Anaesth Crit Care Pain Med 39 (2020) 143–161

Guidelines

Management of liver failure in general intensive care unit☆,☆☆

C. Paugam-Burtz [1,2], E. Levesque [3,4], A. Louvet [5], D. Thabut [6], R. Amathieu [7,8], C. Bureau [9,10,11], C. Camus [12], G. Chanques [13], S. Faure [14], M. Ferrandière [15], C. Francoz [16,17], A. Galbois [18], T. Gustot [19,20], C. Ichai [21], P. Ichai [22,23,24], S. Jaber [25], T. Lescot [26], R. Moreau [27,28,29,30], S. Roullet [31,32], F. Saliba [33], T. Thévenot [34], L. Velly [35,36], E. Weiss [37,38,*]

[1] *Department of Anaesthesiology and Critical Care, Beaujon Hospital, DMU Parabol, AP–HP Nord, Université de Paris, 92110 Clichy, France*
[2] *UMR_S1149, Centre de recherche sur l'inflammation, Inserm, Université de Paris, France*
[3] *Department of Anaesthesiology and Critical Care, Henri-Mondor Hospital, Assistance Publique–Hôpitaux de Paris, 94010 Créteil, France*
[4] *EA Dynamyc UPEC, ENVA Faculté de Médecine de Créteil, 94000 Créteil, France*
[5] *Department of Digestive Diseases, Claude Huriez Hospital, 59037 Lille, France*
[6] *Department of Hepathology, Pitié-Salpêtrière Hospital, Assistance publique–Hôpitaux de Paris, 75013 Paris, France*
[7] *Université Paris 13–UFR SMBH–CNRS UMR 7244, Paris, France*
[8] *Critical Care Department, Diaconesses Croix Saint Simon Hospital Group, 75020 Paris, France*
[9] *Department of Hepathology, Purpan Hospital, Toulouse University Hospital, 31300 ToulouseFrance*
[10] *Institut Cardiomet, Cardiovascular and Metabolic Department, Rangueil Hospital, TSA 50032, 31059 Toulouse cedex 9, France*
[11] *Paul Sabatier University, 31330 Toulouse, France*
[12] *Department of Infectious Diseases and Medical Resuscitation, Rennes University Hospital, 35000 Rennes, France*
[13] *Department of Anaesthesia and Intensive Care, Saint Eloi Montpellier University Hospital, and PhyMedExp, University of Montpellier, INSERM, CNRS, 34295 Montpellier cedex 5, France*
[14] *Department of Hepathology, Saint Eloi Montpellier University Hospital, 34090 Montpellier, France*
[15] *Surgical Intensive Care Unit, Tours University Hospital, 37044 Tours cedex 9, France*
[16] *Department of Hepathology, Beaujon Hospital, AP–HP, 92110 Clichy, France*
[17] *UMR_S1149, Centre de recherche sur l'inflammation, INSERM and Paris Diderot University, 75013 Paris, France*
[18] *Ramsay Générale de Santé, Claude Galien Private Hospital, Department of Polyvalent Resuscitation, 91480 Quincy-sous-Sénart, France*
[19] *Department of Gastroenterology and Hepato-Pancreatology, Erasme Hospital, Route de Lennik, 808, 1070 Bruxelles, Belgium*
[20] *Laboratory of Experimental Gastroenterology, Faculté de Médecine, Université Libre de Bruxelles, avenue Franklin-Roosevelt, 50, 1050 Bruxelles, Belgium*
[21] *University of Côte D'Azur, Nice University Hospital, Department of Polyvalent Resuscitation, Pasteur 2 Hospital, 06000 Nice, France*
[22] *Hepato-Biliary Center, Paul-Brousse Hospital, AP–HP, Liver Intensive Care Unit, 94800 Villejuif, France*
[23] *INSERM, Unité 1193, Université Paris-Saclay, 94800 Villejuif, France*
[24] *DHU Hepatinov, 94800 Villejuif, France*
[25] *Department of Anaesthesia and Intensive Care, Saint Eloi Montpellier University Hospital, and PhyMedExp, University of Montpellier, INSERM, CNRS, 34295 Montpellier cedex 5, France*
[26] *Sorbonne Université, Department of Anesthesiology and Critical Care Medicine, Saint-Antoine Hospital, Assistance Publique-Hôpitaux de Paris, ParisFrance*
[27] *Inserm, Université Paris Diderot, Centre de Recherche sur l'Inflammation (CRI), 75018 Paris, France*
[28] *Department of Hepatology, Beaujon Hospital, AP–HP, 92110 Clichy, France*
[29] *European Foundation for the study on chronic liver failure (EF Clif), Barcelona, Spain*
[30] *Institute for Liver and Biliary Sciences (ILBS), New Delhi, India*
[31] *Anaesthesiology and Critical Care Department 1, Bordeaux University Hospital, 33000 Bordeaux, France*
[32] *University of Bordeaux, INSERM U 1034, Biology of Cardiovascular Diseases, 33000 Bordeaux, France*
[33] *Hepato-Biliary Center, Paul Brousse Hospital, AP-HP, INSERM Unité 935 and Unité 1193, 94800 Villejuif, France*
[34] *Department of Hepatology and Digestive Critical Care, Department of Hepatology, Jean Minjoz University Hospital, 25030 BesançonFrance*
[35] *Aix Marseille University, CNRS, Institut de Neuroscience de la Timone (INT), 13005 Marseille, France*
[36] *Department of Anaesthesiology and Critical Care Medicine, University Hospital La Timone, 13005 Marseille, France*
[37] *Department of Anesthesiology and Critical Care, Beaujon Hospital, DMU Parabol, AP–HP Nord, University of Paris, France*
[38] *UMR_S1149, Centre de recherche sur l'inflammation, INSERM and University of Paris, Paris, France*

☆ Validated by the SFAR Council on June 21st, 2018.
☆☆ With the collaboration of the following societies: Société française d'anesthésie et de réanimation, Association française pour l'étude du foie.

* Corresponding author at: Service d'anesthésie-réanimation, hôpital Beaujon, 100, boulevard du Général-Leclerc, 92110 Clichy, France.
E-mail address: emmanuel.weiss@aphp.fr (E. Weiss).

https://doi.org/10.1016/j.accpm.2019.06.014

ARTICLE INFO

Article history:
Available online 13 September 2019

Keywords:
Acute liver failure
Acute-on-chronic liver failure
Guidelines
Cirrhosis
Intensive care unit

ABSTRACT

Objective: To produce French guidelines on Management of Liver failure in general Intensive Care Unit (ICU).
Design: A consensus committee of 23 experts from the French Society of Anesthesiology and Critical Care Medicine (Société française d'anesthésie et de réanimation, SFAR) and the French Association for the Study of the Liver (Association française pour l'étude du foie, AFEF) was convened. A formal conflict-of-interest (COI) policy was developed at the start of the process and enforced throughout. The entire guideline process was conducted independently of any industrial funding. The authors were advised to follow the principles of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to guide their assessment of the quality of evidence. The potential drawbacks of making strong recommendations in the presence of low-quality evidence were emphasised. Some recommendations were ungraded.
Methods: Two fields were defined: acute liver failure (ALF) and cirrhotic patients in general ICU. The panel focused on three questions with respect to ALF: (1) Which etiological examinations should be performed to reduce morbidity and mortality? (2) Which specific treatments should be initiated rapidly to reduce morbidity and mortality? (3) Which symptomatic treatment should be initiated rapidly to reduce morbidity and mortality? Seven questions concerning cirrhotic patients were addressed: (1) Which criteria should be used to guide ICU admission of cirrhotic patients in order to improve their prognosis? (2) Which specific management of kidney injury should be implemented to reduce morbidity and mortality in cirrhotic ICU patients? (3) Which specific measures to manage sepsis in order to reduce morbidity and mortality in cirrhotic ICU patients? (4) In which circumstances, human serum albumin should be administered to reduce morbidity and mortality in cirrhotic ICU patients? (5) How should digestive haemorrhage be treated in order to reduce morbidity and mortality in cirrhotic ICU patients? (6) How should haemostasis be managed in order to reduce morbidity and mortality in cirrhotic ICU patients? And (7) When should advice be obtained from an expert centre in order to reduce morbidity and mortality in cirrhotic ICU patients? Population, intervention, comparison and outcome (PICO) issues were reviewed and updated as required, and evidence profiles were generated. An analysis of the literature and recommendations was then performed in accordance with the GRADE® methodology.
Results: The SFAR/AFEF Guidelines panel produced 18 statements on liver failure in general ICU. After two rounds of debate and various amendments, a strong agreement was reached on 100% of the recommendations: six had a high level of evidence (Grade 1 ±), seven had a low level of evidence (Grade 2 ±) and six were expert judgments. Finally, no recommendation was provided with respect to one question.
Conclusions: Substantial agreement exists among experts regarding numerous strong recommendations on the optimum care of patients with liver failure in general ICU.

Working groups

French Society of Anesthesiology and Critical Care Medicine (Société Française d'Anesthésie-Réanimation, SFAR) and the French Association for the Study of the Liver (Association française pour l'étude du foie, AFEF)

Experts' coordinators

C. Paugam-Burtz
E. Levesque
A. Louvet
D. Thabut
Organisers
E. Weiss
L. Velly

Experts

R. Amathieu
C. Bureau
C. Camus
G. Chanques
S. Faure
M. Ferrandière
C. Francoz
A. Galbois
T. Gustot
P. Ichai
C. Ichai
S. Jaber
T. Lescot
R. Moreau
S. Roullet
F. Saliba
T. Thevenot

1. Introduction

Liver failure is a condition that can be managed or may occur in general critical care under two very different circumstances: on the one hand, acute liver failure (ALF) corresponding to a sudden deterioration in liver function due to toxic or infectious agents occurring in the absence of underlying liver disease. Although ALF is uncommon, it is mandatory to recognise it at an early stage so that a first-line diagnostic and therapeutic strategy can be adopted, and expert advice sought. On the other hand, the hospitalisation in critical care of cirrhotic patients is common, either for the complications of cirrhosis itself or for medical events likely to decompensate preexisting liver disease.

The French Society of Anaesthesia and Critical Care (Société française d'anesthésie et de réanimation, SFAR) and the French Association for the Study of the Liver (Association française pour l'étude du foie, AFEF) have joined forces to generate original guidelines dedicated to the management of liver failure in critical care setting. These guidelines are intended for a wide audience of intensivists. The aim is not to detail the specific measures adopted in specialised or dedicated liver ICU to manage these patients, but rather to specify the first-line diagnostic and therapeutic management that should be initiated in any critical care unit. The recommendations also focus on specifying the circumstances where expert advice from dedicated centres, most often backed by liver transplant units, is required. Twenty French-speaking experts were thus selected by an organising committee that had been appointed by the guideline committees approved by the executive boards of the two scientific societies. These experts were asked to produce guidelines covering two specific areas: acute liver failure and cirrhotic disease. Two bibliographic experts also used predefined key words to review all the literature in the field published during the past twenty years.

2. Aim of the guidelines

The aim of these guidelines is to provide a decision-making framework for physicians practicing in a general critical care setting who need to treat patients with suspected liver failure. The group tried to produce a minimum number of recommendations so as to highlight the important features to be retained in the two predefined fields. In situations of doubt, the weight of the literature was considered to be more important than the experts' opinions. The basic rules of universal good medical practice in intensive care were considered to be known and were excluded from the recommendations. The target audience is large, focusing on all professional intensivists with the exception of those working in structures dedicated to liver diseases, often backed by liver transplant centres.

3. Definitions

Two fields were defined:

- Acute Liver Failure (ALF) corresponding to a sudden deterioration in liver function due to the appearance of toxic or infectious agents in the absence of underlying liver disease;
- liver failure in patients with underlying chronic liver disease or cirrhosis, frequently associated with Acute on Chronic Liver Failure (ACLF).

4. Methods

These guidelines were drawn up by a group of experts acting on behalf of the Association française pour l'étude du foie (AFEF) and the Société française d'anesthésie et de réanimation (SFAR). The organising committee defined a list of questions to be addressed and designated experts to be responsible for each question. The questions were formulated using the Patient Intervention Comparison Outcome (PICO) model.

The Grade Method (Grade of Recommendation Assessment, Development and Evaluation) was used to compile these guidelines. Following a quantitative analysis of the literature, the method can be used to separately determine the quality of the evidence available, i.e. to estimate the level of confidence required to analyse the effects of the quantitative intervention, and the level of recommendation. The quality of evidence is rated as follows:

- high quality of evidence: further research is very unlikely to affect confidence in the estimate of the effect;
- moderate quality of evidence: further research is likely to have an impact on confidence in the estimate of the effect and could change this estimate of the effect;
- low quality of evidence: further research is very likely to have an impact on confidence in the estimate of the effect and is likely to change this estimate of the effect;
- very low quality of evidence: any estimate of the effect is very unlikely.

The level of recommendation is binary (either positive or negative) and strong or weak:

- strong recommendation: we recommend (grade 1 +) or do not recommend (grade 1 −) this action;
- weak recommendation: we suggest (grade 2 +) or do not suggest (grade 2 −) this action.

The strength of the recommendations was determined according to key factors and validated by the experts after a vote using the Grade Grid method [1].

The compilation of a guideline required that at least 50% of voting participants had an opinion and that fewer than 20% of participants voted for the opposite proposal. The compilation of a strong agreement required the approval of at least 70% of the voting participants.

5. Results

Nineteen experts and four coordinators agreed to address questions concerning the treatment of liver failure and its practical implementation in the general intensive care setting in two specific contexts:

- acute liver failure (ALF) defined as the development of hepatocellular dysfunction in patients without preexisting liver disease;
- liver failure in patients with underlying chronic liver disease or cirrhosis, frequently associated with acute on chronic liver failure (ACLF).

ACLF is defined as a clinical syndrome of sudden hepatic decompensation observed in patients with chronic liver disease and associated with the failure of one or more extrahepatic organs.

The experts summarised the work and applied the Grade methods, which resulted in 18 recommendations and three management algorithms. Six of these recommendations were strong (grade 1), six were weak (grade 2) and six were expert opinions. No recommendation was formulated in response to one question. After two rounds of scoring and various amendments, a strong agreement from all voting participants was obtained for all recommendations (100%).

5.1. First area. Acute liver failure

Acute liver failure (ALF) is a rare disease (fewer than 10 cases per million persons per year in the developed world), characterised by rapidly progressive liver dysfunction associated with a fall in prothrombin time (PT) ratio levels observed in patients without any preexisting liver disease and in less than 26 weeks.

Severe ALF defines a syndrome characterised by a PT ratio less than 50%.

Serious ALF defines a syndrome characterised by a PT ratio less than 50% in combination with encephalopathy.

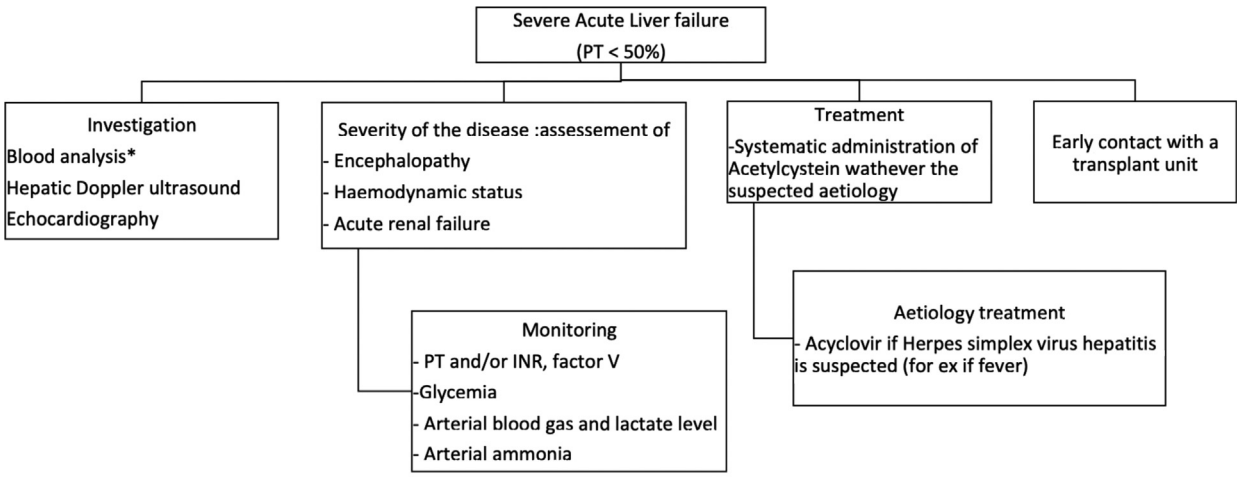

Fig. 1. Proposed algorithm for the management of acute liver failure.

There are also several definitions based on the time elapsing between jaundice and the development of encephalopathy. Fulminant hepatitis refers to the occurrence of encephalopathy within 15 days of the onset of jaundice, although the original term ''fulminant hepatitis'' is classically used to describe severe ALF. The terms ''severe'' or ''serious'' ALF are used in the remainder of this text. The prognosis of ALF has gradually improved in recent years, with a 2-year survival rate of about 90% in the event of transplantation and of 90% after severe ALF due to paracetamol without transplantation [2].

An algorithm (Fig. 1) and a table (Table 1) summarising ALF management are proposed.

6. Question 1: In patients with acute liver failure, which etiological exams should be performed to reduce morbidity and mortality?

R1 – In patients with severe acute liver failure, we recommend the determination of serum acetaminophen levels, serology for Hepatitis A (IgM VHA) and Hepatitis B (HBsAg and anti-HBc IgM) viruses, urinary toxins (amphetamine, cocaine), and the performance of an echocardiography and hepatic echo-Doppler.
(GRADE 1+), STRONG AGREEMENT

Table 1
Management of extrahepatic organ failure in patients with acute liver failure.

