Management of critically-ill cirrhotic patients

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Summary

Cirrhotic patients are prone to develop life-threatening complications that require emergency care and ICU admission. They can present specific decompensations related to cirrhosis such as variceal bleeding and hepatorenal syndrome (HRS) or other critical events also observed in the general population such as severe sepsis or septic shock. Clinical management of all these entities requires a specific approach in cirrhosis. Cirrhotic patients have a hyperdynamic circulation with high cardiac output and low systemic vascular resistance in the absence of infection[1,2]. Circulatory dysfunction increases the susceptibility of critically-ill cirrhotic patients to develop multiple organ failure and attenuates vascular reactivity to vasopressor drugs[3]. HRS, a severe functional renal failure occurring in patients with advanced cirrhosis and ascites, is also secondary to this circulatory dysfunction that leads to an extreme renal vasoconstriction[2]. Moreover, hypotensive cirrhotic patients require a carefully balanced replacement of volemia, since overtransfusion increases portal hypertension and the risk of variceal bleeding and undertransfusion causes tissue hypoperfusion which increases the risk of multiple organ failure[4,5]. Cirrhotic patients are also at a high risk for development of other bleeding complications and are more susceptible to nosocomial infections[6,7]. This extreme complexity of critically-ill cirrhotic patients requires a specific medical approach that should be known by general intensivists since it has a negative impact on patient prognosis. This review will focus on the diagnostic approach and treatment strategies currently recommended in the critical care management of patients with cirrhosis.

Acute variceal bleeding

The impact of acute variceal bleeding in cirrhotic patients

The face of variceal bleeding in cirrhotic patients has changed over the last two decades. Overall hospital mortality decreased from 42% in 1980 to 14% in 2000 in a specialized European center[8]. In recent years, mortality rates related to variceal bleeding were close to zero in patients with Child–Pugh grade A or B cirrhosis but remain over 30% in Child–Pugh grade C patients with active bleeding[8].

Bleeding etiologies and prognostic factors

Variceal rupture is essentially related to the severity of portal hypertension, resulting from an increase in intrahepatic resistance, and is more likely to occur when the hepatic venous pressure gradient is >12mmHg. Currently, variceal homeostasis is achieved in more than 90% of the patients. Death is most likely to occur in patients with active bleeding at time of endoscopy, advanced cirrhosis (Child–Pugh grade C or MELD >20), extraparenchymal organ failure or high hepatic venous pressure gradient (>20mmHg)[9].

Management of acute variceal bleeding

A care bundle for ICU management of cirrhotic patients with variceal bleeding combines fluid resuscitation, optimal blood transfusion, antibiotic prophylaxis, pharmacological vasoactive therapy, as well as diagnostic and therapeutic endoscopy. All indicated tasks should be performed as soon as possible after admission and preferably within 6–12 hours. Guidelines have been recently updated at the Baveno V conference[5].

Fluid resuscitation and administration of blood products

Volume restitution should be initiated early in order to restore tissue perfusion with a mean arterial pressure >65mmHg. Colloids are widely used as first-line treatment usually in combination with crystalloids. The use of fresh frozen plasma as plasma expander is not recommended. Nevertheless, judicious use of fresh frozen plasma or platelet transfusion in bleeding patients with very severe coagulopathy may be theoretically useful, but a specific recommendation on their use could not be made in the Baveno V consensus workshop on portal hypertension because of insufficient data[5]. The use
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of recombinant activated factor seven for the management of variceal bleeding is not recommended[5,9,10]. A transfusion threshold of 7–8 g/dl is recommended in the Baveno V consensus conference for cirrhotic patients with variceal bleeding[5].

Nasogastric aspiration and lavage or erythromycin infusion
Since erythromycin infusion has shown in randomized trials improvement in gastric emptying and in the quality of endoscopy performed in patients with upper gastrointestinal bleeding, the use of nasogastric lavage has declined[11–13]. Theoretically, nasogastric aspiration may be helpful in preventing hepatic encephalopathy by reducing the amount of blood reaching the gut.

Pharmacological treatment
Since Levacher et al.[14] showed that early administration of terlipressin improves control bleeding and reduces bleeding mortality in cirrhosis, vasoactive drugs (terlipressin, then somatostatin and somatostatin analogues: octreotide and vaptatile) have been recommended as first-line therapy. They should be started as soon as possible, before endoscopy and continued for up to 5 days. Terlipressin is the only vasoactive drug that has shown to improve survival in a placebo-controlled RCT and several meta-analyses[15,16] but is contraindicated in patients with cardiovascular diseases. Somatostatin and somatostatin analogues improve control bleeding, have a good safety profile but do not reduce mortality[15,16].

Antibiotic prophylaxis
The incidence of bacterial infection in patients with cirrhosis and upper gastrointestinal bleeding ranges from 22% to 66%[17]. Short-term antibiotic prophylaxis reduces the rate of bacterial infections and increases short-term survival[17,18]. Although all antibiotics showed a reduction of the risk of infection, the beneficial effect seems to be higher when using cefalosporin (RR 0.16; 95%CI 0.05–0.48) followed by quinolones (RR 0.27; 95%CI 0.18–0.39)[18]. Patients with advanced cirrhosis should be treated with IV cefalosporins, while patients with less advanced liver disease should be given oral quinolones[5].

