Seminar

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Management of the critically ill patient with cirrhosis: A multidisciplinary perspective

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Introduction

The occurrence of complications in patients with cirrhosis such as jaundice, ascites, encephalopathy, infection, renal dysfunction or variceal bleeding requiring hospitalization alters the natural history of the disease with an increase in 5-year mortality as high as 40–50% [1]. A significant proportion of these patients with acute decompensation require management in the intensive care unit (ICU) with organ support and have a high rate of in-hospital mortality. This category of patients with cirrhosis, acute decom-

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Abbreviations: ICU, intensive care unit; ACLF, acute on chronic liver failure, CLIF, chronic liver failure organ failure; AST, American society of transplantation; ASTS, American society of transplant surgeons; EASL, European association for the study of the liver; AKI, acute kidney injury; Scr, serum creatinine; KDIGO, Kidney disease improving global outcomes; UO, urine output; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; MDRD-6, Modified Diet in Renal Disease 6; ADQI, acute dialysis quality initiative; ICA, international club of ascites, AKIN, acute kidney injury network; HRS, hepatorenal syndrome; CKD, chronic kidney disease, RRT, renal replacement therapy; ATN, acute tubular necrosis; CRRT, continuous renal replacement therapy; PAC, pulmonary artery catheter; ScvO2, venous oxygen saturation; SVV, stroke volume variation; PPV, pulse pressure variation; StO_2, tissue oxygen saturation; HES, hydroxyethyl starch; SBP, spontaneous bacterial peritonitis; GIB, gastrointestinal bleed; TMP-SMX, trimethoprim/sulfamethoxazole; CRP, c-reactive protein; MALDI-TOF, matrix-assisted laser desorption/ionization time-of-flight; BAL, bronchial lavage; FFP, fresh frozen plazma, INR, internationalized ratio; PT, prothrombin time; PCC, prothrombin complex concentrates; HE, hepatic encephalopathy; EEG, electroencephalogram; WHC, west-haven criteria; CHESS, clinical HE staging scale (CHESS); HESA, HE scoring algorithm; MO-log, modified orientation log; GCS, Glasgow coma scale; PEG, polyethylene glycol (PEG); LOLA, L-ornithine L-aspartate.

pensation and organ failure has been recently classified by a consensus conference as having acute on chronic liver failure (ACLF) [2]. Diagnosis of ACLF is made using the Chronic Liver Failure Organ Failure (CLIF) score (Table 1) and its prognosis is determined using the CLIF-ACLF score (www.clifconsortium.com, ACLF calculator). ACLF occurs in approximately 30% of hospitalized cirrhotic patients who present with a complication following an identified or unidentified precipitating event, is characterized by hepatic and/or extrahepatic organ failures, and is associated with a 28-day mortality rate 15 times higher than patients without ACLF [2,3]. In the U.S. each year, approximately 200,000 patients with cirrhosis are hospitalized of which approximately 10% require ICU care [3]. The cost of providing healthcare to these patients amounts to about $13 billion per year [4].

ACLF is a newly recognized and complex condition in which the host response to injury and the type and number of organ failures all play important roles in determining the prognosis of the patient [2,3]. At present, the most effective management of patients with ACLF is unclear because of paucity of clinical trial data and the lack of evidence-based guidance. The occurrence of ACLF increases the mortality risk, but the prognosis might be improved by optimal ICU management involving multiple disciplines, including hepatology, critical care, nephrology, infectious disease and transplant surgery. It is with this in mind that a Consensus meeting, endorsed by the American Society of Transplantation (AST), American Society of Transplant Surgeons (ASTS) and the European Association for the Study of the Liver (EASL), was organized whereby a group of invited experts in the field of liver transplantation reviewed the current knowledge of diagnostic approaches and treatment strategies that currently exist in the critical care management of patients with ACLF who are awaiting liver transplantation. The goal was to develop a consensus of opinions, based on best available evidence, on optimal practices and to articulate a research agenda to focus on important unanswered questions.

Methods

Prior to the conference, the organizing committee identified topics relevant to the management of patients with ACLF. A diverse international panel representing multiple relevant disciplines (nephrology, hepatology, transplant surgery, critical care/anesthesiology and infectious disease), from a variety of countries and scientific societies based on their expertise in this topic were assembled. Panelists were assigned to five person working groups, with each work group addressing one key topic. Prior to the conference, each group identified a list of key questions, conducted a systematic literature search and generated a bibliography of key studies. We then conducted a two and a half day conference, whereby work groups assembled in breakout sessions, as well as in plenary sessions where their findings were presented, debated and refined. A series of summary statements was then developed during the breakout sessions and presented to the entire group, revising each statement as needed until a final version was agreed upon by all members of the Consensus meeting.