	What to do	What not to do
Central nervous system	Encephalopathy should be monitored frequently Maintain serum sodium levels between 140 and 145 mmol/L Monitoring of blood glucose will probably be required at least every 2 hours Tracheal intubation and sedation in the event of progressive HE (Glasgow < 8) Practices to minimise the depth of sedation are recommended Transcranial Doppler ultrasound ICP: no specific treatment	Administration of sedatives such as benzodiazepines and psychotropic drugs (such as metoclopramide) Use of treatments (lactulose, rifaximin) to lower ammonia levels
Respiratory system	Standard lung protective ventilator strategy (according to specific recommendations)	
Cardiovascular system	Assessment of volume status, cardiac output and cardiac function (right and left-sided function) Fluid expansion using crystalloid fluids as first choice Norepinephrine infusion for refractory hypotension	
Renal system	Renal replacement therapy according to specific recommendations	Use of nephrotoxic drugs, including non-steroidal anti-inflammatory drugs
Gastrointestinal system	Stress ulcer prophylaxis according to specific recommendations	
Coagulation		Routine correction of coagulation: restrict clotting factors administration unless active bleeding
Immune system	Empirical broad spectrum antibiotics should be administered to patients with worsening HE or signs of SIRS	

HE: hepatic encephalopathy; ICP: intracranial pressure; SIRS: systemic inflammatory response syndrome.

6.1. Rationale

Among the most common causes of ALF, acetaminophen-induced hepatotoxicity (whether intentional or not) is the most common cause of severe ALF and an indication for emergency liver transplantation (22% in France) [3,4]. ALF may also be caused by Hepatitis A and B infections (14.6%), other drugs (antimicrobial and antiepileptic agents, statins) (9.4%) or other various toxic agents (herbal supplements, cocaine, ecstasy or the ingestion of mushrooms) (4.8%).

Less frequently, others causes of ALF may be identified such as autoimmune hepatitis, Wilson's disease, metabolic disease, etc. These account for 28.8% of patients on the liver transplant waiting list. Noteworthy, the cause of ALF remains unknown in 25% of patients, despite intensive investigation. Clinical assessment and extensive search in patient's medical history are important elements to determine the cause of ALF.

Early recognition of the reason for ALF is crucial to guide potential specific management and predict its outcome [3]. The transplant-free survival of patients with ALF related to acetaminophen, hepatitis A, hypoxic hepatitis or pregnancy is 50%. Conversely, when ALF is associated with hepatitis B, drugs other than acetaminophen, autoimmune hepatitis, Wilson's disease or Budd–Chiari syndrome, the transplant-free survival rate is lower than 25%.

Abdominal Doppler ultrasound should be performed rapidly to exclude chronic liver disease suggested by ascites, hepatomegaly, dysmorphic liver or malignant infiltration of the liver, and to verify the permeability of vessels (hepatic veins, portal vein). Echocardiography should also be performed when acute ischemic hepatocellular injury is suspected [critically ill patients with primary cardiac or circulatory failure, elderly individuals, underlying history of heart disease or arrhythmia, patients with acute renal failure, serum level of aspartate transaminase (AST) exceeding those of alanine aminotransferase (ALT)] [5].

7. Question 2: In patients with acute liver failure, which specific treatments should be initiated rapidly to reduce morbidity and mortality?

R2.1 – In patients with acetaminophen-induced acute liver failure, we recommend the initiation of N-acetylcysteine therapy without waiting for, and regardless of, the results of serum acetaminophen determinations.
(GRADE 1+) STRONG AGREEMENT

R2.2 – In patients with acute liver failure whatever the aetiology, we suggest the initiation of N- acetylcysteine therapy to improve morbidity and mortality.
(GRADE 2+) STRONG AGREEMENT

7.1. Rationale

In a retrospective analysis of patients with acetaminophen-induced liver failure, fewer patients in the group treated with acetylcysteine compared to non-treated group progressed to grade III–IV encephalopathy (21/41 [51%] versus 43/57 [75%], $P < 0.05$) or died (15/41 [37%] treated versus 26/41 [63%] non-treated, $P < 0.05$) [6]. A placebo-controlled randomised trial in patients with acetaminophen-induced liver failure demonstrated an increase in the 21-day survival rate of those treated with acetylcysteine (12/25 [48%] versus 5/25 [25%] respectively, $P = 0.037$) [7]. Additionally, fewer treated patients developed clinical signs of cerebral oedema (40% versus 68%, $P = 0.047$) and needed vasoconstrictors to maintain blood pressure (48% versus 80%; $P = 0.018$) [7]. A recent meta-analysis found that acetylcysteine was significantly superior to placebo, resulting in lower levels of hepatotoxicity (18% versus 58% [RR 0.31, 95% CI 0.26–0.39]) and mortality (0.7% versus 6% [RR = 0.12, 95% CI 0.04–0.38]) [8].

It has been suggested that the therapeutic use of acetylcysteine may also benefit patients with non-acetaminophen-related ALF. A recent meta-analysis analysed the results of four prospective clinical trials regarding the safety and efficacy of acetylcysteine in patients (both adults and children) with ALF not related to acetaminophen poisoning [9]. A total of 331 patients received treatment with acetylcysteine as compared to 285 patients in control group [10–12]. No statistical difference was seen between the two groups in terms of overall mortality. However, liver transplant-free survival (41% versus 30%, OR = 1.61, 95% CI 1.11–2.34, $P = 0.01$) and post-transplant survival (85.7% versus 71.4%, OR = 2.44, 95% CI 1.11–5.37, $P = 0.03$) were significantly greater in treated patients. We performed a new meta-analysis including adult patients only and two recent studies [13,14] [10,15], which displayed improvements in overall survival (four studies with 499 patients: 76% versus 59%, OR = 2.30, 95% CI 1.54–3.45 $P < 0.0001$) and liver transplant-free survival (three studies with 419 patients: 64% versus 26%, OR = 4.81, 95% CI 3.22–7.18, $P < 0.0001$). However, because of methodological bias, we have produced a lower grade (GRADE 2) recommendation for the use of acetylcysteine in non-acetaminophen-related ALF.

During these studies, acetylcysteine was predominantly administered intravenously, at varying doses. The adverse effects identified included nausea, vomiting, diarrhea or constipation. Acetylcysteine could cause skin rash (< 5%) or transient bronchospasm (1–2%).

In the prospective double-blind trial performed by Lee et al. [10], the beneficial effects of acetylcysteine on transplant-free survival were confined to patients with grades I–II coma. This suggests that the interval between drug ingestion and treatment with acetylcysteine is closely related to the outcome, so that acetylcysteine should be started as early as possible. Acetylcysteine has complex antioxidant and immunologic effects whose mechanisms of action are not completely understood.

R2.3 – In patients with acute liver failure, whatever the aetiology, the experts suggest that advice should be obtained from a liver transplantation centre in order to discuss:
1. Second-line aetiological investigations if the results of first-line examinations (see R1) are negative
2. An indication for liver transplantation
EXPERT OPINION, STRONG AGREEMENT

7.2. Rationale

7.2.1. Secondary etiologies

In France, other causes of ALF identified after second-line investigations (autoimmune hepatitis, Wilson's disease, metabolic disease, etc.) account for 28.8% of the cases on the liver transplant waiting list for ALF. If the initial investigation is negative, the following investigations should be carried out:

Antinuclear antibodies, antimitochondrial antibodies, anti-LKM antibodies, smooth muscle antibodies (autoimmune hepatitis); anti-HEV IgM (hepatitis E virus); Anti-HSV IgM (herpes simplex virus types 1 and 2); serum and urinary copper, serum caeruloplasmin, (Wilson's disease). Pregnancy related ALF: there are two hepatic emergencies which can occur during the third trimester of pregnancy: HELLP syndrome and acute fatty liver of pregnancy.

7.2.2. Liver transplantation

Severe ALF defines a syndrome characterised by a PT ratio < 50%. There should be a contact with a liver transplantation centre for each patient with severe ALF allowing discussion about diagnostic and consideration for transfer in a dedicated centre.

Hepatic encephalopathy (HE) is of key prognostic importance in ALF. Neurological symptoms are associated with overall survival (90.1% in ALF patients without HE versus 37.8% in ALF patients with HE; $P < 0.0001$) [16]. HE grades are associated with outcome. Short-term transplant-free survival (three weeks) has been shown to vary considerably, from 52% in patients with grade 1–2 HE to 33% in those with grade 3–4 HE [3]. The development of grade 3–4 HE is associated with brain oedema and intracranial hypertension in 38% to 81% of patients [17,18]. HE is the key indicator for LT. This criterion is used to select candidates for LT (King's College criteria in ALF patients related or not to paracetamol; Clichy–Villejuif criteria) [4,19]. These criteria are prognostic indicators of transplant-free survival and are used in the selection of patients for LT. The historical criteria are those developed by King's College Hospital: in acetaminophen-induced liver failure a poor prognosis is correlated with a pH lower than 7.3, prothrombin time longer than 100 s, a creatinine level higher than 300 mol/l and HE more severe than grade 3. Furthermore, blood lactate levels higher than 3.5 mmol/L after 4 hours, or 3.0 mmol/L after 12 hours of management and the early restoration of intravascular volume, are indicative of a poor prognosis. Recent studies have confirmed the clinically acceptable specificity but more limited sensitivity of these systems (50% to 60%) [20–23]. In order to address these limitations, a wide variety of alternative prognostic systems and markers have been proposed to replace or supplement existing criteria (for example, to identify a patient for transfer to an LT centre). These include the use of factor V levels less than 20% [4], or the combination of criteria: vasopressors need in a context of organ failure [20,24], the routine laboratory measurements including those such as ammonia (with a threshold of 100 μmol/L) [17,18,25,26] or bilirubin (threshold ranging from 140 μmol/L to 200 μmol/L [4,27]), or composite laboratory determinations such as the MELD score [22,27,28].

There is a close relationship between elevated arterial ammonia levels and the development of encephalopathy, there being a greater risk of intracranial hypertension when ammonia levels are sustained between 150 and 200 μmol/L [17,18,26].

All these clinical and biological criteria are correlated to the severity of liver failure but they nevertheless have an independent prognostic value [4,17,22,26–28].

8. Question 3: In patients with acute liver failure, which symptomatic treatment should be initiated to reduce morbidity and mortality?

R3 – In order to reduce morbidity and mortality in patients with acute liver failure, the experts suggest that extrahepatic organ failure should be treated early and any aggravating factors should be prevented, as shown in the Table below.
EXPERT OPINION, STRONG AGREEMENT

8.1. Rationale

Patients with ALF develop hypotension with systemic vasodilation and volume depletion that reflect the severity of the underlying liver failure [29]. Most patients with ALF will have a hyperdynamic circulation. Haemodynamic assessment is necessary to determine volume depletion and both right and left-sided cardiac function, because some patients can develop right or left cardiac dysfunction [1]. There is no specific literature to guide the type of fluids to use or the choice of vasopressor agents [30,31].

There is an evidence of adrenal dysfunction in 50% of patients with ALF, which is at least relative [32,33]. Only one retrospective study including 40 patients, reported that the use of hydrocortisone (300 mg per day) could reduce the need for vasopressors [34]. In the ICU population, the diagnosis and management of critical illness-related corticosteroid insufficiency remains a matter of debate [35–37].

Tracheal intubation is usually indicated when Glasgow coma score is less than 8. Mechanical ventilation settings should be protective, as stipulated in guidelines from specialist critical care societies [38]. There have not been any specific studies on ALF populations [38,39]. High levels of PEEP (> 10 cmH_2O) could be associated with a potential risk of hepatic congestion [40–42].

No randomised controlled trials (RCT) have evaluated sedation practices in patients with ALF. In the ICU population, studies have shown that protocol-based sedation (to minimise its depth and duration) seems to reduce overall morbidity and mortality. The use of benzodiazepines should be avoided [43,44]. In patients with acute or chronic encephalopathy, a meta-analysis (8 RCTs; $n = 736$ patients) showed that flumazenil lowered the encephalopathy score, also suggesting a deleterious effect of benzodiazepines in this population [45]. Dexmedetomidine should be used with caution, as its metabolism is exclusively hepatic [46]. No studies have recommended or not the systematic use of sedation in patients with an altered Glasgow Coma score without intracranial hypertension (ICH), a classically described complication of HE that affects 20% of patients with ALF [16]. Regular monitoring must be ensured of patients with high-grade encephalopathy (grades 3 and 4). Two multicentre observational studies in patients with severe encephalopathy did not demonstrate a significant difference in 1-month mortality, whether the patients were monitored using ICP devices or not (pooled data: RR = 0.79, 95% CI 0.61–1.02) [47,48]; ICP devices have been associated with haemorrhagic complications (7% to 20% of cases in patients with ALF) [47–49]. Transcranial Doppler ultrasound is a useful monitoring tool that could be used first-line in this context. There are no specific therapeutic options for raised intracranial pressure in patients with ALF [50–55].

8.1.1. Coagulation

A recent multicentre observational study including 1770 patients with ALF reported bleeding complications in only 187 patients (10%), which included 22 (1.5%) post-procedural bleeding episodes [56]. Eighty-four per cent of spontaneous bleeding episodes originated from the upper gastrointestinal tract. An in-depth analysis of coagulation abnormalities (thrombocytopenia and prolongation of the INR) in ALF patients suggested that most patients had rebalanced haemostasis between pro- and anticoagulant factors [57]. Prophylactic administration of coagulation factors precludes the assessment of the natural evolution of the disease. There is no support for the use of coagulation factors and this should be limited to active bleeding or invasive procedures with a high risk of complications.

8.1.2. Renal replacement therapy

No RCT have been performed specifically to evaluate the strategy and timing of its initiation in patients with ALF [16]. Regional citrate anticoagulation should be monitored because of its potential metabolic effects in patients with ALF [58].

8.1.3. Liver support devices

Two well-designed RCT including 115 patients with ALF (not related to hypoxic hepatitis) failed to demonstrate a significant

reduction in mortality (pooled data: RR = 0.82; 95% CI 0.42–1.59) [59,60]. The place of liver support systems in the management of patients with ALF need to be better defined. In any case, these techniques should not delay transfer to a liver transplantation centre.

ALF is frequently associated with electrolyte and metabolic disturbances, particularly in patients with hyperacute ALF or when it is associated with acute kidney injury [61]. Hypoglycaemia is a well-known complication of severe ALF [2,61]. Its clinical features can be confused with those of hepatic encephalopathy. Blood glucose parameters should therefore be monitored at least every 2 hours. No studies have evaluated the optimal target for blood glucose levels. Hyponatremia (sodium < 130 mmol/L) is common in patients with ALF [62]. There is a correlation between hyponatremia and intracranial pressure. It has been shown that the infusion of hypertonic saline to maintain serum sodium levels at between 145 and 155 mmol/L significantly decreased ICP [54]. However, a serum sodium level above 150 mmol/L is deleterious and should be avoided. In practice, we recommend targeting the sodium level at between 140 and 145 mmol/L. Any corrections should not exceed 10 mmol/L per 24 h [63]. Electrolyte disturbances, such as serum phosphate, are commonly observed in patients with ALF, and should be monitored and corrected.

Patients with ALF and organ failure have increased energy expenditure similar to that of other ICU patients. There are no specific nutritional guidelines in patients with ALF.

The use of osmotic laxatives (lactulose) or non-absorbable antibiotics (rifaximin) to lower ammonia levels is not recommended [61].

Although there are no data to support its use, stress ulcer prophylaxis is usually recommended in this at-risk population [61].

Patients with ALF have increased susceptibility to infections. Bacterial infections have been documented in 60%–80% of patients with ALF, and fungal infections occur in one third of patients [64]. Empirical broad-spectrum antibiotics should be administrated to ALF patients if there are signs of sepsis and/or of worsening encephalopathy [65]. These broad-spectrum antibiotics should cover common organisms such as enterobacteria, staphylococcal or streptococcal species, or as a function of the ecology in the unit [64].

8.2. Second area. Cirrhotic ICU patients and acute-on-chronic liver failure

Cirrhosis is an end-stage form of chronic liver disease. The prevalence of cirrhosis is estimated at between 2000 and 3300 people per million inhabitants. There are approximately 700,000 patients with cirrhosis in France, 10,000 to 15,000 of whom die every year. A wide range of diseases and conditions can damage the liver and lead to cirrhosis. Ninety per cent of cirrhosis cases are related to chronic alcohol abuse, chronic viral hepatitis (hepatitis B and C) and fatty liver disease in a context of metabolic syndrome. In terms of its pathophysiology, cirrhosis consists in the gradual replacement of healthy liver tissue by annular fibrosis that is responsible for destroying the architecture of the liver parenchyma and blocking intrahepatic portal blood flow. These architectural changes are associated with life-threatening complications related to portal hypertension and/or hepatic dysfunction that may require ICU hospitalisation. These complications may be either specific to liver disease (ascites, spontaneous bacterial peritonitis, variceal haemorrhage, hepatic encephalopathy or hepatorenal syndrome) or non-specific (infection, acute kidney failure). In addition, given the prevalence of this disease, it is frequent that the reason for initial ICU admission is not a complication of cirrhosis but rather another condition likely to lead to organ failure such as pneumonia-related septic shock, community-acquired peritonitis, stroke, trauma, etc. Under these circumstances, even if cirrhosis was compensated or even often not diagnosed at admission, the precipitating event is likely to decompensate the liver disease.

Cirrhotic patients requiring ICU hospitalisation have a high rate of in-hospital mortality (ranging from 30% to 50%). The severity of cirrhosis was initially established by the Child–Turcotte score [66] subsequently modified by Pugh [67]. A new entity named ACLF has recently been described [68] as a combination of acute decompensation of cirrhosis, one or several extrahepatic organ failures and high short-term mortality [68]. ACLF is a dynamic syndrome and can occur in patients with or without a prior history of acute decompensation. The diagnosis of ACLF and its classification in four grades of severity based on the number of organs failing is made using the CLIF SOFA score Supplementary Tables 1 and 2, [68–70]. It should also be noted that an ACLF grade based on organ failure has been shown to better predict the outcomes of ICU cirrhotic patients than standard prognostic methods such as the MELD or Child–Pugh scores.