Prevention of hepatic encephalopathy
Few data regarding prevention and management of encephalopathy in patients with cirrhosis and upper gastrointestinal bleeding are available. In a randomized study, the use of lactulose was associated with a lower rate of hepatic encephalopathy compared to a control group (14% vs. 40%, respectively)[19].

Endoscopic treatment
Endoscopy should be performed as soon as possible within 6–12 hours in an ICU setting. In those patients with massive bleeding and/or presence of signs of overt hepatic encephalopathy, airway protection with orotracheal intubation and mechanical ventilation should be performed, as the risk of aspiration is high. Propofol is currently the preferred agent for sedation.

In patients with esophageal variceal bleeding, both band ligation and sclerotherapy are effective in the control of bleeding. However, compared with sclerotherapy, band ligation was significantly better in the control of bleeding and associated with better survival and less adverse events[20]. Currently, endoscopic band ligation is the treatment of choice and should be performed at the time of diagnostic endoscopy. In patients with bleeding from gastric varices, obliteration with cyanoacrylate (glue) is the first-line treatment[21].

Transjugular portosystemic shunt (TIPS)
Traditionally, TIPS has been considered as a salvage therapy for uncontrolled variceal bleeding with 90% bleeding control rate and a one-year survival rate of 52%[22]. Currently, however, TIPS is being considered early if there is failure to combined pharmacological and endoscopic treatment. More challenging, a recent RCT compared early covered TIPS (performed within 24–48 hours of admission) to vasoactive drugs and endoscopic therapy in patients at high-risk of treatment failure (Child–Pugh grade C and 10–13 points or Child–Pugh grade B with active bleeding). The results showed that early TIPS was associated with a significant reduction in treatment failure at 1 yr (30% in the control group vs. 3% in the TIPS group) and 1-yr mortality (39% vs. 14%, respectively) without differences in encephalopathy[23].

Salvage therapy
Balloon tamponade (Sengstaken–Blakemore and Linton tubes for esophageal and gastric varices, respectively) are used in patients with massive bleeding and hemodynamic instability as a temporary “bridge” until definitive endoscopic or derivative (mainly TIPS or surgery) treatment is instituted. These patients must be intubated in order to protect airway from aspiration. A self-expanding esophageal metal stent has been used as an alternative to balloon tamponade in few patients with active bleeding from esophageal varices with promising results[24].

Prevention of rebleeding
Secondary prophylaxis should be started early after stopping the pharmacological treatment, usually the sixth day of the bleeding episode. Band ligation combined with beta-blockers is the preferred therapy[4]. TIPS with covered stents should be considered in patients with hepatic venous pressure gradient higher than 20 mmHg or bleeding recurrence. In addition to its beneficial effect in preventing bacterial infections, antibiotic prophylaxis has been shown to reduce the incidence of early rebleeding[5].

Management of severe sepsis and septic shock
Sepsis is the consequence of host response to infection and is characterized by the release of pro- and anti-inflammatory cytokines and pro- and anti-coagulant substances in response to pathogens. Systemic response to infection is more intense in cirrhosis[25], which translates into a greater risk of developing sepsis, severe sepsis (when patients develop acute organ failure attributed to sepsis), septic shock (when hypotension is refractory to volume administration and requires the use of vasopressor drugs), and multiple organ failure[6,7,26]. Hospital mortality of severe sepsis and septic shock in cirrhosis is higher than that in the general population, with rates exceeding 40% in severe sepsis[27] and 70% in septic shock in some series[28,29].

Initial resuscitation
Early goal-directed therapy, a prompt and stepwise emergent resuscitation in the early phase of sepsis (within the first 6 hours), improves the outcome of non-cirrhotic patients with severe sepsis and septic shock in terms of organ dysfunction and survival[30]. The following goals are targeted to treat sepsis-induced tissue hypoperfusion: mean arterial pressure ≥65 mmHg, central venous pressure between 8 and 12 mmHg, central venous oxygen saturation ≥70% and urine output ≥0.5 ml kg⁻¹ h⁻¹. These goals are achieved through the
sequential institution of fluids, vasopressors, blood transfusion, and inotropes.

Although no study has assessed the clinical efficacy of this strategy in cirrhosis, clinical practice suggests that early resuscitation is also essential in these patients. Its goals, however, may differ from the general population. Mean arterial pressure is lower and central venous oxygen saturation higher in cirrhosis due to the hyperdynamic circulation[2,31]. Moreover, urine output and hematocrit levels are lower and lactate metabolism is compromised in these patients[31]. Specific goals for patients with cirrhosis should be defined in future studies. Early goal-directed therapy in the emergency area should be followed by a rapid admission of the patient to the ICU.

Early diagnosis and antibiotic treatment

An early diagnosis of the infection and the initiation of IV antibiotics are essential in the management of cirrhotic patients with severe sepsis or septic shock as occurs in the general population[30]. A systematic clinical evaluation of the patient, aimed at identifying the source of the infection, must be performed including a diagnostic paracentesis, urinary sediment, chest X-ray and blood, urine and ascitic fluid cultures before starting antibiotics. Other possible sources of infection should also be excluded[7] (Fig. 1).

