inhibitors [H4]

Blockade of phosphodiesterase-5 inhibitors facilitate the vasodilatory effects of nitric oxide, through reduced metabolism of cGMP. Small case series suggest that sildenafil improves functional capacity and increases cardiac output [577-579]. It should be noted that sildenafil can precipitate variceal bleeding and as such, caution should be exercised [580].

Prostacyclin analogues [H4]

Prostacyclin analogues have many potential benefits including vasodilatory, reduced vascular smooth muscle proliferation and anti-thrombotic. Case series suggest improved pulmonary haemodynamics with i.v. epoprostenol and the potential for improved five-year

survival compared to registry data in pulmonary artery hypertension (70 *vs.* 40%) [581-584]. However, lower doses than those used in idiopathic pulmonary hypertension are suggested to reduce the development of thrombocytopenia and splenomegaly. Other studies have also looked at use of inhaled iloprost and reported short-term haemodynamic benefit [585].

Impact of the management of other complications of cirrhosis [H3]

Caution should be exercised when considering TIPS placement for the treatment of other complications of cirrhosis in patients with proven PPHT. The anticipated increase in right ventricular filling pressures and cardiac output may precipitate marked increases in PVR and right-sided pressure overload [586,587]. Moderate PPHT (mPAP >35 and <45 mmHg) is a relative contraindication for TIPS placement, and severe PPHT is an absolute contraindication [587].

Recommendations [Note to the typesetter: the Recommendation boxes should be typeset according to the approved mock-up for typeset Recommendation boxes]

- **Screening for PPHT should be via TDE in patients deemed potential recipients for TIPS or LT; in those with a positive screening test, right heart catheterisation should be performed (II-1;1).**

- **In patients with PPHT who are listed for transplantation, echocardiography should be repeated on the waitlist, albeit, the specific interval is unclear (III;1).**

- **Beta-blockers should be stopped and varices managed by endoscopic therapy in cases of proven PPHT (II-3;1).**

- **Therapies that have been approved for primary pulmonary arterial hypertension may have benefit in PPHT to improve exercise tolerance and**

haemodynamics. However, endothelin antagonists should be used with caution because of concerns over hepatic impairment (II-2;1).

- **TIPS should not be used in patients with PPHT (II-3;1).**

Liver transplantation [H3]

Historically, severe PPHT has been a relative contraindication for LT because of very poor outcomes. However, with the advent of improved haemodynamic control with agents such as i.v. prostacyclin, there are case series showing normal pulmonary haemodynamics almost two years post LT [588,589].

Stratifying risk for LT [H4]

In patients with an mPAP ≥45-50 mmHg, most centres would deem this an absolute contraindication to transplantation irrespective of therapy applied [563,588,590]. Patients with an mPAP >35 have increased risk post LT, associated with increased hospital stay and longer ventilator requirements [563,591,592]. If LT is considered in such patients, it is suggested that their PPHT is treated aggressively to lower mPAP and improve right ventricular function [589,593,594].

To facilitate access to LT before there is further progression of PPHT to a point where transplantation risks are deemed too high, MELD exception (MELD 22 points) has been granted to patients with PPHT (mPAP >25 mmHg and PVR >240 dynes/s per cm^{-5}) with at least moderate disease severity (baseline mPAP >35 mmHg) [595]. Patients are considered surgical candidates if, after targeted therapy to lower PAP, they have improved mPAP (<35 mmHg) and PVR (<400 dyne/s per cm^{-5}) and/or normalise their PVR. Applying this exception has been noted to reduce waitlist mortality [596].

Per-operative considerations [H4]

All patients should be monitored with a pulmonary artery catheter. Therapy to lower mPAP should be continued throughout the operative period, given that there is often a rise in cardiac output post re-perfusion and this may add more stress on any pre-existing impaired right ventricle function [596-598]. Indeed, in some cases, a severe acute rise in PAP may lead to graft failure because of hepatic congestion through a failing right ventricle. The management of such adverse haemodynamics, in addition to i.v. prostacyclin or inhaled nitric oxide includes the use of extracorporeal membrane oxygen therapy (ECMO) [599,600].