These guidelines will focus on the management of cirrhosis and its complications requiring ICU hospitalisation, and provide recommendations based on the best evidence available in the literature.

9. Question 4: In patients with cirrhosis, which criteria should be used to guide admission or non-admission to an ICU to improve their prognosis?

R4 – We do not suggest denying the admission of patients with cirrhosis to the ICU solely because of their underlying cirrhotic condition.
(GRADE 2−) STRONG AGREEMENT

9.1. Rationale

The proportion of cirrhotic patients admitted to ICUs is increasing [71–74]. However, to date, there have been no objective and specific criteria to guide the admission of these patients to critical care.

The recent definition of a new clinical entity, Acute-on-Chronic Liver Failure (ACLF), as an acute decompensation of cirrhosis associated with organ failure(s) defined using the CLIF-SOFA score could be useful to ensure the early identification of patients who could benefit from ICU admission. Indeed, ACLF is associated with a 28-day mortality rate of at least 15% [68].

Among the elements that can guide a decision of ICU admission, initial severity scores have been analysed in several reviews of the literature [75–79] including observational studies that evaluated these scores [69,70,80–99], as well as the most recent ones [100–108]. To predict short-term mortality (in the ICU or in hospital), standard organ failure scores such as SOFA (23 studies, AUC: 0.70 to 0.95), CLIF-SOFA (7 studies, AUC: 0.72 to 0.83) or CLIF-C Acute on Chronic Liver Failure (1 study, C-index 0.76) display similar performance [99,100,106]. Their performance is better than that of general ICU scores such as APACHE2 (20 studies, AUC: 0.66 to 0.90), APACHE3 (5 studies, AUC: 0.72 to 0.91) or SAPS2 (6 studies, AUC: 0.74 to 0.89). Studies reporting the prognosis at 6 months have found similar results [109]. The performance of liver-specific scores is lower, with MELD (18 studies, AUC: 0.70 to 0.93) being slightly better than Child-Pugh (21 studies, AUC: 0.55 to 0.87) [110]. Scores derived from MELD (MELD-Na, iMELD, MESO) do not have a better prognostic value than MELD [69,70,95]. D'Amico's classification, based on a patient's history

of decompensation of cirrhosis, is not associated with prognosis in the ICU [69,111].

The number of organ failures at admission to the ICU is also associated with short-term mortality [69,70,74,77,82,112,113]. A recent and large multicentre study conducted on 17,044 cirrhotic patients in intensive care reported a hospital mortality rate lower than 50% in patients with three or more organ failures, thus delegitimising decisions not to admit a cirrhotic patient to the ICU based on liver disease alone [113].

In addition, the reason for ICU admission also influences prognosis, with digestive haemorrhage classically being associated with a better prognosis and septic shock with a poorer one [68,70,105,114]. Finally, among cirrhotic patients admitted to an ICU, those who have been directly admitted have a better prognosis than those who were initially admitted to the Hepatology Unit, thus highlighting the value of early admission to ICU [68,69,72,115].

As with non-cirrhotic patients, the prognosis for cirrhotic patients at ICU admission is therefore very largely associated with the presence of organ failure(s) graded using different scores. However, none of these scores has sufficient predictive power to guide individual patient prognosis. There is therefore no reliable indicator of the futility of resuscitation in cirrhotic patients, regardless of the severity of cirrhosis or number of organ failures [116].

Finally, several studies have shown that the ICU prognosis of cirrhotic patients has improved in recent years (period effect independently associated with mortality), [72,89,100,108,113,114,117,118] whether the reason for admission was variceal bleeding [119] or septic shock [74,120]. The maintenance of life-sustaining therapy during the ICU stay is considered in question 10.

10. Question 5: In patients with cirrhosis hospitalised in an ICU, which specific measures to manage acute kidney injury should be used to reduce morbidity and mortality?

R5.1 – To define and assess the severity of acute kidney injury (AKI) in patients with cirrhosis, the experts suggest:
1. Using the modified KDIGO criteria specifically refined by the International Club of Ascites
2. Managing AKI according to its severity and to the algorithm proposed (Fig. 2)
3. Not contraindicating renal replacement therapy in these patients just because of their underlying cirrhotic condition.
EXPERT OPINION, STRONG AGREEMENT

10.1. Rationale

In non-cirrhotic patients, the reference for diagnosing and assessing the severity of acute kidney injury (AKI) is the KDIGO classification [121,122]. The limitation of this classification in patients with cirrhosis is the use of urinary flow. Indeed, in advanced stages, cirrhosis is often associated with oliguria and water and salt retention, oedema and ascites, while renal function remains normal. Conversely, the use of diuretics to treat ascites and oedema can lead to an abnormally high urine output with impaired renal function. Experts in the International Ascites Club have therefore proposed using the KDIGO classification to diagnose and assess the severity of AKI, based on the same criteria as for serum creatinine without the urine output criterion (Table 2) [122]. Several studies have shown that this modified classification has a good prognostic value with early mortality being well

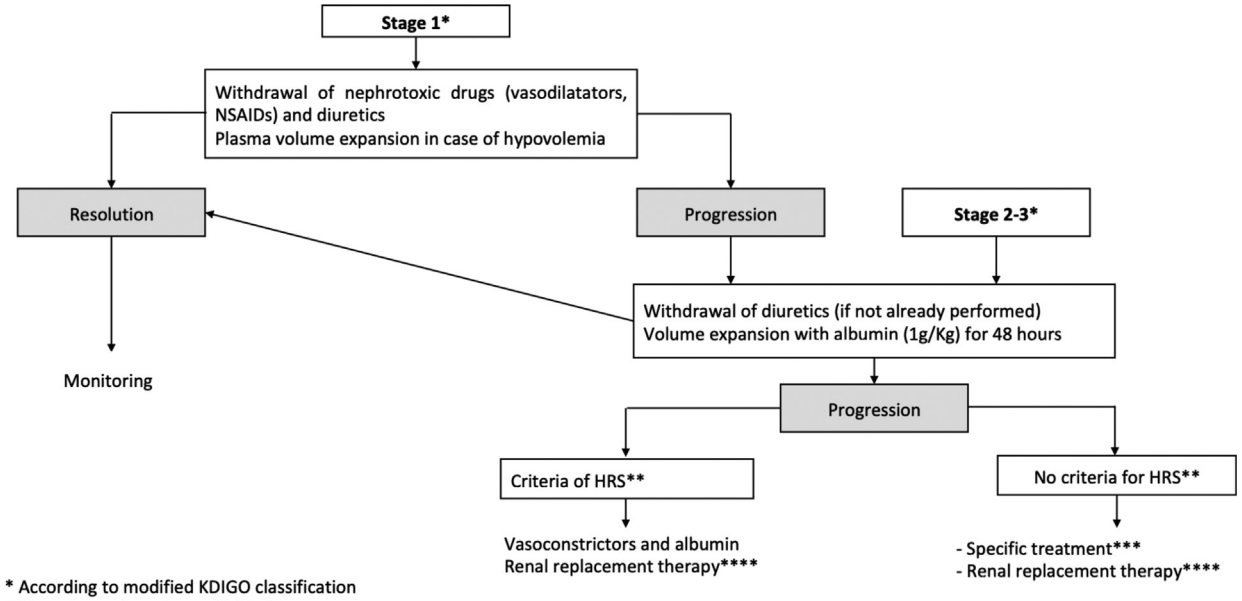

Fig. 2. Algorithm for the management of acute kidney injury according to modified KDIGO classification in patients with cirrhosis.

Table 2
Modified KDIGO criteria for definition of acute kidney injury in patients with cirrhosis.

Baseline serum creatinine
A value of serum creatinine obtained in the previous three months, when available, can be used as baseline serum creatinine
In patients with more than one value within the previous 3 months, the value closest to the admission time to the hospital should be used
In patients without a previous serum creatinine value, the value on admission should be used as baseline
Definition of acute kidney injury
Increase in serum creatinine ≥ 26.5 μmol/L within 48 hours
or
A percentage increase serum creatinine ≥ 50% from baseline, which is known or presumed to have occurred within the prior 7 days
Staging of acute kidney injury
Stage 1: increase in serum creatinine ≥ 26.5 μmol/L or an increase serum creatinine ≥ 1.5-fold to 2-fold from baseline value
Stage 2: increase serum creatinine ≥ 2-fold to 3-fold from baseline value
Stage 3: increase serum creatinine ≥ 3-fold from baseline value or serum creatinine ≥ 353.6 μmol/L with an acute increase ≥ 26.5 μmol/L or initiation of renal replacement therapy

correlated with the severity of AKI [123–127]. It is important to note that the definition is based on the dynamic change in serum creatinine from baseline and no longer on a fixed threshold for serum creatinine. Indeed, as a marker of renal function, serum creatinine has many limitations in patients with cirrhosis, including:

- a decrease in muscle creatine, a precursor of creatinine, related to frequent sarcopenia in these patients [128];
- an increase in the distribution volume related to ascites and oedema;
- interference with creatinine measurement techniques related to elevated serum bilirubin levels [129,130].

Use of the modified KDIGO classification (Table 2) is important because it enables the management of acute renal failure to be adapted as a function of its severity (Fig. 2). So, although the eviction of risk factors may be sufficient at an early stage, albumin fluid therapy is necessary in the event of progression to stages 2 or 3 [121]. Finally, although the prognosis with renal replacement therapy is very poor in cirrhotic patients with AKI, it is not contraindicated provided that its duration is planned to be short and that it is integrated in a therapeutic plan, such as liver transplantation, or in a context of reversible precipitating events, such as sepsis (Table 3) [131].

R5.2 – In patients with cirrhosis hospitalised in the ICU, we suggest treating hepatorenal syndrome with a vasoconstrictor agent (terlipressin as first-line therapy) and concentrated albumin
GRADE 2+, STRONG AGREEMENT

10.2. Rationale

Several meta-analyses have suggested a beneficial effect of the combination of a vasoconstrictor and albumin on short-term survival and hepatorenal syndrome (HRS, defined in Table 2) regression [131–133].

The objective of vasoconstriction is to counterbalance splanchnic arterial vasodilation in order to improve renal perfusion. The reference treatment is terlipressin. A Cochrane meta-analysis that included nine randomised studies (394 patients) comparing different vasoconstrictors in combination with albumin concluded that terlipressin was the most effective in treating HRS [134]. Most recent studies have suggested that the response rate in terms of an improvement in renal function (complete or partial response) ranges from 64% to 76% [134]. However, these rates are significantly lower in the event of recurrent HRS (20% of cases). Terlipressin is usually administered intravenously (bolus injections) at an initial dose of 0.5 mg to 1 mg every 4 to 6 hours. The dose can then be gradually increased to a maximum of 2 mg every 4 to 6 hours if the serum creatinine level does not fall by more than 25%. Treatment should be maintained until a complete response is obtained or for a maximum of 14 days in the case of a partial response. The continuous administration of terlipressin at the same daily doses (2 to 12 mg/24 h IVSE) appears to be an interesting alternative as it remains as effective as boluses but enables lower daily doses, thereby reducing the risk of adverse events such as cardiac or intestinal ischemia, pulmonary oedema, or distal necrosis [135]. More recently, another meta-analysis pointed out that norepinephrine might be a reliable alternative in patients with a central venous catheter (terlipressin can be administered via a peripheral vein) [133]. Indeed, no difference in the reversibility or relapse of HRS was found between the terlipressin + albumin and norepinephrine + albumin arms, although the numbers of patients included in these studies remain small. Conversely, the combination of midodrine and octreotide is less effective and should not be used [135,136].

The addition of albumin can be discussed insofar as its beneficial effects have only been demonstrated in combination with vasoconstrictors. Indeed, while the administration of albumin might improve systemic haemodynamics by increasing cardiac output and through its antioxidant and anti-inflammatory properties [137], no study has ever compared a strategy combining vasoconstrictors and albumin with another that only used vasoconstrictors. Therefore, the doses usually recommended for albumin (1 g/kg before the initiation of vasoconstrictor treatment

Table 3
Diagnostic criteria of hepatorenal syndrome (all the criteria must be respected to retain the HRS).

Diagnosis of cirrhosis and ascites
Diagnosis of acute kidney injury stage 2 or 3 according to KDIGO criteria
No response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin (1 g/kg of body weight)
Absence of shock
No recent use of nephrotoxic drugs (NSAIDs, aminoglycosides, iodinated contrast…)
No macroscopic signs of structural injury defined as
Absence of proteinuria (> 500 mg/day)
Absence of microhaematuria (> 50 RBCs per high power field)
Normal findings on renal ultrasonography

NSAIDs: non-steroidal anti-inflammatory drugs; RBCs: red blood cells.

and then 20 to 40 g/day) [121] and the duration of treatment remain empirical, as do the haemodynamic objectives that are not defined. Uncertainties regarding the specific effect of albumin, and recent changes to the definition of HRS may modify the interpretation of the results of previous studies and result in downgrading the level of evidence of the recommendation.

11. Question 6: In patients with cirrhosis hospitalised in the ICU, which specific management of sepsis should be used to reduce morbidity and mortality?

R6 – In order to reduce the morbidity and mortality of critically ill patients with cirrhosis, whatever the symptoms and organ failure(s), we suggest:

1. Performing a systematic search for infection that should include microbiological and cytological examination of ascites fluid (a concentration of polymorphonuclear cells $> 250/mm^3$ in the ascitic fluid will confirm the diagnosis of spontaneous bacterial peritonitis),
2. Initiating early empirical antibiotic therapy that should be tailored to the suspected site of the infection, the causative pathogen once it has been identified, and the local ecology

GRADE 2+, STRONG AGREEMENT

11.1. Rationale

One third of cirrhotic patients develop an infection at admission or during hospitalisation, which is four to five times higher than the incidence in the general population. Infection is an independent risk factor for mortality, accounting for one third to one half of the causes of death in cirrhotic patients [138,139]. Several retrospective observational studies have shown an association between delayed antibiotic therapy and mortality [140–144]. In a study including 126 cirrhotic patients with spontaneous bacterial peritonitis-related septic shock, the adjusted OR associated with mortality was 1.86 (95% CI 1.10–3.14) per hour of delay ($P = 0.02$) [142]. Another study of 852 cirrhotic patients with bacteraemia showed that a delay of more than 24 hours between the onset of bacteraemia and the initiation of appropriate antibiotic therapy was associated with a six-fold increase in mortality [OR = 6.06 (90% CI 4.28–8.58; $P < 0.0001$)] [143]. Antimicrobial treatment should therefore be started early when there is any clinical or biological suspicion of sepsis. Worthy of note is a worsening of encephalopathy should suggest an infection as its triggering factor [145,146]. CRP and PCT serum levels were reported as being reliable biomarkers of infection in cirrhotic patients in a meta-analysis that included 10 studies ($n = 1144$ patients) [147]. However, it should be remembered that the diagnostic threshold for CRP decreases with the severity of cirrhosis (10 mg/L on average in mild cirrhotic patients, 5 mg/L for Child C patients) [148]. Initial antibiotic therapy should target enterobacteria and Gram+ Cocci, which account for the majority of causal pathogens in this population in whom more than half of infections are spontaneous bacterial peritonitis and urinary tract infections [139]. The local microbiological ecology should also be considered when choosing empirical antibiotic therapy. In a recent meta-analysis (eight studies, 1074 positive ascites cultures) [149], the average resistance rate to 3rd generation cephalosporins (C3G) was one third in community-acquired SBP and two thirds in healthcare-associated infections.

Concerning haemodynamics, cirrhotic patients are prone to develop hypoxic hepatitis that can worsen liver failure. The latter may be multifactorial [29]: hypovolaemia and vasoplegia, as well as right or left heart failure, pulmonary arterial hypertension associated with portal hypertension, hepatopulmonary syndrome and acute pulmonary oedema associated with volume overload. There is a lack of specific data on the management of sepsis in cirrhotic patients, and the approach is currently based on guidelines for the general ICU population [150]. No specific data on the use of vasopressors are available outside observational studies [151]. A meta-analysis (16 studies, 1507 patients) showed that half of cirrhotic patients with septic shock, had, at least a relative, corticosteroid insufficiency, which was associated with higher rates of sepsis and hospital mortality [152]. An observational study [153] and a double-blind RCT [154] included 150 cirrhotic patients with septic shock in order to assess the impact of 50 mg hydrocortisone every 6 h on mortality (very low level of evidence). There was no significant difference in ICU mortality (pooled data: RR = 0.78; 95% CI 0.58–1.05). However, hydrocortisone was associated with a higher rate of shock recovery (pooled data: RR = 1.49; 95% CI 1.17–1.92; $P = 0.001$). The study with the highest level of evidence [154] reported a significantly higher rate of gastrointestinal bleeding in the hydrocortisone arm (RR = 3.00; 95% CI 1.08–8.36; $P = 0.02$). Overall, we are not able to produce a recommendation regarding the use of hydrocortisone in cirrhotic ICU patients; their management needs to be evaluated on a case-by-case basis in a context of refractory shock.

12. Question 7: In patients with cirrhosis hospitalised in ICU, when concentrated albumin should be administered to reduce morbidity and mortality?