Broad-spectrum antibiotics should be started as early as possible and always within the first hour, since this strategy improves survival (Fig. 2)[30,32]. Studies performed in the general population estimate that each hour of delay in the initiation of the appropriated antibiotic increases mortality by 8%[33]. Initial empirical antibiotic treatment should be broad enough to cover all likely pathogens. The choice will depend on several factors: type of infection and site of acquisition (community vs. hospital acquired), prior antibiotic treatment (antibiotics used recently should be avoided) and history of drug intolerance or of documented colonization or infection by multiresistant organisms[30]. The recommended empirical antibiotics for community-acquired infections in cirrhosis are third generation cephalosporins or amoxicillin–clavulanic acid[7]. Empirical treatment of nosocomial infections should be selected considering the local epidemiological pattern of bacterial multiresistance. De-escalation to the most appropriate single antibiotic should be performed as soon as the susceptibility profile is known.

Fluid therapy

Current guidelines for non-cirrhotic patients with severe sepsis or septic shock recommend fluid resuscitation with either albumin or artificial colloids (gelatins or hydroxyethyl starches) or crystalloids[30]. However, a subanalysis of the SAFE study performed in septic patients suggests that albumin administration could decrease mortality in comparison to crystalloids, in this setting[34]. As volume distribution is much larger for crystalloids than for colloids, resuscitation with saline or Ringer’s lactate solutions requires more fluid to achieve the same goals and results in more edema. This phenomenon is more marked in cirrhotic patients who characteristically have an effective hypovolemia and hypoalbuminemia. A RCT in patients

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**Fig. 1. Initial clinical evaluation of cirrhotic patients with severe sepsis or septic shock.** Recommended strategy is based on the assessment of the different organ failures and on the diagnosis of the source of infection. AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio; SIRS, systemic inflammatory response syndrome.

**Fig. 2. Treatment of cirrhotic patients with severe sepsis or septic shock.** Recommended strategy is based on early resuscitation, cardiovascular monitoring, early broad-spectrum antibiotics and organ failure support.
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with cirrhosis and spontaneous bacterial peritonitis (SBP) without shock showed that 20% albumin administration prevents renal failure (from 33% to 10%) and decreases hospital mortality (from 29% to 10%) [35]. Albumin administration increases cardiac preload, cardiac output, and peripheral vascular resistance in patients with SBP. This hemodynamic improvement is not observed with hydroxethyl starch solutions [36]. Future RCTs should compare albumin with other plasma expanders in the fluid resuscitation of patients with cirrhosis and severe sepsis or septic shock.

Vasoactive drugs

Current guidelines consider norepinephrine and dopamine as first-line vasopressor agents in patients with septic shock [30]. They should be administered through a central catheter. There are no differences in survival rates between the two vasopressors but the use of dopamine is associated with a higher rate of cardiac arrhythmias, so that norepinephrine is recommended [37]. Vasopressin constitutes a second-line vasopressor agent that may be added to norepinephrine [38]. Patients with cirrhosis have vascular hyporeactivity to these agents, but no studies have so far evaluated vasopressor drugs in these patients. The use of inotropic agents, mainly dobutamine, is recommended in the presence of myocardial dysfunction induced by sepsis. Cirrhotic patients with septic shock usually have high cardiac output and do not benefit from dobutamine administration [28].

Stress dose steroids

Relative adrenal insufficiency is frequent in non-cirrhotic patients with septic shock (20–60%), and is associated with refractory shock and high mortality [39]. Initial studies suggested that the administration of stress dose steroids (IV hydrocortisone: 50 mg every 6 hours) to non-responders to ACTH test (cortisol increase ≤9 μg/dl) improved shock reversal and reduced mortality. However, a recent European RCT (CORTICUS) failed to show a survival benefit with steroid therapy for septic shock. Steroid treatment was associated with a faster resolution of refractory shock and high mortality [30]. Vasopressin constitutes a second-line vasopressor agent that may be added to norepinephrine [38]. Patients with cirrhosis have vascular hyporeactivity to these agents, but no studies have so far evaluated vasopressor drugs in these patients. The use of inotropic agents, mainly dobutamine, is recommended in the presence of myocardial dysfunction induced by sepsis. Cirrhotic patients with septic shock usually have high cardiac output and do not benefit from dobutamine administration [28].

Stress dose steroids

Relative adrenal insufficiency is very frequent in patients with cirrhosis and severe sepsis or septic shock (51–77%) and is associated with hemodynamic instability, liver and renal failure, critical illness severity and high mortality rate (81% vs. 37% in patients without adrenal dysfunction) [29,41]. The efficacy of stress dose steroids on the outcome of cirrhotic patients with septic shock is unclear. A small, uncontrolled cohort study suggested that the administration of steroids to non-responders to ACTH improved shock reversal (96% vs. 56%) and hospital survival [41]. However, a recent RCT showed no benefit of steroid administration on survival [42]. A large multicenter European RCT is currently underway to address this topic.

Other supportive therapies

Protective mechanical ventilation

The use of low tidal volumes (6 ml/kg of ideal body weight) and limited end-inspiratory plateau pressures (<30 cm H₂O) is associated with an improvement in mortality and is considered the gold standard for acute respiratory distress syndrome (ARDS) ventilation strategies [30]. Although cirrhosis has been identified as a risk factor for ARDS [26], as yet no studies have been performed on ARDS in the cirrhotic population.