Postoperative considerations [H4]

Monitoring PAP response to therapy is via serial transthoracic echo with tissue Doppler at 4-6-month intervals and consideration of tapering pulmonary artery targeted therapy, though no controlled data exists to provide guidance on this [582,601,602]. Case reports and series suggest that 29–64% of patients with moderate to severe PPHT under long-term follow-up post-transplant have been able to discontinue therapy over time [600-603]. Indeed, some suggest a return to normal right ventricle function following therapy for PPHT in the pre-transplant period and then after transplant surgery [582,602]. PPHT MELD exception patients have worse one-year mortality or graft failure than patients without PPHT [604] .

Recommendations [Note to the typesetter: the Recommendation boxes should be typeset according to the approved mock-up for typeset Recommendation boxes]

- **If mPAP <35 mmHg and right ventricular function is preserved, LT should be considered (II-2,1). An mPAP of ≥45 mmHg should be considered an absolute contraindication to LT irrespective of therapy applied (III,1).**

- **Therapy to lower mPAP and improve right ventricular function should be commenced in patients with mPAP ≥35 mmHg. Right ventricular function should be periodically evaluated (II-2,1).**

- **MELD exception can be considered in patients with proven PPHT in whom targeted therapy fails to decrease mPAP <35 mmHg but does facilitate normalisation of PVR to <240 dynes/s cm $^{-5}$ and right ventricular function (II-3;2).**

- **MELD exception should be advocated in patients with proven PPHT of moderate severity (assessment mPAP ≥35 mmHg) in whom targeted treatment lowers mPAP <35 mmHg and PVR <400 dynes/s cm $^{-5}$ (II-2;1).**

Conclusions [H1]

These guidelines on the management of patients with decompensated cirrhosis were developed based on a new pathophysiological background that offers the opportunity for more comprehensive therapeutic or prophylactic approaches to manage the disease. The knowledge of the key pathophysiologic mechanisms makes it possible nowadays to counteract the progression of cirrhosis and so to prevent its complications. This represents a step forward, shifting our approach from treating the complications of decompensated cirrhosis to preventing their occurrence. However, to make this possible it is crucial to think about new models of specialist care for patients with cirrhosis. A care coordination programme, has been proven to improve survival and to reduce emergent readmission to the hospital in these patients (605). Care coordinators can facilitate the development of educational programmes for patients and caregivers optimising their adherence to guideline recommendations; reconcile medications. In addition, they can plan invasive procedure in one day hospital transferring on real-time information to primary physicians. In this way it is possible to prevent unnecessary visits to the emergency department and/or

emergent readmission to the hospital. By this way the burden of cirrhosis will progressively

decline.

Conflict of interest [H1]

Acknowledgments [H1]

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Table 1. Level of Evidence and Grade of Recommendations.

Table 2. Grading of ascites.

Table 3. Contraindications to paracentesis

Table 4. Definition and diagnostic criteria for refractory ascites in cirrhosis.

Table 5. Characteristics and results of six randomised controlled trials comparing bared TIPS and LVP in patients with cirrhosis and refractory or recidivant ascites. HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; INR, international normalized ratio; LVP, large volume paracentesis; PT, prothrombin time; SAAG, serum-ascites albumin gradient; TIPS, transjugular intrahepatic portosystemic shunt. *= significantly lower than TIPS.

Table 6. Classification, prevalence and risk of bleeding of gastric varices. GOV, gastro-oesophageal varices; IGV, isolated gastric varices; OV, oesophageal varices.

Table 7. International Club of Ascites (ICA-AKI) new definitions for the diagnosis and management of acute kidney injury in patients with cirrhosis. AKI, acute kidney injury; sCr, serum creatinine; RRT, renal replacement therapy.

Table 8. Definitions of kidney disease.
AKD, acute kidney disease; AKI, acute kidney injury; CKD, chronic kidney disease; GFR, glomerular filtration rate; sCr, serum creatinine.

Table 10. CLIF-Sequential Organ Failure Assessment (SOFA) score (adapted from reference n° 3). *µg/kg/min. E, epinephrine; FiO2, fraction of inspired oxygen; HE, hepatic encephalopathy; NE, norepinephrine; PaO2, partial pressure of arterial oxygen; SpO2,

pulse oximetric saturation. The shaded area indicates the diagnostic criteria for organ failures.