R7.1 – In cirrhotic patients hospitalised in the ICU, we recommend the use of a concentrated albumin infusion after high-volume paracentesis (more than 4 to 5 litres of ascites fluid removed)

GRADE 1+, STRONG AGREEMENT

12.1. Rationale

Large volume paracentesis (> 5 litres) associated with plasma volume expansion has been shown to be more effective than diuretic therapy in eliminating ascitic fluid and was associated with a lower incidence of complications [155]. In patients treated with paracentesis without plasma expansion, paracentesis-induced circulatory dysfunction (PICD) may be present in 70% of cases. The diagnosis of PICD is based conventionally on an increase in plasma renin activity of > 50% of the pre-treatment value to above 4 ng/mL/h on the sixth day after paracentesis. PICD is associated with an increased rate of recurrent ascites, the development of hepatorenal syndrome, hyponatremia and reduced survival [156]. A recent meta-analysis assessing 17 randomised studies (1225 patients) provided evidence that albumin infusion (8 g/L of ascites fluid removed) after paracentesis is the most effective therapy in the prevention of PICD, as compared to alternative treatments, and reduced the odds of PICD by 61% (OR = 0.39, 95% CI 0.27–0.55) [157]. The ability of albumin to reduce this complication was also shown in a subgroup analysis versus each of the other volume expanders tested (e.g. dextran, gelatin, hydroxyethyl starch, hypertonic saline). With albumin, the odds of hyponatremia and mortality were reduced by 42% (OR = 0.58, 95% CI 0.39–0.87) and by 36% (OR = 0.64, 95% CI95% 0.41–0.98), respectively [157]. The findings of two other recent randomised studies [158,159] did not alter the conclusions of the meta-analysis [160]. Another recent meta-analysis contested the effect of albumin on mortality [161]; however, this finding was

dependent on the inclusion of two studies with unsuitable controls (no treatment in one and mannitol in the other). If these two studies were excluded, the benefit of albumin on mortality remained significant in the whole cohort of patients (OR = 0.58, 95% CI 0.40–0.86) and in the subgroup of patients without hepatocellular carcinoma (OR = 0.60, 95% CI 0.39–0.91). The administration of albumin (6 to 8 g per L ascites fluid removed) is recommended to prevent PICD after large volume paracentesis (> 5 litres) [162,163]. In patients whose paracentesis produces less than 5 L ascites, the risk of developing PICD is low. However, EASL clinical practice guidelines state that these patients should still be treated with albumin because of concerns about the use of alternative plasma expanders such as Dextran.

One controversial issue remains the dose of albumin that should be administered, but only a few studies addressed this question. The results of an unblinded randomised pilot study showed in 70 patients with low severity cirrhosis (mean MELD Score at 16 to 17) that treatment with a half dose of albumin (4 g per L versus 8 g per L ascites fluid removed) was effective and safe in preventing PICD [164]. As the PICD risk is greater when more than 8 litres of ascites fluid are removed, it seems preferable to limit ascites removal of less than 8 litres during a paracentesis procedure [165]. Finally, although there have been no studies, it is recommended that the albumin infusion should be done slowly in order to prevent any potential cardiac overload promoted by preexisting cardiomyopathy.

R7.2 – In patients with cirrhosis hospitalised in the ICU, we suggest that concentrated albumin infusions should be used in the event of spontaneous bacterial peritonitis (SBP)
GRADE 2+, STRONG AGREEMENT

12.2. Rationale

Spontaneous bacterial peritonitis (SBP) is an acute bacterial infection of ascitic fluid common in patients with cirrhosis (prevalence: 10% to 30%). Diagnosis requires paracentesis, or sampling of the peritoneal fluid from the peritoneal cavity. When fluid contains large numbers of white blood cells (neutrophils) (> 250 cells/mm^3), the infection is confirmed.

Sort et al. showed that treatment with combination of intravenous albumin (1.5 g/kg on day 1 and 1 g/kg on day 3) and antimicrobial therapy could reduce the incidence of renal impairment (10% versus 33%; $P = 0.002$) and death (22% versus 41%; $P = 0.03$), as compared to antibiotic alone [166]. Since this publication, numerous studies about fluid resuscitation in septic context affecting cirrhotic patients have been published. Six randomised controlled trials (RCTs) including 577 patients with cirrhosis and SBP (4 studies) or other types of bacterial infection (2 studies), compared patients assigned to receive antibiotic or antibiotics plus albumin (0.14 to 1.5 g/kg on days 1 and 3) (5 studies) or antibiotics plus hydroxyethyl starch (one study) [166–171]. None of these studies were double-blinded and included patients hospitalised in ICU. We performed a meta-analysis including additional data [172] showing that when compared to standard antibiotic therapy alone, treatment involving albumin plus antibiotics improved survival at 3 months (OR = 0.66; 95% CI 0.45–0.96, $P = 0.03$). Albumin has beneficial effects on renal function involving lower incidence of renal impairment (6 RCTs: OR = 0.46, 95% CI 0.30–0.71, $P < 0.001$). Since none of these studies have been performed in ICU patients, the level of the recommendation is lowered because it is based on indirect evidence.

In addition, only the oldest studies, which included only SBP, showed that albumin infusions significantly improved survival at 3 months (OR = 0.36, 95% CI 0.21–0.61; $P = 0.0001$) and renal impairment (OR = 0.21, 95% CI 0.11–0.42; $P < 0.0001$). These data restricted the recommendation to patients with SBP (studies carried out between 1999 and 2009). The benefits of albumin infusions in patients with SBP could be explained by haemodynamic effects after paracentesis, although they may merely be due to these products' expanding properties. Albumin is believed to be effective in patients with SBP because of its ability to improve intravascular volume (altered by paracentesis) and to bind pro-inflammatory molecules. However, the ideal dose has yet to be determined and an albumin infusion should be associated with haemodynamic monitoring (volume status, cardiac output).

In cirrhotic patients with an infection other than SBP, two RCTs failed to show that albumin infusion improved the survival, although it delayed the onset of renal failure [169,170]. The use of HES should be proscribed in patients with cirrhosis. The administration of HES may favour liver failure, particularly in cirrhosis setting. The rational for these adverse effects is the lysosomal storage of HES in Kupffer cells and hepatocytes.

13. Question 8: In patients with cirrhosis hospitalised in the ICU, which management of acute upper gastrointestinal bleeding should be initiated to reduce morbidity and mortality?

R8.1.1 – In patients with cirrhosis and acute upper gastrointestinal bleeding, we recommend the introduction as soon as possible of intravenous vasoactive therapy (with octreotide, somatostatin or terlipressin) and prophylactic antibiotic therapy.
GRADE 1+, STRONG AGREEMENT

R8.1.2 – In patients with cirrhosis and acute upper gastrointestinal bleeding, we suggest the use of proton pump inhibitors as soon as possible.
GRADE 2+, STRONG AGREEMENT

R8.1.3 – In patients with cirrhosis and acute upper gastrointestinal bleeding, we recommend the performance of an upper endoscopy as soon as possible.
GRADE 1+, STRONG AGREEMENT

13.1. Rationale

Splanchnic vasoconstrictor agents such as somatostatin, octreotide and terlipressin exert their vasoactive effects and decrease splanchnic blood flow and portal pressure. In patients with acute variceal bleeding who are undergoing endoscopic sclerotherapy, several studies showed that the early intravenous administration of a vasoactive agent was more effective than placebo in the overall control of haemorrhage [173–175]. In one meta-analysis published in 2012 [176], the use of vasoactive agents was associated with a significantly lower risk of mortality at 7 days (RR 0.74; 95% CI 0.57–0.95; $P = 0.02$), fewer transfusion requirements and a shorter duration of hospitalisation. This meta-analysis included 19 studies with several vasoactive medications (octreotide, $n = 9$; somatostatin, $n = 3$; terlipressin, $n = 4$; vasopressin, $n = 2$; and vapreotide, $n = 1$). In a multicentre, randomised trial that included 780 patients, the proportion of treatment failure within the first 5 days, was not different with three well-known

vasoactive drugs (octreotide, somatostatin or terlipressin) as adjuvant therapy to standard endoscopic treatments [177].

Bacterial infections are a common cause of mortality in patients with cirrhosis and upper gastrointestinal bleeding. A meta-analysis including 12 controlled trials concluded that antibiotic prophylaxis was associated with a significant reduction in overall mortality (RR 0.79, 95% CI 0.63–0.98), in mortality from bacterial infections (RR 0.43, 95% CI 0.19–0.97) [178] and a marked reduction in overall re-bleeding episodes among patients under antibiotic prophylaxis (RR 0.53, 95% CI 0.38–0.74). Trials to evaluate length of hospital stay have shown that patients receiving antibiotic prophylaxis tended to be admitted for shorter periods [178]. In the meta-analysis of these trials, twelve studied antibiotic prophylaxis using quinolones (five trials), quinolones plus beta-lactams (two trials), cephalosporins (three trials), carbapenems (one trial) and non-absorbable antibiotics (one trial) versus no intervention or a placebo. All the antibiotics tested achieved a beneficial effect on the bacterial infection.

One study found that a high-dose infusion of a proton-pump inhibitor before endoscopy accelerated the resolution of signs of bleeding in ulcers and reduced the need for endoscopic therapy [179]. This reaffirms that optimal acid suppression facilitates clot formation over arteries in bleeding peptic ulcers. Fewer than 5% of the patients included in this study had cirrhosis. However, because the bleeding is not related to portal hypertension in 30% of patients with cirrhosis, the expected benefit of proton-pump inhibitors prior to endoscopy in these patients led the experts to overstate the level of evidence for proton-pump inhibitors in this indication.

Upper gastrointestinal endoscopy enables the examination and also the treatment of most upper gastrointestinal bleeding. A combination of banding ligation and vasoactive therapy for 2 days was superior to the infusion of vasoactive therapy for 5 days alone in reducing very early re-bleeding [180]. Per-endoscopic treatments usually consist of banding ligation of oesophageal varices and glue therapy for gastric varices. Patients with upper gastrointestinal bleeding and features suggestive of cirrhosis should undergo endoscopy within 12 hours of presentation [180–182]. This is supported by data from a non-randomised study, which reported less recurrence of haemorrhage and better survival when endoscopy was performed within the first 12 hours [183]. This period also allows for a rapid discussion on the advisability of TIPS in the event of variceal haemorrhage uncontrolled by endoscopy and drug therapy (refractory bleeding).

R8.3 – In patients with cirrhosis and acute upper gastrointestinal bleeding, we suggest to consider Transjugular intrahepatic portosystemic shunt (TIPS) with a covered stent within 24 to 72 hours of the bleeding for episodes in Child–Pugh class C patients (< 14) or in Child–Pugh class B patients with initially active bleeding at endoscopy (early TIPS).
GRADE 2+, STRONG AGREEMENT

13.2. Rationale

A randomised controlled trial evaluated the early use of TIPS in cirrhotic patients in Child–Pugh class C or class B [182]. A total of 63 patients with acute variceal bleeding were included. This study showed that the early use of TIPS was associated with a significant reduction in mortality at 2 years. However, this study suffered from several limitations that deserve consideration: the main endpoint was the rate of failure to control bleeding within 5 days; seventeen patients were treated with sclerotherapy, which is not the recommended endoscopic treatment, and the recruitment delay was long as 359 patients were screened and 63 were included between 2004 and 2007. The two other studies did not have a controlled design (low level of evidence) [187,188]. Another old randomised controlled study specifically analysed early TIPS in this indication, but with an uncoated stent and the selection of high-risk patients, using the hepatic venous pressure gradient [189]. Finally, a meta-analysis assessed the effects of early TIPS on patient prognosis, but it was of poor quality because of large heterogeneity between the types of stents used (coated or not) or the selection criteria for patients [190].

R8.4 – In patients with cirrhosis and acute upper gastrointestinal bleeding, the experts suggest considering emergency Transjugular intrahepatic portosystemic shunt (TIPS) with a covered stent in the event of variceal bleeding refractory to endoscopic treatment (salvage TIPS).
EXPERT OPINION, STRONG AGREEMENT

13.3. Rationale

In a study of patients with cirrhosis and variceal haemorrhage uncontrolled by endoscopy and drug therapy, TIPS (salvage TIPS) was able to halt the haemorrhage in 80% of cases [191]. In this setting of active bleeding and a failure of standard medical and endoscopic haemostasis, alternative measures include balloon tamponade (Blakemore or Linton tube) or a self-expandable oesophageal stent. Both these treatments could be recommended as a bridge to definitive therapy (TIPS therapy) in patients with cirrhosis and massive or refractory oesophageal variceal bleeding. There has only been one randomised controlled trial, which included 28 patients to compare self-expandable oesophageal stents and balloon tamponade in the treatment of acute and refractory bleeding from oesophageal varices [192]. There were no significant differences in 15-day survival rates between the oesophageal stent and balloon tamponade groups. The availability of oesophageal stents is limited. Consequently, the experts were not able to make a recommendation about their use.

14. Question 9: In patients with cirrhosis hospitalised in the ICU, which measures to manage haemostasis should be initiated to reduce morbidity and mortality?

R9 – The experts suggest that routine prophylactic fresh frozen plasma, platelets or fibrinogen concentrates should not be systematically administrated before invasive procedures in cirrhotic patients in order to reduce bleeding.
EXPERT OPINION, STRONG AGREEMENT

14.1. Rationale

Although conventional coagulation tests are altered in patients with cirrhosis, the balance between pro- and anticoagulant factors is respected and the generation of thrombin is normal [193,194]. Post-procedural bleeding is not predicted by these tests (platelet count or international normalised ratio) [195]. Nor is there consensus regarding the platelet or plasma transfusion thresholds or any evidence of their clinical efficacy [196]. The French Medicines Agency (Agence nationale de sécurité du médicament et des produits de santé) and the European Society of Hepatology (EASL) recommend an infusion of platelets when the count is < 50 G/L but this has not been substantiated by any publication [197,198].

Standard doses of fresh frozen plasma rarely correct coagulopathy in patients with cirrhosis. To achieve that, large amounts of

plasma need to be transfused, associated with adverse effects such as increased vascular volume and portal pressure, or nonspecific blood products adverse effects [199].

Although the optimal fibrinogen level is uncertain, the preventive administration of fibrinogen is also a matter of considerable debate. A benefit/risk assessment should be performed on a case-by-case basis, depending on the patient's haemostatic parameters.

Use of a thrombopoietin receptor agonist (eltrombopag) could raise the platelet count and avoid the use of platelet transfusions in cirrhotic patients prior to an invasive procedure. However, other reports have suggested an increased risk of thrombosis. The risk/benefit ratio is therefore unfavourable [200].

Four randomised controlled trials [201–204], and one meta-analysis [205] assessed the effects of rFVIIa prophylaxis on preventing mortality and bleeding resulting from hepatobiliary surgery (liver resection or liver transplantation). There were no significant differences between rFVIIa and placebo with respect to mortality (OR 0.96; 95% CI 0.35–2.62), red blood cell units (MD 0.32; 95% CI −0.08 to 0.72) or adverse events (OR 1.55; 95% CI 0.97–2.49) [205].

No recommendation: the experts were not able to produce recommendations concerning thromboprophylaxis in critically ill patients with cirrhosis.

14.2. Rationale

Despite their low levels of coagulation factors, thrombin formation and clot formation are normal in cirrhotic patients [193,206]. These patients have a frequent imbalance between procoagulant and anticoagulant activity, which frequently results in a hypercoagulable state [207,208]. Several studies have demonstrated an increase in thrombotic events in cirrhotic patients versus a control population [209,210]. Very few studies have examined the value of thromboprophylaxis in patients with cirrhosis; the level of evidence is low and only based on one meta-analysis of non-randomised retrospective series [211]. The heterogeneity of the studies in this meta-analysis did not allow to formally conclude as to the effectiveness of thromboprophylaxis to prevent venous thromboembolism (pooled OR 0.87 95% CI 0.34–2.18) [211]. In the same meta-analysis, thromboprophylaxis was not associated with a higher rate of bleeding in patients with cirrhosis. Other retrospective non-randomised cohort studies confirmed no extra risk of bleeding. Only one retrospective study including 256 cirrhotic patients showed an increase in overall haemorrhages but not an increased risk of major haemorrhage [212,213].

Prophylactic treatment with unfractionated heparin has been shown to be associated with an increased risk of bleeding events [214]. We recommend assessing the individual risk of venous thromboembolism, particularly in patients with cirrhosis who are undergoing surgery. For patients at high risk of thromboembolism and with a high bleeding risk, use of an intermittent pneumatic compression device as prophylaxis for venous thromboembolism may be an alternative [215,216], but it has not been evaluated in patients with cirrhosis.

15. Question 10: In patients with cirrhosis hospitalised in the ICU, when should expert advice be obtained in order to reduce morbidity and mortality?

R10 – The experts suggest that expert advice should be sought regarding patients with cirrhosis who are hospitalised in the ICU:

1. At admission, if the patient is already on the liver transplantation waiting list.
2. Soon after ICU admission to discuss the intensity of care to be provided as a function of the number of organ failures and their course.
3. In order to discuss the benefits of a liver support technique.
4. At discharge from the ICU in order to organise hepatology management, with a view to potential possible liver transplantation

EXPERT OPINION, STRONG AGREEMENT

15.1. Rationale

1. The onset of complications in patients with cirrhosis who are on the liver transplant waiting list should be reported to the LT centre. Indeed, acute decompensation does not contraindicate liver transplantation and might even favour it by prioritising the patient on the list.