Sedation and analgesia

Sedation protocols with a sedation goal and daily interruption/lightening of continuous sedation infusion should be used in mechanically ventilated cirrhotic patients [30]. Drugs with short-half life such as propofol and remifentanil are the preferred options. Benzodiazepines (i.e. midazolam) should be avoided in these patients. Impaired drug elimination, which may prolong half-life very markedly, and brain hypersensitivity to benzodiazepines contribute to the development of hepatic encephalopathy and prolong the time of mechanical ventilation [43].

Renal replacement therapy (RRT)

Continuous renal replacement therapies and intermittent hemodialysis are equivalent in septic patients with acute renal failure. Continuous therapies are preferred in hemodynamically unstable patients to facilitate fluid balance [30]. Current data indicate that intensive renal support (35 ml/kg body weight/hour or daily intermittent hemodialysis) is not superior to conventional renal support strategies (20 ml/kg body weight/hour) [44]. No data on renal replacement therapy modalities have been published in cirrhotic patients with severe sepsis or shock.

Glucose control

Current guidelines recommend that patients with severe sepsis and hyperglycemia, who are admitted to the ICU, receive intravenous insulin therapy to normalize blood glucose levels since hyperglycemia may act as procoagulant, induce apoptosis and impair neutrophil function. However, tight glucose control (80–110 mg/dl) in septic patients is not recommended because it induces more hypoglycemic events and may increase mortality compared to conventional glucose control [45]. Less strict glucose targets (144–180 mg/dl) are currently recommended in the clinical management of critically-ill patients and this is also applicable in cirrhosis.

Blood product administration

Current guidelines recommend, for the general population, a transfusion threshold of 7 g/dl once tissue hypoperfusion has resolved [30]. Fresh frozen plasma should not be used to correct clotting abnormalities in the absence of bleeding. However, in patients bleeding from non-variceal sources, either fresh-frozen plasma, coagulation factors, or platelet transfusion should be considered. Recent reports have shown the advantage of thromboelastography over conventional coagulation tests in the assessment of hemostasis in patients with cirrhosis [46].

Other prophylactic strategies

Stress ulcer prophylaxis using H2 blockers or proton pump inhibitors should be instituted in cirrhotic patients with severe sepsis or septic shock. Thrombocytopenia and severe coagulopathy preclude deep vein thrombosis prophylaxis in these patients.

Management of acute renal failure

Acute renal failure (also known as Acute Kidney Injury in the most recent nephrology literature) is a very frequent and
challenging complication of cirrhotic patients. Its incidence in hospitalized patients with cirrhosis is of approximately 25%[47] and increases up to 40–60% in those admitted to the ICU[48]. These incidences are higher than those reported in the general population (20% and 36%, respectively)[49,50]. The development of renal failure in patients with cirrhosis is a poor prognostic sign, because it is associated with high frequency of complications, particularly infections and hepatic encephalopathy, and increased mortality[51].

Assessment of renal function in the ICU

Renal function should be monitored daily in all patients with cirrhosis admitted to the ICU. Patients with higher risk of development of renal failure are those with bacterial infections, gastrointestinal bleeding, and hyponatremia[52–54]. Several methods of assessment of glomerular filtration rate (GFR) in cirrhosis have been used. State-of-the-art techniques such as inulin clearance or radioisotopic methods are impractical in the acute setting, expensive, and not generally available. Formulas to assess glomerular filtration rate, such as the Cockcroft–Gault and Modification of Diet in Renal Disease (MDRD), which are based on serum creatinine concentration and other variables, may be helpful for patients with chronic renal failure but are not regularly used in the acute setting. Creatinine clearance overestimates GFR, requires a very accurate urine collection, and is not better than just measuring serum creatinine concentration. Finally, serum creatinine is not a very accurate marker of GFR in cirrhosis, mainly because of the low creatinine production due to reduced muscle mass[51]. Nonetheless, in clinical practice, serum creatinine concentration is the most widely used method for estimating renal function in cirrhosis[55,56]. The most commonly accepted cut-off level for defining renal failure in cirrhosis is a serum creatinine concentration of greater than 1.5 mg/dl (133 μmol/L)[57]. However, this definition has two major drawbacks. Firstly, it identifies only patients with a severely reduced renal function (approximately GFR lower than 30 ml/min). Second, it does not take into account changes in serum creatinine with respect to a baseline value, which does not allow differentiating between chronic renal failure and acute renal failure. Accordingly, a new definition of renal failure in cirrhosis is needed, particularly for the acute setting, which should ideally include a cut-off level lower than that currently used together with the assessment of changes in serum creatinine concentration. Criteria that could be useful are those of AKIN or RIFLE definitions, which are based on changes (either absolute or percent increases) in serum creatinine with respect to a baseline value, which may be that of admission, and/or changes in urine output[58,59]. Although the results of some studies suggest that these classifications may be useful for cirrhotic patients[47] and a recent consensus conference has advocated their use[60], they have not been validated in large prospective studies. Moreover, it is important to point out that a significant proportion of patients with cirrhosis are admitted to hospital with high serum creatinine values but without a baseline value available, which is necessary for defining renal impairment; and urine output, which is also used in the definition, may be low in cirrhosis because of sodium retention and ascites. It is also important to emphasize that these classifications do not consider the type of renal failure that is relevant in cirrhosis because the treatment approach depends on the type of renal failure.