Each work group conducted literature searches related to their topic questions via MEDLINE, PubMed, and the bibliographies of all articles that met the search criteria. The majority of the work group resources were devoted to the reviewing of randomized trials, as these were deemed to be the most likely to provide data to support level 1 recommendations with high quality evidence. The quality of the overall evidence and the strength of recommendations were graded using the Grading of Recommendations Assessment, Development and Evaluation system (Supplementary Table 1) [5]. Recommendations were "not graded" if they were not based on systematic evidence and used to provide guidance where the topic did not allow adequate application of evidence.

Table 1. Chronic Liver Failure (CLIF) Consortium Organ Failure Score. (www.clifconsortium.com).

Organ system	Score = 1	Score = 2	Score = 3
Liver, bilirubin (mg/dl)	<6	6-≤12	>12
Kidney, creatinine (mg/dl)	<2	2-<3.5	≥3.5 or renal replacement therapy
Brain, grade (West-Haven)	0	1-2	3-4
Coagulation, INR	<2	2-<2.5	≥2.5
Circulation, MAP (mmHg)	≥70	<70	Vasopressors
Respiratory PaO_2/FiO_2 or SpO_2/FiO_2	>300 >358	≤300 and >200 >214 and ≤357	≤200 ≤214

MAP, mean arterial pressure; FiO_2, fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen; SpO_2, pulse oximetric saturation.

Renal dysfunction

Acute kidney injury (AKI) occurs in up to 50% of patients admitted with cirrhosis and represents one of the criteria that define ACLF [6–9]. This increased risk of AKI is due to the combination of an impaired effective arterial blood volume secondary to arterial vasodilation, with increased intra-renal vasoconstriction and impaired renal autoregulation. Factors such as bacterial infections and gastrointestinal bleeding (GIB) that further impair circulatory status and reduce renal perfusion can precipitate AKI [10–12]. The development of AKI not only increases the risk of mortality, but also reduces kidney function in the long-term following liver transplantation [13–17].

Defining and classifying renal dysfunction

Recommendations

1. *We recommend that serum creatinine (Scr) values be interpreted with caution in cirrhotic patients especially those with ascites and fluid due to an overestimation of values (**1A**).*
2. *Diagnose and stage AKI in patients with liver disease guided by Kidney Disease Improving Global Outcomes (KDIGO), Scr and urine output (UO) criteria (**Ungraded**).*
3. *Use a value of Scr obtained in the previous 3 months as baseline Scr. In patients with more than one value within the previous 3 months, the value closest to the hospital admission when the patient was stable can be used as the baseline. In patients without a baseline Scr value, the admission Scr should be used as the reference Scr (**Ungraded**).*
4. *We do not recommend the use of estimated glomerular filtration rate (eGFR) equations for assessing renal function in patients with AKI (**1D**).*

Rationale. In the setting of cirrhosis, Scr tends to overestimate renal function due to decreased creatinine production by the

Table 2. Definition and staging of acute kidney injury.