2. The need for ICU admission, whatever the reason, is associated with high mortality rates in patients with cirrhosis (ICU and 6-month mortality rates of respectively 42.7% and 75%) [114]. The prognosis for these patients depends on the severity of both hepatic failure (evaluated using the MELD score at ICU discharge) and extrahepatic organ failures (respiratory, neurological, haemodynamic, renal, coagulation, hepatic) [104,114,217]. Depending on the number of organ failures, 28-day mortality rate ranges from 4.7% in patients without organ failure to 76.7% in patients with ACLF grade 3 [68]. Evolution of the SOFA score and/or the number of organ failures during the ICU stay is a crucial prognostic factor. A retrospective study that included 138 patients with cirrhosis supported the conclusion that the most important risk factor for in-hospital mortality was the modified SOFA score (without haematological failure) assessed after 3 days [69]. In another study, the SOFA score proved to be the most accurate, with a score >10 predictive of mortality in 93% of cases [90]. However, the delta SOFA score (difference between baseline and at 48 h or 3-day) seems to display various prognostic values when compared to the score value at 48 h or 3-day with respect to short-term mortality [69,90,217]. Persistence of 3 or 4 non-haematological organ failures at 3-day [69] or between 3-day and 7-day [29–220] predicted inhospital mortality with a specificity of 93% or 100%. The same results were observed regarding the use of organ replacement methods (vasopressors, mechanical ventilation, renal replacement therapeutic or artificial liver support systems) during the stay of patients in intensive care [77,115]. In the CANONIC study, assessment of the ACLF grade variation between J3 and J7 after diagnosis was significantly better able to predict 28-day and 90-day mortality rates than the ACLF grade at diagnosis (AUROC 0.86 versus 0.65 and 0.81 versus 0.62 $P < 0.0001$, respectively) [220].

Prognosis assessment for cirrhotic patients admitted in ICU is more accurate if performed with analysis of the number of failing organs, or the SOFA score a few days after ICU admission than on ICU admission. The number of organ failures must be taken into account when identifying a patient in whom aggressive treatment may offer recovery or determine candidacy for transplantation, in order to optimise care [69,116,221]. In recent years, liver transplantation in patients with ACLF has been considered to be feasible. Retrospectives studies that included patients with ACLF grade >2 showed that liver transplantation improved the poor prognosis of the most severely ill patients with cirrhosis [220–229]. The probability of survival was 78% at one year in patients receiving an early transplant compared to less than 10% in those not transplanted [222–229]. However, in a context of organ shortage, individual benefice should be considered together with the general interest, since an increased postoperative mortality has also been reported after transplantation for the most severe patients. Numerous studies have tried to identify factors predictive of early post-LT mortality in order to avoid futile LT. Thus, several specific scoring systems based

on pre-LT variables (organ failure, organ support, sepsis, comorbidities, MELD score, SOFA score, etc.) have been developed [223,227–229]. However, none of them have been included as delisting criteria in current allocation systems. To obtain good results, rapid decision-making by a multidisciplinary specialised team (including societal and clinical criteria) is necessary because the "transplantation window" is often narrow in these patients [221].

3. Appropriate artificial liver supports use in the context of ACLF might be:

(1) Allowing the liver to regenerate (bridge to recovery), or (2) use of supportive therapy until liver transplantation (bridge to transplant).

To date, the best-known devices are based on the principle of albumin dialysis. The MARS® and Prometheus® systems have been the most widely studied in France. Two multicentre randomised European studies in patients with acute decompensation compared MARS® or Prometheus® with standard medical treatment. These studies did not demonstrate any benefit on survival at 28 and 90 days [230,231]. However, a significant improvement in hepatic encephalopathy and hepatorenal syndrome was seen in a post-hoc analysis using albumin dialysis with MARS versus standard medical therapy. It should be noted that the inclusion criterion for these two studies was decompensated cirrhosis, but the presence of ACLF was not known. These studies were therefore able to include patients with acute decompensation without organ failure (ACLF grade 0) or with multiple organ failures (ACLF grade 3) whose prognosis and mortality differed markedly, ranging from 4% to 80% [68]. Artificial support systems were originally used in patients with a severe stage of liver disease and multiorgan failure. More recently, these systems have been used as supportive therapy to await liver transplantation. An observational study [232] and a meta-analysis [233] showed that use of an artificial liver support system was associated with improved short-term survival (14-day and 28-day) in patients with ACLF and multiple organ failure. This short-term improvement could allow these patients to access liver transplantation, which remains the essential therapy in patients with end-stage liver disease [225,227,228]. Current data are pointing to potential interest in liver support systems to provide a "bridge" to final treatment. The indications need to be explored and the future of these devices requires new research protocols. The experts therefore suggest that patients should be referred to an expert centre at an early stage after decompensation of their cirrhosis.

4. Patients with cirrhosis alive at discharge from ICU have a poor prognosis, with a 1-year survival rate of less than 25% without transplantation [114]. These patients should therefore be referred systematically to a liver transplant unit.

Disclosure of interest

Catherine Paugam-Burtz and Emmanuel Weiss report speaker fees from Baxter.

Lionel Velly reports consulting and speaker fees from Baxter.

The other authors declare that they have no competing interest.

Funding

This work was sponsored by the Société française d'anesthésie et de réanimation (SFAR) and the Association française pour l'étude du foie (AFEF).

Appendix A

Supplementary Table 1.

Organ/system	0	1	2	3	4
Liver (bilirubin, μmol/L)	< 20	> 20 to ≤ 34	> 34 to ≤ 102	> 102 to ≤ 204	> 204
Kidney (creatinine, μmol/L)	< 105	> 105 to ≤ 170	> 170 to ≤ 305	$>$ to ≤ 440	> 440 or use RRT
Cerebral (HE grade)	No HE	I	II	III	IV
Coagulation (INR)	< 1.1	≥ 1.1 to < 1.25	$\geq .25$ to < 1.5	≥ 1.5 to < 2.5	≥ 2.5 or platelet count $\leq 20 \times 10^9$/L
Circulation (MAP, mmHg or vasopressor, μg/kg/min)	≥ 70	< 70	Dopamine ≤ 5 or dobutamine or terlipressin	Dopamine > 5 or epinephrine ≤ 0.1 or norepinephrine ≤ 0.1	Epinephrine > 0.1 or norepinephrine > 0.1
Lungs (PaO_2/FiO_2 or SpO_2/FiO_2)	> 400 > 512	> 300 to ≤ 400 > 357 to ≤ 512	> 200 to ≤ 300 > 214 to ≤ 357	> 100 to ≤ 200 > 89 to ≤ 214	≤ 100 ≤ 89

HE: hepatic encephalopathy; INR: international normalised ratio; MAP: mean arterial pressure; RRT: renal replacement therapy; PaO_2: partial pressure of arterial oxygen; FiO_2: fraction of inspired oxygen; SpO_2: pulse oximetry saturation.

Appendix B

Supplementary Table 2 Diagnostic and severity criteria of Acute-on-Chronic-Liver-Failure (ACLF) based on the organ failure (predefined by the CLIF-SOFA).

	ACLF grade
Patients with no organ failure	No ACLF
Patients with single liver or coagulation or circulation or respiration failure and serum creatinine level < 132 to 170 μmol/L without hepatic encephalopathy	
Patients with single cerebral failure and creatinine level ranging to 132 to 170 μmol/L	
Patients with single kidney failure	Grade 1
Patients with single liver or coagulation or circulation or respiration failure and serum creatinine level ranging from 132 to 170 μmol/L and/or hepatic encephalopathy (grade 1 or 2)	
Patients with single cerebral failure and creatinine level ranging to 132 to 170 μmol/L	
Patients with two organ failures	Grade 2
Patients with three organ failures or more	Grade 3

References

[1] Atkins D, Eccles M, Flottorp S, Guyatt GH, Henry D, Hill S, et al. Systems for grading the quality of evidence and the strength of recommendations I: critical appraisal of existing approaches. The GRADE Working Group. BMC Health Serv Res 2004;4(1):38.

[2] Bernal W, Wendon J. Acute liver failure. N Engl J Med 2013;369:2525–34. http://dx.doi.org/10.1056/NEJMra1208937.

[3] Ostapowicz G, Fontana RJ, Schiødt FV, Larson A, Davern TJ, Han SHB, et al. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. Ann Intern Med 2002;137:947–54.

[4] Ichai P, Legeai C, Francoz C, Boudjema K, Boillot O, Ducerf C, et al. Patients with acute liver failure listed for superurgent liver transplantation in France: reevaluation of the Clichy–Villejuif criteria: outcome of acute liver failure in France. Liver Transplant 2015;21:512–23. http://dx.doi.org/10.1002/lt.24092.

[5] Fuhrmann V, Kneidinger N, Herkner H, Heinz G, Nikfardjam M, Bojic A, et al. Hypoxic hepatitis: underlying conditions and risk factors for mortality in critically ill patients. Intensive Care Med 2009;35:1397–405. http://dx.doi.org/10.1007/s00134-009-1508-2.

[6] Harrison PM, Keays R, Bray GP, Alexander GJM, Williams R. Improved outcome of paracetamol-induced fulminant hepatic failure by late administration of acetylcysteine. Lancet 1990;335:1572–3.

[7] Keays R, Harrison PM, Wendon JA, Forbes A, Gove C, Alexander GJ, et al. Intravenous acetylcysteine in paracetamol induced fulminant hepatic failure: a prospective controlled trial. BMJ 1991;303:1026–9.

[8] Brok J, Buckley N, Gluud C. Interventions for paracetamol (acetaminophen) overdose. Cochrane Database Syst Rev 2018;2. http://dx.doi.org/10.1002/14651858.CD003328.pub2.

[9] Hu J, Zhang Q, Ren X, Sun Z, Quan Q. Efficacy and safety of acetylcysteine in "non-acetaminophen" acute liver failure: a meta-analysis of prospective clinical trials. Clin Res Hepatol Gastroenterol 2015;39:594–9. http://dx.doi.org/10.1016/j.clinre.2015.01.003.

[10] Lee WM, Hynan LS, Rossaro L, Fontana RJ, Stravitz RT, Larson AM, et al. Intravenous N-acetylcysteine improves transplant-free survival in early stage non-acetaminophen acute liver failure. Gastroenterology 2009;137. http://dx.doi.org/10.1053/j.gastro.2009.06.006. 856–864.e1.

[11] Kortsalioudaki C, Taylor RM, Cheeseman P, Bansal S, Mieli-Vergani G, Dhawan A. Safety and efficacy of N-acetylcysteine in children with non-acetaminophen-induced acute liver failure. Liver Transpl 2008;14:25–30. http://dx.doi.org/10.1002/lt.21246.

[12] Squires RH, Dhawan A, Alonso E, Narkewicz MR, Shneider BL, Rodriguez-Baez N, et al. Intravenous N-acetylcysteine in pediatric patients with nonacetaminophen acute liver failure: a placebo-controlled clinical trial. Hepatology 2013;57:1542–9. http://dx.doi.org/10.1002/hep.26001.

[13] Darweesh SK, Ibrahim MF, El-Tahawy MA. Effect of N-acetylcysteine on mortality and liver transplantation rate in non-acetaminophen-induced acute liver failure: a multicenter study. Clin Drug Invest 2017;37:473–82. http://dx.doi.org/10.1007/s40261-017-0505-4.

[14] Nabi T, Nabi S, Rafiq N, Shah A. Role of N-acetylcysteine treatment in non-acetaminophen-induced acute liver failure: a prospective study. Saudi J Gastroenterol 2017;23:169.

[15] Mumtaz K, Azam Z, Hamid S, Abid S, Memon S, Ali Shah H, et al. Role of N-acetylcysteine in adults with non-acetaminophen-induced acute liver failure in a center without the facility of liver transplantation. Hepatol Int 2009;3:563–70. http://dx.doi.org/10.1007/s12072-009-9151-0.

[16] Bernal W, Hyyrylainen A, Gera A, Audimoolam VK, McPhail MJW, Auzinger G, et al. Lessons from look-back in acute liver failure? A single centre experience of 3300 patients. J Hepatol 2013;59:74–80. http://dx.doi.org/10.1016/j.jhep.2013.02.010.

[17] Bernal W, Hall C, Karvellas CJ, Auzinger G, Sizer E, Wendon J. Arterial ammonia and clinical risk factors for encephalopathy and intracranial hypertension in acute liver failure. Hepatology 2007;46:1844–52. http://dx.doi.org/10.1002/hep.21838.

[18] Clemmesen JO, Larsen FS, Kondrup J, Hansen BA, Ott P. Cerebral herniation in patients with acute E liver failure is correlated with arterial ammonia concentration. Hepatology 1999;29:648–53. http://dx.doi.org/10.1002/hep.510290309.

[19] O'Grady JG, Alexander GJM, Hayllar KM, Williams R. Early indicators of prognosis in fulminant hepatic failure. Gastroenterology 1989;97:439–45. http://dx.doi.org/10.1016/0016-5085(89)90081-4.

[20] Bailey B, Amre DK, Gaudreault P. Fulminant hepatic failure secondary to acetaminophen poisoning: a systematic review and meta-analysis of prognostic criteria determining the need for liver transplantation. Crit Care Med 2003;31:299–305. http://dx.doi.org/10.1097/00003246-200301000-00048.

[21] Craig DGN, Ford AC, Hayes PC, Simpson KJ. Systematic review: prognostic tests of paracetamol-induced acute liver failure. Aliment Pharmacol Ther 2010;31:1064–76. http://dx.doi.org/10.1111/j.1365-2036.2010.04279.x.

[22] McPhail MJW, Farne H, Senvar N, Wendon JA, Bernal W. Ability of King's College Criteria and model for end-stage liver disease scores to predict mortality of patients with acute liver failure: a meta-analysis. Clin Gastroenterol Hepatol 2016;14. http://dx.doi.org/10.1016/j.cgh.2015.10.007. 516–525.e5.

[23] McPhail MJW, Wendon JA, Bernal W. Meta-analysis of performance of Kings's College Hospital Criteria in prediction of outcome in non-paracetamol-induced acute liver failure. J Hepatol 2010;53:492–9. http://dx.doi.org/10.1016/j.jhep.2010.03.023.

[24] Figorilli F, Putignano A, Roux O, Houssel-Debry P, Francoz C, Paugam-Burtz C, et al. Development of an organ failure score in acute liver failure for transplant selection and identification of patients at high risk of futility. PLoS ONE 2017;12:e0188151. http://dx.doi.org/10.1371/journal.pone.0188151.

[25] Bhatia V. Predictive value of arterial ammonia for complications and outcome in acute liver failure. Gut 2006;55:98–104. http://dx.doi.org/10.1136/gut.2004.061754.

[26] Kumar R, Shalimar, Sharma H, Prakash S, Panda SK, Khanal S, et al. Persistent hyperammonemia is associated with complications and poor outcomes in patients with acute liver failure. Clin Gastroenterol Hepatol 2012;10:925–31. http://dx.doi.org/10.1016/j.cgh.2012.04.011.

[27] Hadem J, Stiefel P, Bahr MJ, Tillmann HL, Rifai K, Klempnauer J, et al. Prognostic implications of lactate, bilirubin, and etiology in German patients with acute liver failure. Clin Gastroenterol Hepatol 2008;6:339–45. http://dx.doi.org/10.1016/j.cgh.2007.12.039.

[28] Rutherford A, King LY, Hynan LS, Vedvyas C, Lin W, Lee WM, et al. Development of an accurate index for predicting outcomes of patients with acute liver failure. Gastroenterology 2012;143:1237–43. http://dx.doi.org/10.1053/j.gastro.2012.07.113.

[29] Henrion J. Hypoxic hepatitis. Liver Int 2012;32:1039–52. http://dx.doi.org/10.1111/j.1478-3231.2011.02655.x.

[30] Patel A, Laffan MA, Waheed U, Brett SJ. Randomised trials of human albumin for adults with sepsis: systematic review and meta-analysis with trial sequential analysis of all-cause mortality. BMJ 2014;349:g4561.

[31] Avni T, Lador A, Lev S, Leibovici L, Paul M, Grossman A. Vasopressors for the treatment of septic shock: systematic review and meta-analysis. PLoS ONE 2015;10:e0129305. http://dx.doi.org/10.1371/journal.pone.0129305.

[32] Harry R, Auzinger G, Wendon J. The clinical importance of adrenal insufficiency in acute hepatic dysfunction. Hepatology 2002;36:395–402. http://dx.doi.org/10.1053/jhep.2002.34514.

[33] Etogo-Asse F-E, Atogo-Asse F-E, Vincent RP, Hughes SA, Auzinger G, Le Roux CW, et al. High density lipoprotein in patients with liver failure; relation to sepsis, adrenal function and outcome of illness. Liver Int 2012;32:128–36. http://dx.doi.org/10.1111/j.1478-3231.2011.02657.x.

[34] Harry R, Auzinger G, Wendon J. The effects of supraphysiological doses of corticosteroids in hypotensive liver failure. Liver Int 2003;23:71–7.

[35] Annane D, Pastores SM, Rochwerg B, Arlt W, Balk RA, Beishuizen A, et al. Guidelines for the diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) in critically ill patients (Part I): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. Intensive Care Med 2017;43:1751–63. http://dx.doi.org/10.1007/s00134-017-4919-5.

[36] Venkatesh B, Finfer S, Cohen J, Rajbhandari D, Arabi Y, Bellomo R, et al. Adjunctive glucocorticoid therapy in patients with septic shock. N Engl J Med 2018;378:797–808. http://dx.doi.org/10.1056/NEJMoa1705835.

[37] Annane D, Renault A, Brun-Buisson C, Megarbane B, Quenot J-P, Siami S, et al. Hydrocortisone plus fludrocortisone for adults with septic shock. N Engl J Med 2018;378:809–18. http://dx.doi.org/10.1056/NEJMoa1705716.

[38] Fan E, Del Sorbo L, Goligher EC, Hodgson CL, Munshi L, Walkey AJ, et al. An official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine Clinical Practice guideline: mechanical ventilation in adult patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 2017;195:1253–63. http://dx.doi.org/10.1164/rccm.201703-0548ST.

[39] Audimoolam VK, McPhail MJW, Wendon JA, Willars C, Bernal W, Desai SR, et al. Lung injury and its prognostic significance in acute liver failure. Crit Care Med 2014;42:592–600. http://dx.doi.org/10.1097/01.ccm.0000435666.15070.d5.