Differential diagnosis of renal failure

Critically-ill cirrhotic patients may develop different types of renal failure, particularly HRS, hypovolemia-related renal failure, renal failure due to parenchymal nephropathy, renal failure due to bacterial infections, and nephrotoxicity (Table 1). Some of these, particularly bacterial infections and hypovolemia, when associated with persistent shock, and also nephrotoxicity, may lead to acute tubular necrosis, a condition characterized by acute renal failure due to necrosis or dysfunction of renal tubules. The differential diagnosis between these types of renal failure is important because of different prognosis[61]. Currently, the
differential diagnosis is performed on clinical grounds because of the lack of specific markers for each of these conditions [50,61]. There is intensive research on the potential use of urine biomarkers, particularly kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin gene (NGAL), but no definitive conclusion on their use can be made as yet.

**Management of renal failure**

Early identification and treatment of the cause of renal failure is key to the success of therapy. In this review only the management of HRS is discussed. The management of other causes of renal failure in cirrhosis can be found elsewhere [50,51,62].

**Hepatorenal syndrome**

HRS is a type of prerenal failure that results from a very intense vasoconstriction of the renal circulation without any identifiable kidney pathology and occurs in patients with advanced cirrhosis [63]. Because of the lack of specific diagnostic markers, the diagnosis of HRS is currently made using criteria to exclude other causes of renal failure that can occur in cirrhosis (Table 1). There are two clinical types of HRS. Type 1 HRS is an acute and rapidly progressive form of renal failure with a rise of serum creatinine >2.5 mg/dl with an expected survival of only two weeks if not treated or transplanted [2,50]. In type 2 HRS, renal failure is usually less severe (serum creatinine 1.5–2.5 mg/dl). HRS is triggered by SBP or other bacterial infections in approximately 30% of cases [2,50,51]. Therefore, signs of infection should be sought after in all patients with cirrhosis and renal failure, and antibiotics given promptly if there is any suspicion of infection.

The vasopressin analogue terlipressin, together with albumin administration, is the first-line treatment for type 1 HRS [51,64]. Other vasoconstrictors that have been used are alpha-adrenergic agonists, particularly noradrenaline, but information is limited [65]. Albumin (1 g/kg at the start of treatment, followed by 20–40 g/day) is concomitantly used with vasoconstrictors to help improve effective arterial blood volume. Randomized and non-randomized studies indicate that terlipressin is effective in type 1 HRS in approximately 50% of patients [51,64]. There is limited data on the role of terlipressin or other vasoconstrictors in type 2 HRS. Recommended doses of terlipressin are 1 mg/4–6 h IV bolus, with a dose increased up to a maximum of 2 mg/4–6 h after 2–3 days if there is no response to therapy as defined by a reduction of serum creatinine >25% compared to pre-treatment values. Terlipressin has also been used as continuous IV infusion, but data available is very limited [65–67]. Complete response to therapy is considered when serum creatinine levels decrease below 1.5 mg/dl. Treatment response usually occurs within the first 7–10 days and is associated with an increase in arterial pressure and urine volume, and improvement of hyponatremia [68,69]. The most frequent side effects of vasoconstrictors are ischemic complications that are usually reversible after discontinuation of treatment and occur in up to 10% of patients treated.

TIPS may improve renal function in HRS, but its applicability in patients with type 1 HRS is limited because of the severe liver failure of these patients [64]. However, the observation that vasoconstrictor therapy followed by TIPS was successful in a small and selected series of patients with type 1 HRS suggests that the use of combined or sequential therapies of vasoconstrictors and TIPS in HRS should be explored in special patient populations [70]. Renal replacement therapy is not considered the first treatment option of HRS, but it may serve as temporary option in patients with no response to vasoconstrictors or in those that develop severe volume overload, intense metabolic acidosis or refractory hyperkalemia [63]. The use of the Molecular Adsorbent Recirculating System (MARS®), an alternative dialysis that clears albumin-bound substances, including vasodilator factors, is currently being investigated but more data are needed in order to consider it as a therapeutic tool for HRS [71]. A recent study using the extracorporeal liver device system Prometheus® suggests that this system may improve survival in patients with type 1 HRS [72]. However, these results require confirmation in larger studies.

Liver transplantation is the optimal treatment for suitable candidates with HRS. However, patients with type 1 HRS have a high mortality while on the waiting list. Treatment of these patients with terlipressin and albumin while on the waiting list has the potential advantage of transplanting patients with normal or near-normal renal function, which may improve the post-operative course of the patients by reducing the need for dialysis after transplantation, the complications associated with renal failure, and the length of hospital stay [73,74].