Table 11. Classification and grades of ACLF (adapted from reference 3).

ACLF, acute-on-chronic liver failure; HE, hepatic encephalopathy.

Table 12. Chronic Liver Failure – Organ Failure score system (adapted from reference 420). FIO2, fraction of inspired oxygen; HE, hepatic encephalopathy; INR, international normalized ratio; MAP, mean arterial pressure; PaO2, partial pressure of arterial oxygen; SpO2, pulse oximetric saturation.

Note: The shaded area denotes criteria for diagnosing organ failures.

[a]Patients submitted to mechanical ventilation due to HE and not to a respiratory failure were considered as presenting a cerebral failure (cerebral score = 3).

[b]Other patients enrolled in the study with mechanical ventilation were considered as presenting a respiratory failure (respiratory score = 3).

Table 13. CLIF-C Acute Liver Failure (ACLF) score (reference 420).

Table 14. Diagnostic criteria of hepatopulmonary syndrome.

All criteria were determined by means of positive contrast-enhanced echocardiography (*i.e.*, microbubble opacification of the left heart chambers three to six cycles after right atrial passage). The abbreviated formula for the alveolar–arterial gradient is as follows:

$PaO_2 - PaO_2 = (FIO_2 [Patm - PH_2O] - [PaCO_2/0.8]) - PaO_2$, where PaO_2 denotes partial pressure of alveolar oxygen, PaO_2 partial pressure of arterial oxygen, FIO_2 fraction of inspired oxygen, Patm atmospheric pressure, PH_2O partial pressure of water vapor at body temperature, and $PaCO_2$ partial pressure of arterial carbon dioxide (0.8 corresponds

to the standard gas-exchange respiratory ratio at rest); the normal range is 4 to 8 mmHg.

Fig. 1. The new theory on the development of complications and organ failure/s in patients with cirrhosis (adapted from reference 5).

DAMP, damage-associated molecular pattern; HE, hepatic encephalopathy; HPS, hepatopulmonary syndrome; PAMP, pathogen-associated molecular pattern; RNS, reactive nitrogen species; ROS, reactive oxygen species.

Fig. 2. Algorithm for the management of acute gastrointestinal bleeding in patients with cirrhosis (adapted from reference 168). TIPS, transjugular portosystemic shunts.

Fig. 3. Algorithm for the application of qSOFA and Sepsis-3 criteria in patients with cirrhosis and bacterial infections (adapted form reference 271). ICU, intensive care unit.

Fig. 4. Recommended empirical antibiotic treatment of SBP or SBE (adapted from reference 6). SBE, spontaneous bacterial empyema; SBP, spontaneous bacterial peritonitis; MDRO, multidrug resistant organism.

Fig. 5. Recommended empirical antibiotic treatment of soft tissue infections (adapted from reference 6). MDRO, multidrug resistant organism.

Fig. 6. Recommended empirical antibiotic treatment of pneumonia (adapted from reference 6). MDRO, multidrug resistant organism.

Fig. 7. Recommended empirical antibiotic treatment of UTI (adapted from reference 6). MDR, multidrug resistant; UTI, urinary tract infection.

Fig. 8. Algorithm for the management of AKI in patients with cirrhosis (adapted from

reference 318). AKI, acute kidney injury; HRS, hepatorenal syndrome; NSAID, non-steroidal anti-inflammatory.

Fig. 9. Criteria based on urinary output for the diagnosis of AKI (adapted from reference 310). AKI, acute kidney injury; B.W., body weight.

Fig. 10. The pathophysiology of hepatopulmonary syndrome (adapted from reference 499). HPS, hepatopulmonary syndrome.

Fig. 11. The pathogenesis of hepatopulmonary syndrome. ET, endothelin; eNOS, endothelial nitric oxide synthase; iNOS, inducible nitric oxide synthase; NO, nitric oxide; HO, Heme oxygenase-1; CO, carbon monoxide; CX3CL1, fractalkine; VGF-A, vascular endothelial growth factor A