[40] Brienza N, Revelly JP, Ayuse T, Robotham JL. Effects of PEEP on liver arterial and venous blood flows. Am J Respir Crit Care Med 1995;152:504–10. http://dx.doi.org/10.1164/ajrccm.152.2.7633699.

[41] Neuschwander A, Futier E, Jaber S, Pereira B, Eurin M, Marret E, et al. The effects of intraoperative lung protective ventilation with positive end-expiratory pressure on blood loss during hepatic resection surgery: a secondary analysis of data from a published randomised control trial (IMPROVE). Eur J Anaesthesiol 2016;33:292–8. http://dx.doi.org/10.1097/EJA.0000000000000390.

[42] Ukere A, Meisner S, Greiwe G, Opitz B, Benten D, Nashan B, et al. The influence of PEEP and positioning on central venous pressure and venous hepatic hemodynamics in patients undergoing liver resection. J Clin Monit Comput 2017;31:1221–8. http://dx.doi.org/10.1007/s10877-016-9970-1.

[43] Minhas MA, Velasquez AG, Kaul A, Salinas PD, Celi LA. Effect of protocolized sedation on clinical outcomes in mechanically ventilated intensive care unit patients: a systematic review and meta-analysis of randomized controlled trials. Mayo Clin Proc 2015;90:613–23. http://dx.doi.org/10.1016/j.mayocp.2015.02.016.

[44] Society of Critical Care Medecine. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility and sleep disruption in adult patients in the intensive care unit. Crit Care Med 2018;46(9):e825–73. http://dx.doi.org/10.1097/CCM.0000000000003299.

[45] Als-Nielsen B, Kjaergard LL, Gluud C. Benzodiazepine receptor antagonists for acute and chronic hepatic encephalopathy. Cochrane Database Syst Rev 2001;CD002798. http://dx.doi.org/10.1002/14651858.CD002798.

[46] Weerink MAS, Struys MMRF, Hannivoort LN, Barends CRM, Absalom AR, Colin P. Clinical pharmacokinetics and pharmacodynamics of dexmedetomidine. Clin Pharmacokinet 2017;56:893–913. http://dx.doi.org/10.1007/s40262-017-0507-7.

[47] Karvellas CJ, Fix OK, Battenhouse H, Durkalski V, Sanders C, Lee WM. Outcomes and complications of intracranial pressure monitoring in acute liver failure: a retrospective cohort study. Crit Care Med 2014;42:1157–67. http://dx.doi.org/10.1097/CCM.0000000000000144.

[48] Vaquero J, Polson J, Chung C, Helenowski I, Schiodt FV, Reisch J, et al. Infection and the progression of hepatic encephalopathy in acute liver failure. Gastroenterology 2003;125:755–64. http://dx.doi.org/10.1016/S0016-5085(03)01051-5.

[49] Blei AT, Olafsson S, Webster S, Levy R. Complications of intracranial pressure monitoring in fulminant hepatic failure. Lancet 1993;341:157–8.

[50] Bernal W, Murphy N, Brown S, Whitehouse T, Bjerring PN, Hauerberg J, et al. A multicentre randomized controlled trial of moderate hypothermia to prevent intracranial hypertension in acute liver failure. J Hepatol 2016;65:273–9. http://dx.doi.org/10.1016/j.jhep.2016.03.003.

[51] Bhatia V, Batra Y, Acharya SK. Prophylactic phenytoin does not improve cerebral edema or survival in acute liver failure—a controlled clinical trial. J Hepatol 2004;41:89–96. http://dx.doi.org/10.1016/j.jhep.2004.03.017.

[52] Acharya SK, Bhatia V, Sreenivas V, Khanal S, Panda SK. Efficacy of L-Ornithine L-aspartate in acute liver failure: a double-blind, randomized, placebo-controlled study. Gastroenterology 2009;136:2159–68. http://dx.doi.org/10.1053/j.gastro.2009.02.050.

[53] Canalese J, Gimson AE, Davis C, Mellon PJ, Davis M, Williams R. Controlled trial of dexamethasone and mannitol for the cerebral oedema of fulminant hepatic failure. Gut 1982;23:625–9. http://dx.doi.org/10.1136/gut.23.7.625.

[54] Murphy N, Auzinger G, Bernel W, Wendon J. The effect of hypertonic sodium chloride on intracranial pressure in patients with acute liver failure. Hepatology 2004;39:464–70. http://dx.doi.org/10.1002/hep.20056.

[55] Wijdicks EF, Nyberg S. Propofol to control intracranial pressure in fulminant hepatic failure. Transplant Proc 2002;34:1220–2. http://dx.doi.org/10.1016/S0041-1345(02)02804-X.

[56] Stravitz RT, Ellerbe C, Durkalski V, Schilsky M, Fontana RJ, Peterseim C, et al. Bleeding complications in acute liver failure: liver failure/cirrhosis/portal hypertension. Hepatology 2018;67:1931–42. http://dx.doi.org/10.1002/hep.29694.

[57] Habib M, Roberts LN, Patel RK, Wendon J, Bernal W, Arya R. Evidence of rebalanced coagulation in acute liver injury and acute liver failure as measured by thrombin generation. Liver Int 2014;34:672–8. http://dx.doi.org/10.1111/liv.12369.

[58] Schultheiß C, Saugel B, Phillip V, Thies P, Noe S, Mayr U, et al. Continuous venovenous hemodialysis with regional citrate anticoagulation in patients with liver failure: a prospective observational study. Crit Care 2012;16:R162. http://dx.doi.org/10.1186/cc11485.

[59] Schmidt L. Systemic hemodynamic effects of treatment with the molecular adsorbents recirculating system in patients with hyperacute liver failure: a prospective controlled trial. Liver Transplant 2003;9:290–7. http://dx.doi.org/10.1053/jlts.2003.50051.

[60] Saliba F, Camus C, Durand F, Mathurin P, Letierce A, Delafosse B, et al. Albumin dialysis with a noncell artificial liver support device in patients with acute liver failure: a randomized, controlled trial. Ann Intern Med 2013;159:522–31.

[61] European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu, Clinical practice guidelines panel, Wendon, Panel members, Cordoba J, Dhawan A, et al. EASL clinical practical guidelines on the management of acute (fulminant) liver failure. J Hepatol 2017;66:1047–81. http://dx.doi.org/10.1016/j.jhep.2016.12.003.

[62] O'Riordan A, Brummell Z, Sizer E, Auzinger G, Heaton N, O'Grady JG, et al. Acute kidney injury in patients admitted to a liver intensive therapy unit with paracetamol-induced hepatotoxicity. Nephrol Dial Transplant 2011;26:3501–8. http://dx.doi.org/10.1093/ndt/gfr050.

[63] Klinck J, McNeill L, Di Angelantonio E, Menon DK. Predictors and outcome impact of perioperative serum sodium changes in a high-risk population. Br J Anaesth 2015;114:615–22. http://dx.doi.org/10.1093/bja/aeu409.

[64] Rolando N, Philpott-Howard J, Williams R. Bacterial and fungal infection in acute liver failure. Semin Liver Dis 1996;16:389–402. http://dx.doi.org/10.1055/s-2007-1007252.

[65] Karvellas CJ, Pink F, McPhail M, Cross T, Auzinger G, Bernal W, et al. Predictors of bacteraemia and mortality in patients with acute liver failure. Intensive Care Med 2009;35:1390–6. http://dx.doi.org/10.1007/s00134-009-1472-x.

[66] Child C, Turcotte J. Surgery and portal hypertension. Philadelphia: Saunders; 1964. p. 50–64.

[67] Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973;60:646–9.

[68] Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology 2013;144. http://dx.doi.org/10.1053/j.gastro.2013.02.042. 1426–1437.e9.

[69] Das V, Boelle P-Y, Galbois A, Guidet B, Maury E, Carbonell N, et al. Cirrhotic patients in the medical intensive care unit: early prognosis and long-term survival. Crit Care Med 2010;38:2108–16. http://dx.doi.org/10.1097/CCM.0b013e3181f3dea9.

[70] Levesque E, Hoti E, Azoulay D, Ichaï P, Habouchi H, Castaing D, et al. Prospective evaluation of the prognostic scores for cirrhotic patients admitted to an intensive care unit. J Hepatol 2012;56:95–102. http://dx.doi.org/10.1016/j.jhep.2011.06.024.

[71] McPhail MJW, Parrott F, Wendon JA, Harrison DA, Rowan KA, Bernal W. Incidence and outcomes for patients with cirrhosis admitted to the United Kingdom critical care units. Crit Care Med 2018;46:705–12. http://dx.doi.org/10.1097/CCM.0000000000002961.

[72] O'Brien AJ, Welch CA, Singer M, Harrison DA. Prevalence and outcome of cirrhosis patients admitted to UK intensive care: a comparison against dialysis-dependent chronic renal failure patients. Intensive Care Med 2012;38:991–1000. http://dx.doi.org/10.1007/s00134-012-2523-2.

[73] Welch C, Harrison D, Short A, Rowan K. The increasing burden of alcoholic liver disease on United Kingdom critical care units: secondary analysis of a high quality clinical database. J Health Serv Res Policy 2008;13(Suppl. 2):40–4. http://dx.doi.org/10.1258/jhsrp.2007.007101.

[74] Galbois A, Aegerter P, Martel-Samb P, Housset C, Thabut D, Offenstadt G, et al. Improved prognosis of septic shock in patients with cirrhosis: a multicenter study. Crit Care Med 2014;42:1666–75. http://dx.doi.org/10.1097/CCM.0000000000000321.

[75] Galbois A, Das V, Carbonell N, Guidet B. Prognostic scores for cirrhotic patients admitted to an intensive care unit: which consequences for liver transplantation? Clin Res Hepatol Gastroenterol 2013;37:455–66. http://dx.doi.org/10.1016/j.clinre.2013.05.001.

[76] Karvellas CJ, Bagshaw SM. Advances in management and prognostication in critically ill cirrhotic patients. Curr Opin Crit Care 2014;20:210–7. http://dx.doi.org/10.1097/MCC.0000000000000067.

[77] Saliba F, Ichaï P, Levesque E, Samuel D. Cirrhotic patients in the ICU: prognostic markers and outcome. Curr Opin Crit Care 2013;19:154–60. http://dx.doi.org/10.1097/MCC.0b013e328350c17.

[78] Cholongitas E, Senzolo M, Patch D, Shaw S, Hui C, Burroughs AK. Review article: scoring systems for assessing prognosis in critically ill adult cirrhotics. Aliment Pharmacol Ther 2006;24:453–64. http://dx.doi.org/10.1111/j.1365-2036.2006.02998.x.

[79] Berry PA, Thomson SJ, Rahman TM, Ala A. Review article: towards a considered and ethical approach to organ support in critically-ill patients with cirrhosis. Aliment Pharmacol Ther 2013;37:174–82. http://dx.doi.org/10.1111/apt.12133.

[80] Zauner CA, Apsner RC, Kranz A, Kramer L, Madl C, Schneeweiss B, et al. Outcome prediction for patients with cirrhosis of the liver in a medical ICU: a comparison of the APACHE scores and liver-specific scoring systems n.d.:5.

[81] Zauner C, Schneeweiss B, Schneider B, Madl C, Klos H, Kranz A, et al. Short-term prognosis in critically ill patients with liver cirrhosis: an evaluation of a new scoring system. Eur J Gastroenterol Hepatol 2000;12:517–22.

[82] Wehler M, Kokoska J, Reulbach U, Hahn EG, Strauss R. Short-term prognosis in critically ill patients with cirrhosis assessed by prognostic scoring systems. Hepatology 2001;34:255–61. http://dx.doi.org/10.1053/jhep.2001.26522.

[83] Tsai M-H, Chen Y-C, Ho Y-P, Fang J-T, Lien J-M, Chiu C-T, et al. Organ system failure scoring system can predict hospital mortality in critically ill cirrhotic patients. J Clin Gastroenterol 2003;37:251–7.

[84] Chen YC, Tsai MH, Ho YP, Hsu CW, Lin HH, Fang JT, et al. Comparison of the severity of illness scoring systems for critically ill cirrhotic patients with renal failure. Clin Nephrol 2004;61:111–8.

[85] Ho Y-P, Chen Y-C, Yang C, Lien J-M, Chu Y-Y, Fang J-T, et al. Outcome prediction for critically ill cirrhotic patients: a comparison of APACHE II and Child–Pugh scoring systems. J Intensive Care Med 2004;19:105–10. http://dx.doi.org/10.1177/0885066603261991.

[86] Rabe C, Schmitz V, Paashaus M, Musch A, Zickermann H, Dumoulin F-L, et al. Does intubation really equal death in cirrhotic patients? Factors influencing outcome in patients with liver cirrhosis requiring mechanical ventilation. Intensive Care Med 2004;30:1564–71. http://dx.doi.org/10.1007/s00134-004-2346-x.

[87] Tsai M-H, Peng Y-S, Lien J-M, Weng H-H, Ho Y-P, Yang C, et al. Multiple organ system failure in critically ill cirrhotic patients. A comparison of two multiple organ dysfunction/failure scoring systems. Digestion 2004;69:190–200. http://dx.doi.org/10.1159/000078789.

[88] Chen Y-C, Tian Y-C, Liu N-J, Ho Y-P, Yang C, Chu Y-Y, et al. Prospective cohort study comparing sequential organ failure assessment and acute physiology, age, chronic health evaluation III scoring systems for hospital mortality prediction in critically ill cirrhotic patients: Sofa and Apache III in Liver Cirrhosis. Int J Clin Pract 2005;60:160–6. http://dx.doi.org/10.1111/j.1742-1241.2005.00634.x.

[89] Cholongitas E, Senzolo M, Patch D, Kwong K, Nikolopoulou V, Leandro G, et al. Risk factors, Sequential Organ Failure Assessment and Model for End-stage Liver Disease scores for predicting short-term mortality in cirrhotic patients admitted to intensive care unit. Aliment Pharmacol Ther 2006;23:883–93. http://dx.doi.org/10.1111/j.1365-2036.2006.02842.x.

[90] Cholongitas E, Betrosian A, Senzolo M, Shaw S, Patch D, Manousou P, et al. Prognostic models in cirrhotics admitted to intensive care units better predict outcome when assessed at 48 h after admission. J Gastroenterol Hepatol 2008;23:1223–7. http://dx.doi.org/10.1111/j.1440-1746.2007.05269.x.

[91] Juneja D, Gopal PB, Kapoor D, Raya R, Sathyanarayanan M, Malhotra P. Outcome of patients with liver cirrhosis admitted to a specialty liver intensive care unit in India. J Crit Care 2009;24:387–93. http://dx.doi.org/10.1016/j.jcrc.2008.12.013.

[92] Karvellas CJ, Pink F, McPhail M, Austin M, Auzinger G, Bernal W, et al. Bacteremia, acute physiology and chronic health evaluation II and modified end stage liver disease are independent predictors of mortality in critically ill nontransplanted patients with acute on chronic liver failure. Crit Care Med 2010;38:121–6. http://dx.doi.org/10.1097/CCM.0b013e3181b42a1c.

[93] Filloux B, Chagneau-Derrode C, Ragot S, Voultoury J, Beauchant M, Silvain C, et al. Short-term and long-term vital outcomes of cirrhotic patients admitted to an intensive care unit. Eur J Gastroenterol Hepatol 2010;22:1474–80. http://dx.doi.org/10.1097/MEG.0b013e32834059cd.