**Management of severe hepatic encephalopathy**

Hepatic encephalopathy is a complex and potentially reversible neuropsychiatric syndrome frequently observed in patients with...
advanced cirrhosis[75,76]. The West-Haven criteria are widely used to subjectively classify these patients attending to the degree of depressed level of consciousness, personality changes, and neuropsychiatric abnormalities (Table 2)[75]. Owing to the lack of pathognomonic features, clinical diagnosis requires a detailed neurological examination in order to exclude other causes of altered mental status. Focal neurological defects are rare (excluding bilateral Babinski’s sign and hyper-reflexia). Their presence and/or a history of an extremely rapid coma (within hours) should lead to perform imaging studies (CT scan) and/or lumbar puncture in order to rule out an organic disease (e.g. subdural hematoma, meningitis).

**General treatment principles**

The basis of therapy is appropriate supportive care and identification and treatment of precipitating factors. Comatose patients (with severe hepatic encephalopathy: stages 3 or 4) should be transferred to the ICU and intubated in order to protect the airway. In patients with concurrent upper gastrointestinal bleeding, the threshold for airway intubation should be decreased (stage 2 hepatic encephalopathy) to prevent aspiration. Moreover, a systematic clinical evaluation of the patient, including a complete infectious work-up (see above), should be carried out to detect and treat the precipitating event. Bacterial infections, upper gastrointestinal bleeding, and renal failure are the most frequent cause of hepatic encephalopathy (Table 3). However, a precipitating event is absent in between 20% and 30% of patients[77,78]. Since ammonia levels do not provide any additional information and do not predict or correlate with clinical outcomes, their systematic determination is not recommended[79]. Assessment of benzodiazepines in blood may be useful particularly in patients with no evident cause for encephalopathy.

**Table 3. Mechanisms and main precipitating factors of hepatic encephalopathy.**

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<tr>
<th>Increase in nitrogen load</th>
<th>Metabolic alterations</th>
<th>Drugs</th>
<th>Miscellaneous</th>
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<td>Upper gastrointestinal bleeding</td>
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<td>Constipation</td>
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<td>Renal failure</td>
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<td>Excessive dietary protein intake</td>
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<td>Morphine derivatives</td>
<td>Diuretics</td>
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**Specific interventions**

Non-absorbable disaccharides (lactulose or lactitol) are currently the mainstay of specific treatment of hepatic encephalopathy despite data showing no superiority of these drugs over placebo[80]. They decrease ammonia levels in portal and systemic circulation through several mechanisms. Oral daily doses of 40–60g of lactulose or 30–50g of lactitol result in 2–3 soft stools per day; diarrhea must be avoided. Lactulose enemas (colonic cleansing) must be administered to comatose patients (1 to 3 per day)[75,76]. Oral rifaximin (1100 or 1200 mg/d), a non-absorbable derivative of rifamycin capable of modulating gut flora, is also effective in the treatment of acute hepatic encephalopathy with resolution rates similar or even higher than those observed with lactulose or lactitol[77]. Rifaximin is also effective in the secondary prevention of hepatic encephalopathy[81]. Protein restriction is not recommended. A normal protein diet is safe and in fact nutritionally better for patients with hepatic encephalopathy[82].

**Acute-on-chronic liver failure (ACLF)**

The term ACLF has been used mainly for severely-ill patients with end-stage liver disease and extrahepatic organ failure. There is still very limited data on the definition, diagnosis, and outcome of ACLF. Initially, Jalan et al. defined ACLF as an acute deterioration of the liver function following a triggering event leading to jaundice, hepatic encephalopathy, and/or HRS with organ dysfunction[83]. A working group of the Asian Pacific Association for the Study of the Liver (APASL) defined ACLF as an “acute hepatic insult manifesting as jaundice and coagulopathy, complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease”[84]. More recently, a working group from the American Association for the Study of Liver Disease (AASLD) and the European Association for the Study of the Liver (EASL) made a proposal of the definition of ACLF as an “acute deterioration of preexisting, chronic liver disease, usually related to a precipitating event and associated with increased mortality at 3 months due to multisystem organ failure”[85]. A large prospective European multicenter study is currently underway by the European Association for the Study of the Liver Chronic Liver Failure (EASL-CLIF) consortium group in order to better define this entity and its prognosis.

**The concept of albumin dialysis**

In recent years, systems using dialysis techniques to remove both hydrophilic and non-hydrophilic substances from plasma have become available. The most extensively used of these systems, MARS®, uses albumin to remove a variety of endogenous substances and albumin-bound toxins from the blood, including bilirubin, bile salts, long-chain fatty acids, and nitric oxide, among others[86]. The albumin in the system is used to uptake these substances from the blood. In addition to MARS®, two other systems using a similar approach have been developed, the fractionated plasma separation and absorption system (Prometheus®) and the Single-pass albumin dialysis (SPAD®).
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Pathophysiological evidence of efficacy of MARS® therapy in ACLF

A number of proof-of-concept and randomized studies have shown that albumin dialysis with MARS® has significant beneficial effects, that may be summarized as follows [78, 87, 88]: 1) significant reduction of the levels of total and conjugated bilirubin, biliary acids, ammonia, aromatic amino acids, benzdiazepines and derivative substances, long- and short-chain fatty acids, copper, urea, creatinine and lactate; 2) improvement of systemic hemodynamics, with increase in mean arterial pressure, stroke volume and systemic vascular resistance, reduction in the activity of the renin–aldosterone and sympathetic nervous systems, and reduction in cardiac output and nitric oxide levels, and 3) improvement in splanchic circulation by increasing hepatic blood flow and hepatic delivery of oxygen, and decreasing portal pressure.