	AKI definition	AKI stage Serum creatinine criteria			AKI stage Urine output criteria		
		1	2	3	1	2	3
AKIN (2007) [36]	Increase Scr ≥0.3 mg/dl (26.5 μmol/L) within 48 h; or increase Scr ≥1.5 x baseline within 48 h; or UO <0.5 ml/kg/h x 6 h Baseline Scr is first Scr measured	Increase ≥0.3 mg/dl (>26.5 μmol/L) within 48 h or ≥1.5-2 x baseline	Increase 2-3 x baseline	Increase 3 x baseline or Scr >4 mg/dl (>354 μmol/L) with an acute rise >0.5 mg/dl (44 μmol/L) or on RRT	<0.5 ml/kg/h x 6-12 h	<0.5 ml/kg/h x 12 h	<0.3 ml/kg/h x 24 h or anuria x 12 h
KDIGO (2012)[37]	Increase Scr ≥0.3 mg/dl (26.5 μmol/L) within 48 h; or increase Scr ≥1.5 x baseline, which is known or presumed to have occurred within the prior 7 days; or UO <0.5 ml/kg/h for 6 h Unknown baseline Scr estimation based on the MDRD formula, assuming a normal GFR of approximately 75 to 100 ml/min/1.73 m^2	Increase ≥0.3 mg/dl (>26.5 μmol/L) within 48 h or ≥1.5-2 x baseline	Increase 2-3 x baseline	Increase 3 x baseline or Scr >4 mg/dl (>354 μmol/L) with an acute rise >0.5 mg/dl (44 μmol/L) or on RRT	<0.5 ml/kg/h x 6-12 h	<0.5 ml/kg/h x 12 h	<0.3 ml/kg/h x 24 h or anuria x 12 h
ADQI (2010) [30] AKI in cirrhosis	Increase Scr ≥0.3 mg/dl (26.5 μmol/L) within 48 h; or increase Scr ≥1.5 x baseline HRS-1 is a specific form of AKI	Increase ≥0.3 mg/dl (>26.5 μmol/L) within 48 h or ≥1.5-2 x baseline	Increase 2-3 x baseline	Increase 3 x baseline or Scr >4 mg/dl (>354 μmol/L) with an acute rise >0.5 mg/dl (44 μmol/L) or on RRT	-	-	-
ICA (2015) [38] AKI in Cirrhosis	Increase Scr ≥0.3 mg/dl (≥26.5 μmol/L) within 48 h; or increase Scr ≥50% from baseline which is known, or presumed to have occurred within 7 days prior. Scr within 3 months can be used as baseline. In patients with more than one Scr value, value closest to hospital admission should be used. In patients without previous Scr, Scr on admission should be used	Increase ≥0.3 mg/dl (>26.5 μmol/L) within 48 h or ≥1.5-2 x baseline	Increase 2-3 x baseline	Increase 3 x baseline or Scr >4 mg/dl (>354 μmol/L) with an acute rise >0.5 mg/dl (44 μmol/L) or on RRT	-	-	-

AKI, acute kidney injury; Scr, serum creatinine; RRT, renal replacement therapy; AKIN, acute kidney injury network; KDIGO, Kidney Disease Improving Global Outcomes; ADQI, Acute Dialysis Quality Initiative; ICA, International Club of Ascites.

liver, protein calorie malnutrition, muscle wasting, reduced physical activity and enlarged volume of distribution in the setting of fluid overload [18]. In addition, in the setting of AKI, Scr can lag by several hours to days despite a decrease in GFR especially in the setting of fluid overload [19,20]. Serum cystatin C has not been shown to be superior to Scr in patients with cirrhosis [18,21,22]. Exogenous clearance markers such as inulin and iothalamate, are confounded by changes in volume of distribution, due to ascites and extracellular volume expansion. Among creatinine-based equations, it has been shown that the Modified Diet in Renal Disease 6 (MDRD-6) is the most accurate in cirrhosis [23–25]. Equations based on cystatin C, with or without Scr (i.e., CKD-EPI creatinine-cystatin C equation) may be superior to creatinine-based equation [26,27], however all equations tend to overestimate the true GFR and have been developed in study populations consisting of patients with chronic kidney disease (CKD) with stable Scr [28,29].

In 2010, the Acute Dialysis Quality Initiative (ADQI) and the International Club of Ascites (ICA) proposed an adaptation of the Acute Kidney Injury Network (AKIN) criteria to define AKI in patients with cirrhosis, which has been validated in several studies of hospitalized patients with cirrhosis [6–8,30–35]. These criteria were irrespective of whether the presumed cause of AKI was related to a functional or structural disorder. As such, type 1 hepatorenal syndrome (HRS) was categorized as a specific type of AKI [6–8,32–35]. The current definitions of AKI depend on absolute or relative changes in Scr and UO (Table 2) [30,36–38]. UO has been found to be a sensitive and early marker for AKI in ICU patients and to be associated with adverse outcomes [39–41]. Although the severity of oliguria in the diagnosis of AKI has yet to be validated in patients with cirrhosis, worsening oliguria or development of anuria should be considered as AKI until proven otherwise, regardless of any rise in Scr (Fig. 1).

There remains some debate as to the most appropriate reference to use for Scr to diagnose and stage AKI [38,42–44]. The ICA recently suggested that a baseline Scr result within the previous 3 months should be used as the reference, if available, or if no baseline exists, then the admission Scr can be used as the reference [38]. Note that sometimes the reference Scr will only become apparent after renal function recovers. These patients have a bet-