[94] Tu K-H, Jenq C-C, Tsai M-H, Hsu H-H, Chang M-Y, Tian Y-C, et al. Outcome scoring systems for short-term prognosis in critically ill cirrhotic patients. Shock 2011;36:445–50. http://dx.doi.org/10.1097/SHK.0b013e31822fb7e2.
[95] Cavallazzi R, Awe OO, Vasu TS, Hirani A, Vaid U, Leiby BE, et al. Model for End-Stage Liver Disease score for predicting outcome in critically ill medical patients with liver cirrhosis. J Crit Care 2012;27. http://dx.doi.org/10.1016/j.jcrc.2011.11.014. 424.e1–6.
[96] Cholongitas E, Agarwal B, Antoniadis N, Burroughs AK. Patients with cirrhosis admitted to an intensive care unit. J Hepatol 2012;57:230–1. http://dx.doi.org/10.1016/j.jhep.2012.01.024 [author reply 231–232].
[97] Juneja D, Gopal PB, Kapoor D, Raya R, Sathyanarayanan M. Profile and outcome of patients with liver cirrhosis requiring mechanical ventilation. J Intensive Care Med 2012;27:373–8. http://dx.doi.org/10.1177/0885066611400277.
[98] Olmez S, Gümürdülü Y, Tas A, Karakoc E, Kara B, Kidik A. Prognostic markers in cirrhotic patients requiring intensive care: a comparative prospective study. Ann Hepatol 2012;11:513–8.
[99] Jalan R, Saliba F, Pavesi M, Amoros A, Moreau R, Ginès P, et al. Development and validation of a prognostic score to predict mortality in patients with acute-on-chronic liver failure. J Hepatol 2014;61:1038–47. http://dx.doi.org/10.1016/j.jhep.2014.06.012.
[100] Theocharidou E, Pieri G, Mohammad AO, Cheung M, Cholongitas E, Agarwal B, et al. The Royal Free Hospital score: a calibrated prognostic model for patients with cirrhosis admitted to intensive care unit. Comparison with current models and CLIF-SOFA score. Am J Gastroenterol 2014;109:554–62. http://dx.doi.org/10.1038/ajg.2013.466.
[101] Bao Q, Wang B, Yu L, Weng H, Ge J, Li L. A modified prognostic score for critically ill patients with cirrhosis: an observational study: prognostic score for cirrhosis. J Gastroenterol Hepatol 2016;31:450–8. http://dx.doi.org/10.1111/jgh.13076.
[102] Peeraphatdit T, Naksuk N, Thongprayoon C, Harmsen WS, Therneau TM, Ricci P, et al. Prognostic value of model for End-Stage Liver Disease Score measurements on a daily basis in critically ill patients with cirrhosis. Mayo Clin Proc 2015;90:1196–206. http://dx.doi.org/10.1016/j.mayocp.2015.06.017.
[103] Campbell J, McPeake J, Shaw M, Puxty A, Forrest E, Soulsby C, et al. Validation and analysis of prognostic scoring systems for critically ill patients with cirrhosis admitted to ICU. Crit Care 2015;19:364. http://dx.doi.org/10.1186/s13054-015-1070-y.
[104] Levesque E, Saliba F, Ichaï P, Samuel D. Outcome of patients with cirrhosis requiring mechanical ventilation in ICU. J Hepatol 2014;60:570–8. http://dx.doi.org/10.1016/j.jhep.2013.11.012.
[105] Gustot T, Felleiter P, Pickkers P, Sakr Y, Rello J, Velissaris D, et al. Impact of infection on the prognosis of critically ill cirrhotic patients: results from a large worldwide study. Liver Int 2014;34:1496–503. http://dx.doi.org/10.1111/liv.12520.
[106] Emerson P, McPeake J, O'Neill A, Gilmour H, Forrest E, Puxty A, et al. The utility of scoring systems in critically ill cirrhotic patients admitted to a general intensive care unit. J Crit Care 2014;29. http://dx.doi.org/10.1016/j.jcrc.2014.06.027. 1131.e1–1131.e6.
[107] Annamalai A, Harada MY, Chen M, Tran T, Ko A, Ley EJ, et al. Predictors of mortality in the critically ill cirrhotic patient: is the model for End-Stage Liver Disease enough? J Am Coll Surg 2017;224:276–82. http://dx.doi.org/10.1016/j.jamcollsurg.2016.11.005.
[108] McPhail MJW, Shawcross DL, Abeles RD, Chang A, Patel V, Lee G-H, et al. Increased survival for patients with cirrhosis and organ failure in liver intensive care and validation of the chronic liver failure – Sequential Organ Failure Scoring System. Clin Gastroenterol Hepatol 2015;13. http://dx.doi.org/10.1016/j.cgh.2014.08.041. 1353–1360.e8.
[109] Pan H-C, Jenq C-C, Tsai M-H, Fan P-C, Chang C-H, Chang M-Y, et al. Scoring systems for 6-month mortality in critically ill cirrhotic patients: a prospective analysis of Chronic Liver Failure – Sequential Organ Failure Assessment Score (CLIF-SOFA). Aliment Pharmacol Ther 2014;40:1056–65. http://dx.doi.org/10.1111/apt.12953.
[110] Peng Y, Qi X, Guo X. Child–Pugh versus MELD Score for the assessment of prognosis in liver cirrhosis: a systematic review and meta-analysis of observational studies. Medicine 2016;95:e2877. http://dx.doi.org/10.1097/MD.0000000000002877.
[111] D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hepatol 2006;44:217–31. http://dx.doi.org/10.1016/j.jhep.2005.10.013.
[112] Arabi Y, Ahmed QAA, Haddad S, Aljumah A, Al-Shimemeri A. Outcome predictors of cirrhosis patients admitted to the intensive care unit. Eur J Gastroenterol Hepatol 2004;16:333–9.
[113] Majumdar A, Bailey M, Kemp WM, Bellomo R, Roberts SK, Pilcher D. Declining mortality in critically ill patients with cirrhosis in Australia and New Zealand between 2000 and 2015. J Hepatol 2017;67:1185–93. http://dx.doi.org/10.1016/j.jhep.2017.07.024.
[114] Weil D, Levesque E, McPhail M, Cavallazzi R, Theocharidou E, Cholongitas E, et al. Prognosis of cirrhotic patients admitted to intensive care unit: a meta-analysis. Ann Intensive Care 2017;7:33. http://dx.doi.org/10.1186/s13613-017-0249-6.
[115] Bahirwani R, Ghabril M, Forde KA, Chatrath H, Wolf KM, Uribe L, et al. Factors that predict short-term intensive care unit mortality in patients with cirrhosis. Clin Gastroenterol Hepatol 2013;11. http://dx.doi.org/10.1016/j.cgh.2013.03.035. 1194–1200.e2.
[116] Ginès P, Fernández J, Durand F, Saliba F. Management of critically-ill cirrhotic patients. J Hepatol 2012;56(Suppl. 1):S13–24. http://dx.doi.org/10.1016/S0168-8278(12)60003-8.
[117] Galbois A, Trompette M-L, Das V, Boëlle P-Y, Carbonell N, Thabut D, et al. Improvement in the prognosis of cirrhotic patients admitted to an intensive care unit, a retrospective study. Eur J Gastroenterol Hepatol 2012;24:897–904. http://dx.doi.org/10.1097/MEG.0b013e3283544816.
[118] Shawcross DL, Austin MJ, Abeles RD, McPhail MJW, Yeoman AD, Taylor NJ, et al. The impact of organ dysfunction in cirrhosis: survival at a cost? J Hepatol 2012;56:1054–62. http://dx.doi.org/10.1016/j.jhep.2011.12.014.
[119] Carbonell N, Pauwels A, Serfaty L, Fourdan O, Lévy VG, Poupon R. Improved survival after variceal bleeding in patients with cirrhosis over the past two decades. Hepatology 2004;40:652–9. http://dx.doi.org/10.1002/hep.20339.
[120] Sauneuf B, Champigneulle B, Soummer A, Mongardon N, Charpentier J, Cariou A, et al. Increased survival of cirrhotic patients with septic shock. Critical Care 2013;17:R78. http://dx.doi.org/10.1186/cc12687.
[121] European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu, European Association for the Study of the Liver. EASL clinical practice guidelines for the management of patients with decompensated cirrhosis. J Hepatol 2018;69:406–60. http://dx.doi.org/10.1016/j.jhep.2018.03.024.
[122] Angeli P, Ginès P, Wong F, Bernardi M, Boyer TD, Gerbes A, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. J Hepatol 2015;62:968–74. http://dx.doi.org/10.1016/j.jhep.2014.12.029.
[123] Kellum JA, Lameire N, KDIGO AKI Guideline Work Group. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (part 1). Crit Care 2013;17:204. http://dx.doi.org/10.1186/cc11454.
[124] Joannidis M, Metnitz B, Bauer P, Schusterschitz N, Moreno R, Druml W, et al. Acute kidney injury in critically ill patients classified by AKIN versus RIFLE using the SAPS 3 database. Intensive Care Med 2009;35:1692–702. http://dx.doi.org/10.1007/s00134-009-1530-4.
[125] Belcher JM, Garcia-Tsao G, Sanyal AJ, Bhogal H, Lim JK, Ansari N, et al. Association of AKI with mortality and complications in hospitalized patients with cirrhosis. Hepatology 2013;57:753–62. http://dx.doi.org/10.1002/hep.25735.
[126] Piano S, Rosi S, Maresio G, Fasolato S, Cavallin M, Romano A, et al. Evaluation of the Acute Kidney Injury Network criteria in hospitalized patients with cirrhosis and ascites. J Hepatol 2013;59:482–9. http://dx.doi.org/10.1016/j.jhep.2013.03.039.
[127] Fagundes C, Barreto R, Guevara M, Garcia E, Solà E, Rodríguez E, et al. A modified acute kidney injury classification for diagnosis and risk stratification of impairment of kidney function in cirrhosis. J Hepatol 2013;59:474–81. http://dx.doi.org/10.1016/j.jhep.2013.04.036.
[128] Huelin P, Piano S, Solà E, Stanco M, Solé C, Moreira R, et al. Validation of a Staging system for acute kidney injury in patients with cirrhosis and association with acute-on-chronic liver failure. Clin Gastroenterol Hepatol 2017;15. http://dx.doi.org/10.1016/j.cgh.2016.09.156. 438–445.e5.
[129] Sherman DS, Fish DN, Teitelbaum I. Assessing renal function in cirrhotic patients: problems and pitfalls. Am J Kidney Dis 2003;41:269–78. http://dx.doi.org/10.1053/ajkd.2003.50035.
[130] Spencer K. Analytical reviews in clinical biochemistry: the estimation of creatinine. Ann Clin Biochem 1986;23(Pt 1):1–25. http://dx.doi.org/10.1177/000456328602300101.
[131] Gluud LL, Christensen K, Christensen E, Krag A. Systematic review of randomized trials on vasoconstrictor drugs for hepatorenal syndrome. Hepatology 2010;51:576–84. http://dx.doi.org/10.1002/hep.23286.
[132] Facciorusso A, Chandar AK, Murad MH, Prokop LJ, Muscatiello N, Kamath PS, et al. Comparative efficacy of pharmacological strategies for management of type 1 hepatorenal syndrome: a systematic review and network meta-analysis. Lancet Gastroenterol Hepatol 2017;2:94–102. http://dx.doi.org/10.1016/S2468-1253(16)30157-1.
[133] Nanda A, Reddy R, Safraz H, Salameh H, Singal AK. Pharmacological therapies for hepatorenal syndrome: a systematic review and meta-analysis. J Clin Gastroenterol 2018;52:360–7. http://dx.doi.org/10.1097/MCG.0000000000000913.
[134] Israelsen M, Krag A, Allegretti AS, Jovani M, Goldin AH, Winter RW, et al. Terlipressin versus other vasoactive drugs for hepatorenal syndrome. Cochrane Database Syst Rev 2017;9. http://dx.doi.org/10.1002/14651858.CD011532.pub2.
[135] Cavallin M, Kamath PS, Merli M, Fasolato S, Toniutto P, Salerno F, et al. Terlipressin plus albumin versus midodrine and octreotide plus albumin in the treatment of hepatorenal syndrome: a randomized trial. Hepatology 2015;62:567–74. http://dx.doi.org/10.1002/hep.27709.
[136] Cavallin M, Fasolato S, Marenco S, Piano S, Tonon M, Angeli P. The treatment of hepatorenal syndrome. Dig Dis 2015;33:548–54. http://dx.doi.org/10.1159/000375346.
[137] Arroyo V, García-Martinez R, Salvatella X. Human serum albumin, systemic inflammation, and cirrhosis. J Hepatol 2014;61:396–407. http://dx.doi.org/10.1016/j.jhep.2014.04.012.
[138] Bajaj JS, O'Leary JG, Reddy KR, Wong F, Olson JC, Subramanian RM, et al. Second infections independently increase mortality in hospitalized patients with cirrhosis: the North American consortium for the study of end-stage liver disease (NACSELD) experience. Hepatology 2012;56:2328–35. http://dx.doi.org/10.1002/hep.25947.
[139] Jalan R, Fernandez J, Wiest R, Schnabl B, Moreau R, Angeli P, et al. Bacterial infections in cirrhosis: a position statement based on the EASL Special Conference 2013. J Hepatol 2014;60:1310–24. http://dx.doi.org/10.1016/j.jhep.2014.01.024.

[140] Arabi YM, Dara SI, Memish Z, Al Abdulkareem A, Tamim HM, Al-Shirawi N, et al. Antimicrobial therapeutic determinants of outcomes from septic shock among patients with cirrhosis. Hepatology 2012;56:2305–15. http://dx.doi.org/10.1002/hep.25931.
[141] Hsieh C-C, Lee C-C, Chan T-Y, Hong M-Y, Chi C-H, Ko W-C. Clinical features and impact of empirical therapy in cirrhotic adults with community-onset bacteremia. Am J Emergency Med 2015;33:222–8. http://dx.doi.org/10.1016/j.ajem.2014.11.024.
[142] Karvellas CJ, Abraldes JG, Arabi YM, Kumar A, the Cooperative Antimicrobial Therapy of Septic Shock (CATSS) Database Research Group. Appropriate and timely antimicrobial therapy in cirrhotic patients with spontaneous bacterial peritonitis-associated septic shock: a retrospective cohort study. Aliment Pharmacol Ther 2015;41:747–57. http://dx.doi.org/10.1111/apt.13135.
[143] Xie Y, Tu B, Xu Z, Zhang X, Bi J, Zhao M, et al. Bacterial distributions and prognosis of bloodstream infections in patients with liver cirrhosis. Sci Rep 2017;7:11482. http://dx.doi.org/10.1038/s41598-017-11587-1.
[144] Bartoletti M, Giannella M, Lewis R, Caraceni P, Tedeschi S, Paul M, et al. A prospective multicentre study of the epidemiology and outcomes of bloodstream infection in cirrhotic patients. Clin Microbiol Infect 2018;24. http://dx.doi.org/10.1016/j.cmi.2017.08.001. 546.e1–546.e8.
[145] Vilstrup H, Amodio P, Bajaj J, Cordoba J, Ferenci P, Mullen KD, et al. Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study Of Liver Diseases and the European Association for the Study of the Liver: Vilstrup et al. Hepatology 2014;60:715–35. http://dx.doi.org/10.1002/hep.27210.
[146] Merli M, Lucidi C, Pentassuglio I, Giannelli V, Giusto M, Di Gregorio V, et al. Increased risk of cognitive impairment in cirrhotic patients with bacterial infections. J Hepatol 2013;59:243–50. http://dx.doi.org/10.1016/j.jhep.2013.03.012.
[147] Lin K-H, Wang F-L, Wu M-S, Jiang B-Y, Kao W-L, Chao H-Y, et al. Serum procalcitonin and C-reactive protein levels as markers of bacterial infection in patients with liver cirrhosis: a systematic review and meta-analysis. Diagn Microbiol Infect Dis 2014;80:72–8. http://dx.doi.org/10.1016/j.diagmicrobio.2014.03.029.
[148] Deutsch M. Bacterial infections in patients with liver cirrhosis: clinical characteristics and the role of C-reactive protein. Ann Gastroenterol 2018;31:77–83. http://dx.doi.org/10.20524/aog.2017.0207.
[149] Fiore M, Gentile I, Maraolo AE, Leone S, Simeon V, Chiodini P, et al. Are third-generation cephalosporins still the empirical antibiotic treatment of community-acquired spontaneous bacterial peritonitis? A systematic review and meta-analysis. Eur J Gastroenterol Hepatol 2018;30:329–36. http://dx.doi.org/10.1097/MEG.0000000000001057.
[150] Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med 2017;43:304–77. http://dx.doi.org/10.1007/s00134-017-4683-6.
[151] Myc LA, Stine JG, Chakrapani R, Kadl A, Argo CK. Vasopressin use in critically ill cirrhosis patients with catecholamine-resistant septic shock: the CVICU cohort. World J Hepatol 2017;9:106. http://dx.doi.org/10.4254/wjh.v9.i2.106.
[152] Kim G, Huh JH, Lee KJ, Kim MY, Shim KY, Baik SK. Relative adrenal insufficiency in patients with cirrhosis: a systematic review and meta-analysis. Dig Dis Sci 2017;62:1067–79. http://dx.doi.org/10.1007/s10620-017-4471-8.
[153] Fernández J, Escorsell A, Zabalza M, Felipe V, Navasa M, Mas A, et al. Adrenal insufficiency in patients with cirrhosis and septic shock: effect of treatment with hydrocortisone on survival. Hepatology 2006;44:1288–95. http://dx.doi.org/10.1002/hep.21352.
[154] Arabi YM, Aljumah A, Dabbagh O, Tamim HM, Rishu AH, Al-Abdulkareem A, et al. Low-dose hydrocortisone in patients with cirrhosis and septic shock: a randomized controlled trial. Can Med Assoc J 2010;182:1971–7. http://dx.doi.org/10.1503/cmaj.090707.
[155] Solà R, Vila MC, Andreu M, Oliver MI, Coll S, Gana J, et al. Total paracentesis with dextran 40 versus diuretics in the treatment of ascites in cirrhosis: a randomized controlled study. J Hepatol 1994;20(2):282–8.
[156] Salerno F, Guevara M, Bernardi M, Moreau R, Wong F, Angeli P, et al. Refractory ascites: pathogenesis, definition and therapy of a severe complication in patients with cirrhosis. Liver Int 2010;30(7):937–47.
[157] Bernardi M, Caraceni P, Navickis RJ, Wilkes MM. Albumin infusion in patients undergoing large-volume paracentesis: a meta-analysis of randomized trials. Hepatology 2012;55(4):1172–81.
[158] Bari K, Miñano C, Shea M, Inayat IB, Hashem HJ, Gilles H, et al. The combination of octreotide and midodrine is not superior to albumin in preventing recurrence of ascites after large-volume paracentesis. Clin Gastroenterol Hepatol 2012;10(10):1169–75.
[159] Hamdy H, ElBaz AA, Hassan A, Hassanin O. Comparison of midodrine and albumin in the prevention of paracentesis-induced circulatory dysfunction in cirrhotic patients: a randomized pilot study. J Clin Gastroenterol 2014;48(2):184–8.
[160] Bernardi M, Caraceni P, Navickis RJ. Does the evidence support a survival benefit of albumin infusion in patients with cirrhosis undergoing large-volume paracentesis? Expert Rev Gastroenterol Hepatol 2017;11(3):191–2.
[161] Kütting F, Schubert J, Franklin J, Bowe A, Hoffmann V, Demir M, et al. Insufficient evidence of benefit regarding mortality due to albumin substitution in HCC-free cirrhotic patients undergoing large volume paracentesis. J Gastroenterol Hepatol 2017;32(2):327–38.
[162] Runyon BA, AASLD. Introduction to the revised American Association for the Study of Liver Diseases Practice Guideline management of adult patients with ascites due to cirrhosis 2012. Hepatology 2013;57(4):1651–3.
[163] European Association for the Study of the Liver. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. J Hepatol 2010;53(3):397–417.
[164] Alessandria C, Elia C, Mezzabotta L, Risso A, Andrealli A, Spandre M, et al. Prevention of paracentesis-induced circulatory dysfunction in cirrhosis: standard versus half albumin doses. A prospective, randomized, unblinded pilot study. Dig Liver Dis 2011;43(11):881–6.
[165] Tan HK, James PD, Wong F. Albumin may prevent the morbidity of paracentesis-induced circulatory dysfunction in cirrhosis and refractory ascites: a pilot study. Dig Dis Sci 2016;61(10):3084–92.
[166] Sort P, Navasa M, Arroyo V, Aldeguer X, Planas R, Ruiz-del-Arbol L, et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. N Engl J Med 1999;341(6):403–9.
[167] Chen T-A, Tsao Y-C, Chen A, Lo G-H, Lin C-K, Yu H-C, et al. Effect of intravenous albumin on endotoxin removal, cytokines, and nitric oxide production in patients with cirrhosis and spontaneous bacterial peritonitis. Scand J Gastroenterol 2009;44(5):619–25.
[168] Fernández J, Monteagudo J, Bargallo X, Jiménez W, Bosch J, Arroyo V, et al. A randomized unblinded pilot study comparing albumin versus hydroxyethyl starch in spontaneous bacterial peritonitis. Hepatology 2005;42(3):627–34.
[169] Guevara M, Terra C, Nazar A, Solà E, Fernández J, Pavesi M, et al. Albumin for bacterial infections other than spontaneous bacterial peritonitis in cirrhosis. A randomized, controlled study. J Hepatol 2012;57(4):759–65.
[170] Thévenot T, Bureau C, Oberti F, Anty R, Louvet A, Plessier A, et al. Effect of albumin in cirrhotic patients with infection other than spontaneous bacterial peritonitis. A randomized trial. J Hepatol 2015;62(4):822–30.
[171] Xue HP, Lin B, Zhong J, et al. Effect of albumin infusion on preventing the deterioration of renal function in patients with spontaneous bacterial peritonitis. Chin J Dig Dis 2002;42:627–34.
[172] Salerno F, Navickis RJ, Wilkes MM. Albumin infusion improves outcomes of patients with spontaneous bacterial peritonitis: a meta-analysis of randomized trials. Clin Gastroenterol Hepatol 2013;11(2). 123–130.e.
[173] Avgerinos A, Nevens F, Raptis S, Fevery J. Early administration of somatostatin and efficacy of sclerotherapy in acute oesophageal variceal bleeds: the European Acute Bleeding Oesophageal Variceal Episodes (ABOVE) randomised trial. Lancet 1997;350(9090):1495–9.
[174] Besson I, Ingrand P, Person B, Boutroux D, Heresbach D, Bernard P, et al. Sclerotherapy with or without octreotide for acute variceal bleeding. N Engl J Med 1995;333(9):555–60.
[175] Sung JJ, Chung SC, Yung MY, Lai CW, Lau JY, Lee YT, et al. Prospective randomised study of effect of octreotide on rebleeding from oesophageal varices after endoscopic ligation. Lancet 1995;346(8991–8992):1666–9.
[176] Wells M, Chande N, Adams P, Beaton M, Levstik M, Boyce E, et al. Meta-analysis: vasoactive medications for the management of acute variceal bleeds. Aliment Pharmacol Ther 2012;35(11):1267–78.
[177] Seo YS, Park SY, Kim MY, Kim JH, Park JY, Yim HJ, et al. Lack of difference among terlipressin, somatostatin, and octreotide in the control of acute gastroesophageal variceal hemorrhage. Hepatology 2014;60(3):954–63.
[178] Chavez-Tapia NC, Barrientos-Gutierrez T, Tellez-Avila F, Soares-Weiser K, Mendez-Sanchez N, Gluud C, et al. Meta-analysis: antibiotic prophylaxis for cirrhotic patients with upper gastrointestinal bleeding – an updated Cochrane review. Aliment Pharmacol Ther 2011;34(5):509–18.
[179] Lau JY, Leung WK, Wu JCY, Chan FKL, Wong VWS, Chiu PWY, et al. Omeprazole before endoscopy in patients with gastrointestinal bleeding. N Engl J Med 2007;356(16):1631–40.
[180] Lo G-H, Chen W-C, Wang H-M, Lin C-K, Chan H-H, Tsai W-L, et al. Low-dose terlipressin plus banding ligation versus low-dose terlipressin alone in the prevention of very early rebleeding of oesophageal varices. Gut 2009;58(9):1275–80.
[181] de Franchis R, Baveno VI Faculty. Expanding consensus in portal hypertension: report of the Baveno VI Consensus Workshop: stratifying risk and individualizing care for portal hypertension. J Hepatol 2015;63(3):743–52.
[182] García-Pagán JC, Caca K, Bureau C, Laleman W, Appenrodt B, Luca A, et al. Early use of TIPS in patients with cirrhosis and variceal bleeding. N Engl J Med 2010;362(25):2370–9.
[183] Chen P-H, Chen W-C, Hou M-C, Liu T-T, Chang C-J, Liao W-C, et al. Delayed endoscopy increases re-bleeding and mortality in patients with hematemesis and active esophageal variceal bleeding: a cohort study. J Hepatol 2012;57(6):1207–13.
[184] Villanueva C, Colomo A, Bosch A, Concepción M, Hernandez-Gea V, Aracil C, et al. Transfusion strategies for acute upper gastrointestinal bleeding. N Engl J Med 2013;368(1):11–21.
[185] Jairath V, Kahan BC, Gray A, Doré CJ, Mora A, James MW, et al. Restrictive versus liberal blood transfusion for acute upper gastrointestinal bleeding (TRIGGER): a pragmatic, open-label, cluster randomised feasibility trial. Lancet 2015;386(9989):137–44.
[186] Odutayo A, Desborough MJR, Trivella M, Stanley AJ, Dorée C, Collins GS, et al. Restrictive versus liberal blood transfusion for gastrointestinal bleeding: a systematic review and meta-analysis of randomised controlled trials. Lancet Gastroenterol Hepatol 2017;2(5):354–60.
[187] Garcia-Pagán JC, Di Pascoli M, Caca K, Laleman W, Bureau C, Appenrodt B, et al. Use of early-TIPS for high-risk variceal bleeding: results of a post-RCT surveillance study. J Hepatol 2013;58(1):45–50.
[188] Rudler M, Cluzel P, Corvec TL, Benosman H, Rousseau G, Poynard T, et al. Early-TIPSS placement prevents rebleeding in high-risk patients with