Clinical efficacy of MARS® and Prometheus® in patients with ACLF

In the last years, there have been many reports on the use of MARS® in critically-ill patients with cirrhosis and superimposed complications [78, 89, 90]. However, few of these reports have assessed its efficacy in well-defined clinical situations using a randomized controlled approach. For this reason, the usefulness of MARS® in the population of critically-ill cirrhotic patients is still unclear. In one of the few randomized studies, MARS® was more effective than standard medical therapy in improving hepatic encephalopathy in patients with grade 3–4 hepatic encephalopathy and significantly reduced ammonia levels [78]. In another randomized controlled study in patients with ACLF, the use of MARS® improved hepatic encephalopathy and 30-day survival compared to the standard medical group (91% vs. 54%, respectively) [89]. Recently, two large European multicenter RCTs performed in patients with ACLF comparing either MARS® or Prometheus® to standard medical therapy have failed to show any benefit of the two treatments on 28-day survival [71, 72]. Full reports of these two trials are expected to give more insight about therapeutic strategies in this field.

The heterogeneity of patients and definitions of ACLF, the variety and complexity of the precipitating event causing hepatic and extrahepatic organ failure, the major role of SIRS and sepsis and the lack of hepatic cell regeneration in advanced cirrhosis make extremely difficult the evaluation of the efficacy of a single therapeutic strategy. Technical improvements, RCTs re-evaluating indications, timing of treatment and cost-effectiveness are still needed to evaluate the impact of liver support therapies on medical practice.

Role of prognostic systems

General prognosis of critically-ill cirrhotic patients in the ICU

Short-term prognosis in cirrhotic patients who develop multiple organ/system failures remains poor, even with unrestricted ICU support. As an example, data from recent series in patients with cirrhosis have shown ICU and 6-month mortality rates of 41% and 62%, respectively [91, 92]. Hospital mortality rates in patients with 1, 2 or 3 organ/system failures were 48%, 65%, and 70%, respectively [92]. Another study has shown that 59% of cirrhotic patients placed on mechanical ventilation died during their stay in the ICU [93]. Most deaths occur during the first week following admission [92], the main cause of death being multiple organ failure including refractory circulatory failure. However, hospital mortality of cirrhotic patients admitted in the ICU is quite variable from series to series, ranging from 40% [92] to more than 80% [94]. These variations are probably related to different policies concerning admission to the ICU and, to a lesser extent, to non-homogeneous access to salvage transplantation. Nonetheless, mortality rates in ICU cirrhotic patients are still substantially higher, on average, than mortality rates in non-cirrhotic ICU patients receiving vasopressors (about 50% in recent series) [37].

The poor outcome of critically-ill cirrhotic patients in the ICU results from (a) the absence of an efficient artificial liver support system and (b) the cascade of events usually leading to a vicious circle in patients with advanced cirrhosis and acute complications. Indeed, any severe complication in a cirrhotic patient may induce further deterioration of liver function and promote the occurrence of other organ/system failures (including renal failure and circulatory failure). According to this vicious circle, impaired liver function leads to multiple organ/system failure and organ/system failure contributes to the impairment in liver function.

Even though the prognosis of critically-ill cirrhotic patients is poor, renewed interest recently emerged with the generalization of the MELD score-based (“sickest first”) allocation policy, allowing rapid access to transplantation to patients with the highest MELD score.

Limitations of the MELD score and the Child–Pugh score

The MELD score, based on the objective values of serum bilirubin, INR, and creatinine, proved to be a robust predictor of early mortality in cirrhotic patients throughout a wide range of disease severity [95, 96]. However, apart from renal failure, assessed by creatinine, the MELD score does not take into account other organ/system failures. Obviously, the higher the MELD score, the higher early mortality in critically-ill cirrhotic patients. Several reports have highlighted the especially high mortality rate in patients with a high MELD score after admission to the ICU [91, 97, 98]. However, the MELD score may not be accurate enough at identifying the subgroup of critically-ill cirrhotic patients who are likely to have a reasonable chance to survive ICU admission. These limitations are also applicable to the Child–Pugh score.

Usefulness and limitations of general ICU prognostic scores

At least 10 different general ICU scores have been proposed, with the aim of assessing disease severity and outcome (APACHE II, APACHE III, SAPS and MPM scores), stratifying organ failures (LODS, MODS and SOFA scores) or quantifying nursing workload use (TISS, NEMS and NAS scores) [99]. The APACHE II and SOFA scores are the most commonly used for assessing prognosis in the general ICU.

Several studies have compared the accuracy of liver-specific scores (Child–Pugh and MELD) to that of general ICU scores (APACHE II and SOFA) in critically-ill cirrhotic patients (Table 4). These studies suggest that the accuracy of the SOFA score appears to be slightly superior to that of the APACHE II, MELD, and Child–Pugh scores. Mortality rates were especially high in patients with a SOFA score of over 8 [100], as well as in patients with a MELD score of over 25 [97]. Interestingly, the accuracy of the liver-specific MELD score was similar or even superior to that of the general ICU APACHE II score.
General ICU scores are more accurate at grading multiple organ failure, with or without cirrhosis. However, a difficulty comes from the fact that, even when critically-ill cirrhotic patients develop multiple organ failure, the liver is central in the outcome. The assessment of liver function in general ICU scores is inappropriate in the setting of cirrhosis. For instance, the SOFA score relies on markers of neurologic, cardiovascular, renal, respiratory, hematologic, and hepatic dysfunction. Two of the three variables of the MELD score, namely creatinine and bilirubin, are entered in the SOFA score. However, there may be some limitations regarding the use of the SOFA score in cirrhosis. Firstly, the weight given to creatinine and bilirubin in the SOFA score is not the same as that given to the same two variables in the MELD score. Secondly, coagulation, a pivotal marker of liver function, is not entered in the SOFA score. Finally, platelet count, a marker of coagulation changes in the SOFA score, is likely to be biased in patients with cirrhosis and portal hypertension.

In a recent study, it has been suggested that a modified, “non-hematologic” SOFA score, in which platelet count is not taken into account, could be more accurate than other general ICU scores [91].

It must be noted that independent from these scores, some specific indications for admission in the ICU (variceal bleeding and encephalopathy) may be associated with a better prognosis than others (shock and respiratory distress, for instance) [8,92].

### Key Points

- MELD and Child-Pugh scores have important limitations in the establishment of prognosis in critically-ill cirrhotic patients. Non-hematological SOFA score seems to be the most accurate general ICU score in these patients.
- Careful fluid resuscitation and blood transfusion, antibiotic prophylaxis, pharmacological vasoactive therapy and early banding are essential in the management of variceal bleeding in cirrhosis. Early TIPS is indicated in patients with high risk of treatment failure (Child-Pugh B with active bleeding or Child-Pugh C).
- Resuscitation following early goal therapy and prompt broad-spectrum antibiotics and vasoactive support are key to the management of cirrhotic patients with septic shock. Specific goals for initial resuscitation should be investigated in this population.
- Terlipressin and albumin administration is the first line therapy in patients with type 1 hepatorenal syndrome. The role of albumin dialysis in these patients deserves further investigation. Patients with acute tubular necrosis require renal replacement therapy.
- Comatose cirrhotic patients (grade 3 or 4 hepatic encephalopathy) require ICU admission and intubation. Identification and treatment of the precipitating event constitute the cornerstone of treatment of these patients.
- Acute-on-chronic liver failure is characterized by the concurrence of end-stage liver disease and extra-hepatic organ failure in patients with cirrhosis. Albumin dialysis seems to improve hepatic encephalopathy in this setting. Indications and timing of liver support therapies must be defined in future studies.

### The difficult issue of futile versus non-futile intensive care in critically-ill cirrhotic patients

Again, the general prognosis of cirrhotic patients in the ICU is poor. On an individual basis, which probability of survival justifies ICU admission in a critically-ill cirrhotic patient and which patients should be denied from intensive support is still a matter of debate. This controversial issue depends on a number of factors including short- and long-term prognosis, the possibility of “salvage” transplantation, and health care resources. There may be wide variations across different geographical areas with different access to transplantation and health care facilities.

Several series have shown that relatively good results can be obtained in selected critically-ill cirrhotic patients [91–93,97,101,102]. Therefore, reluctance to refer these patients to the ICU should be balanced. In general, any patient with an acute life threatening complication who had a low MELD score (below 15) immediately before developing the complication should be considered for ICU. On the contrary, in patients with end-stage cirrhosis (MELD score over 30), 3 or more organ failures [97] and no perspective of “salvage” transplantation, aggressive management is questionable. In between, a practical approach consisting of a 3-day trial of unrestricted intensive care has been proposed [91]. According to this policy, 3 or 4 non-hematologic organ failures in cirrhotic patients should not be a contraindication for admission to the ICU. However, the persistence of 3 or more of these failures after 3 days spent in the ICU may lead to consider a limitation in life-sustaining treatments as a fatal outcome is almost constant.

### Table 4. Mortality rate and accuracy of different prognostic scores to assess mortality in critically-ill cirrhotic patients admitted to the ICU.

<table>
<thead>
<tr>
<th>Author [Ref.]</th>
<th>Year</th>
<th>Patients</th>
<th>Mortality (%)</th>
<th>Accuracy of prognostic scores (c statistic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wehler, M et al. [100]</td>
<td>2004</td>
<td>76</td>
<td>59*</td>
<td>0.74 - 0.66 - 0.66 - 0.94</td>
</tr>
<tr>
<td>Rabe, C et al. [93]</td>
<td>2005</td>
<td>102</td>
<td>69**</td>
<td>0.74 - 0.79 - 0.94</td>
</tr>
<tr>
<td>Chen, YC et al. [102]</td>
<td>2006</td>
<td>312</td>
<td>65*</td>
<td>0.72 - 0.81 - 0.84†</td>
</tr>
<tr>
<td>Cholongitas, E et al. [97]</td>
<td>2010</td>
<td>138</td>
<td>49*</td>
<td>0.76 - 0.75 - 0.78 - 0.94†</td>
</tr>
</tbody>
</table>

*ICU mortality. **Hospital mortality. † Modified SOFA score (platelet count is not entered).
References


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