variceal bleeding, without improving survival. Aliment Pharmacol Ther 2014;40(9):1074–80.
[189] Monescillo A, Martínez-Lagares F, Ruiz-del-Arbol L, Sierra A, Guevara C, Jiménez E, et al. Influence of portal hypertension and its early decompression by TIPS placement on the outcome of variceal bleeding. Hepatology 2004;40(4):793–801.
[190] Deltenre P, Trépo E, Rudler M, Monescillo A, Fraga M, Denys A, et al. Early transjugular intrahepatic portosystemic shunt in cirrhotic patients with acute variceal bleeding: a systematic review and meta-analysis of controlled trials. Eur J Gastroenterol Hepatol 2015;27(9):e1–9.
[191] Azoulay D, Castaing D, Majno P, Saliba F, Ichaï P, Smail A, et al. Salvage transjugular intrahepatic portosystemic shunt for uncontrolled variceal bleeding in patients with decompensated cirrhosis. J Hepatol 2001;35(5):590–7.
[192] Escorsell À, Pavel O, Cárdenas A, Morillas R, Llop E, Villanueva C, et al. Esophageal balloon tamponade versus esophageal stent in controlling acute refractory variceal bleeding: a multicenter randomized, controlled trial. Hepatology 2016;63(6):1957–67.
[193] Tripodi A, Salerno F, Chantarangkul V, Clerici M, Cazzaniga M, Primignani M, et al. Evidence of normal thrombin generation in cirrhosis despite abnormal conventional coagulation tests. Hepatology 2005;41(3):553–8.
[194] Lisman T, Porte RJ. Rebalanced hemostasis in patients with liver disease: evidence and clinical consequences. Blood 2010;116(6):878–85.
[195] Napolitano G, Iacobellis A, Merla A, Niro G, Valvano MR, Terracciano F, et al. Bleeding after invasive procedures is rare and unpredicted by platelet counts in cirrhotic patients with thrombocytopenia. Eur J Intern Med 2017;38:79–82.
[196] Yates SG, Gavva C, Agrawal D, Sarode R. How do we transfuse blood components in cirrhotic patients undergoing gastrointestinal procedures? Transfusion 2016;56(4):791–8.
[197] HAS, ANSM. Transfusion de plaquettes. Recommandations; 2015.
[198] Nadim MK, Durand F, Kellum JA, Levitsky J, O'Leary JG, Karvellas CJ, et al. Management of the critically ill patient with cirrhosis: a multidisciplinary perspective. J Hepatol 2016;64(3):717–35.
[199] Tripodi A, Chantarangkul V, Primignani M, Clerici M, Dell'era A, Aghemo A, et al. Thrombin generation in plasma from patients with cirrhosis supplemented with normal plasma: considerations on the efficacy of treatment with fresh-frozen plasma. Intern Emerg Med 2012;7(2):139–44.
[200] Afdhal NH, Giannini EG, Tayyab G, Mohsin A, Lee J-W, Andriulli A, et al. Eltrombopag before procedures in patients with cirrhosis and thrombocytopenia. N Engl J Med 2012;367(8):716–24.
[201] Lodge JPA, Jonas S, Jones RM, Olausson M, Mir-Pallardo J, Soefelt S, et al. Efficacy and safety of repeated perioperative doses of recombinant factor VIIa in liver transplantation. Liver Transpl 2005;11(8):973–9.
[202] Lodge JPA, Jonas S, Oussoultzoglou E, Malagó M, Jayr C, Cherqui D, et al. Recombinant coagulation factor VIIa in major liver resection: a randomized, placebo-controlled, double-blind clinical trial. Anesthesiology 2005;102(2):269–75.
[203] Shao Y-F, Yang J-M, Chau G-Y, Sirivatanauksorn Y, Zhong S-X, Erhardtsen E, et al. Safety and hemostatic effect of recombinant activated factor VII in cirrhotic patients undergoing partial hepatectomy: a multicenter, randomized, double-blind, placebo-controlled trial. Am J Surg 2006;191(2):245–9.
[204] Planinsic RM, van der Meer J, Testa G, Grande L, Candela A, Porte RJ, et al. Safety and efficacy of a single bolus administration of recombinant factor VIIa in liver transplantation due to chronic liver disease. Liver Transpl 2005;11(8):895–900.
[205] Chavez-Tapia NC, Alfaro-Lara R, Tellez-Avila F, Barrientos-Gutiérrez T, González-Chon O, Mendez-Sanchez N, et al. Prophylactic activated recombinant factor VII in liver resection and liver transplantation: systematic review and meta-analysis. PLoS ONE 2011;6(7):e22581.
[206] Potze W, Adelmeijer J, Porte RJ, Lisman T. Preserved clot formation detected by the Thrombodynamics analyzer in patients with cirrhosis. Thromb Res 2015;135(5):1012–6.
[207] Tripodi A, Primignani M, Chantarangkul V, Dell'Era A, Clerici M, de Franchis R, et al. An imbalance of pro- versus anti-coagulation factors in plasma from patients with cirrhosis. Gastroenterology 2009;137(6):2105–11.
[208] Tripodi A, Primignani M, Lemma L, Chantarangkul V, Dell'Era A, Iannuzzi F, et al. Detection of the imbalance of procoagulant versus anticoagulant factors in cirrhosis by a simple laboratory method. Hepatology 2010;52(1):249–55.
[209] Søgaard KK, Horváth-Puhó E, Grønbaek H, Jepsen P, Vilstrup H, Sørensen HT. Risk of venous thromboembolism in patients with liver disease: a nationwide population-based case-control study. Am J Gastroenterol 2009;104(1):96–101.
[210] Wu H, Nguyen GC. Liver cirrhosis is associated with venous thromboembolism among hospitalized patients in a nationwide US study. Clin Gastroenterol Hepatol 2010;8(9):800–5.
[211] Gómez Cuervo C, Bisbal Pardo O, Pérez-Jacoiste Asín MA. Efficacy and safety of the use of heparin as thromboprophylaxis in patients with liver cirrhosis: a systematic review and meta-analysis. Thromb Res 2013;132(4):414–9.
[212] Barclay SM, Jeffres MN, Nguyen K, Nguyen T. Evaluation of pharmacologic prophylaxis for venous thromboembolism in patients with chronic liver disease. Pharmacotherapy 2013;33(4):375–82.
[213] Shatzel J, Dulai PS, Harbin D, Cheung H, Reid TN, Kim J, et al. Safety and efficacy of pharmacological thromboprophylaxis for hospitalized patients with cirrhosis: a single-center retrospective cohort study. J Thromb Haemost 2015;13(7):1245–53.
[214] Reichert JA, Hlavinka PF, Stolzfus JC. Risk of hemorrhage in patients with chronic liver disease and coagulopathy receiving pharmacologic venous thromboembolism prophylaxis. Pharmacotherapy 2014;34(10):1043–9.
[215] Ahmed A, Kozek-Langenecker S, Mullier F, Pavord S, Hermans C, ESA VTE Guidelines Task Force. European guidelines on perioperative venous thromboembolism prophylaxis: patients with preexisting coagulation disorders and after severe perioperative bleeding. Eur J Anaesthesiol 2018;35(2):96–107.
[216] Afshari A, Ageno W, Ahmed A, Duranteau J, Faraoni D, Kozek-Langenecker S, et al. European Guidelines on perioperative venous thromboembolism prophylaxis: executive summary. Eur J Anaesthesiol 2018;35(2):77–83.
[217] Boone MD, Celi LA, Ho BG, Pencina M, Curry MP, Lior Y, et al. Model for End-Stage Liver Disease score predicts mortality in critically ill cirrhotic patients. J Crit Care 2014;29(5). 881.e7–13.
[218] McPhail MJW, Auzinger G, Bernal W, Wendon JA. Decisions on futility in patients with cirrhosis and organ failure. Hepatology 2016;64(3):986.
[219] Cardoso FS, Pereira R, Alexandrino G, Bagulho L. Futility of care in patients with acute-on-chronic liver failure. Hepatology 2017;66(1):292–4.
[220] Gustot T, Fernandez J, Garcia E, Morando F, Caraceni P, Alessandria C, et al. Clinical course of acute-on-chronic liver failure syndrome and effects on prognosis. Hepatology 2015;62(1):243–52.
[221] Linecker M, Krones T, Berg T, Niemann CU, Steadman RH, Dutkowski P, et al. Potentially inappropriate liver transplantation in the era of the 'sickest first' policy – A search for the upper limits. J Hepatol 2018;68(4):798–813.
[222] Kavli M, Strøm T, Carlsson M, Dahler-Eriksen B, Toft P. The outcome of critical illness in decompensated alcoholic liver cirrhosis. Acta Anaesthesiol Scand 2012;56(8):987–94.
[223] Karvellas CJ, Lescot T, Goldberg P, Sharpe MD, Ronco JJ, Renner EL, et al. Liver transplantation in the critically ill: a multicenter Canadian retrospective cohort study. Crit Care 2013;17(1):R28.
[224] Bittermann T, Makar G, Goldberg DS. Early post-transplant survival: interaction of MELD score and hospitalization status. J Hepatol 2015;63(3):601–8.
[225] Artru F, Louvet A, Ruiz I, Levesque E, Labreuche J, Ursic-Bedoya J, et al. Liver transplantation in the most severely ill cirrhotic patients: a multicenter study in acute-on-chronic liver failure grade 3. J Hepatol 2017;67(4):708–15.
[226] Finkenstedt A, Nachbaur K, Zoller H, Joannidis M, Pratschke J, Graziadei IW, et al. Acute-on-chronic liver failure: excellent outcomes after liver transplantation but high mortality on the wait list. Liver Transpl 2013;19(8):879–86.
[227] Levesque E, Winter A, Noorah Z, Daurès J-P, Landais P, Feray C, et al. Impact of acute-on-chronic liver failure on 90-day mortality following a first liver transplantation. Liver Int 2017;37(5):684–93.
[228] Michard B, Artzner T, Lebas B, Besch C, Guillot M, Faitot F, et al. Liver transplantation in critically ill patients: Preoperative predictive factors of post-transplant mortality to avoid futility. Clin Transplant 2017;31(12). http://dx.doi.org/10.1111/ctr.13115 [Epub 2017 Oct 31].
[229] Reddy KR, O'Leary JG, Kamath PS, Fallon MB, Biggins SW, Wong F, et al. High risk of delisting or death in liver transplant candidates following infections: Results from the North American Consortium for the Study of End-Stage Liver Disease. Liver Transpl 2015;21(7):881–8.
[230] Bañares R, Nevens F, Larsen FS, Jalan R, Albillos A, Dollinger M, et al. Extracorporeal albumin dialysis with the molecular adsorbent recirculating system in acute-on-chronic liver failure: the RELIEF trial. Hepatology 2013;57(3):1153–62.
[231] Kribben A, Gerken G, Haag S, Herget-Rosenthal S, Treichel U, Betz C, et al. Effects of fractionated plasma separation and adsorption on survival in patients with acute-on-chronic liver failure. Gastroenterology 2012;142(4). 782–789.e3.
[232] Gerth HU, Pohlen M, Thölking G, Pavenstädt H, Brand M, Hüsing-Kabar A, et al. Molecular adsorbent recirculating system can reduce short-term mortality among patients with acute-on-chronic liver failure – a retrospective analysis. Crit Care Med 2017;45(10):1616–24.
[233] Shen Y, Wang X-L, Wang B, Shao J-G, Liu Y-M, Qin Y, et al. Survival benefits with artificial liver support system for acute-on-chronic liver failure: a time series-based meta-analysis. Medicine (Baltimore) 2016;95(3):e2506.