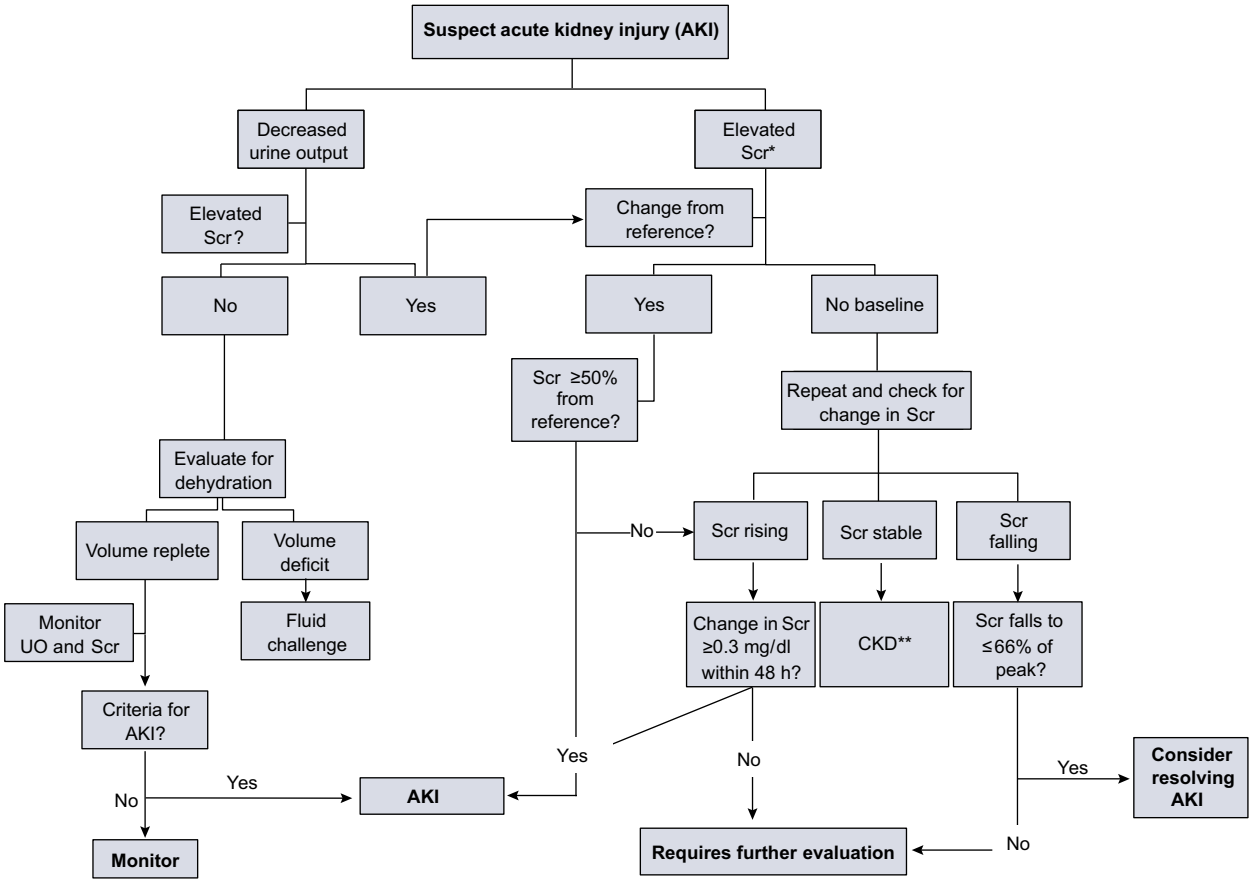

Fig. 1. Diagnostic algorithm to evaluate acute kidney injury in the hospitalized patient with decompensated cirrhosis. AKI, acute kidney injury; Scr, serum creatinine; UO, urine output; CKD, chronic kidney disease; RRT, renal replacement therapy; Na, sodium. *Fluid overload may mask serum creatinine increases. **CKD based on 6-variable MDRD equation eGFR <60 ml/min.

ter prognosis compared to those who do not recover renal function but still are at an increased risk for CKD or death or over the ensuing months to years [38].

Evaluation and management of AKI

Recommendations

1. *We recommend replacement of isotonic crystalloids in cases of volume loss due to diarrhea or over diuresis (**1D**), blood in cases of acute gastrointestinal hemorrhage (**1D**), and 20–25% albumin for infections (**1A**), suspected type-1 HRS (**1A**) or in cases where the cause of AKI is unclear (**1D**).*
2. *We recommend to start treatment with vasoconstrictors and 25% albumin (1 g/kg day 1 followed by 20–40 g/day) either when patients meet the ICA criteria of type-1 HRS (**1A**), or when there are evident signs of AKI progression as judged by a rapid increase in Scr when other causes of AKI have been ruled out (Fig. 2) (**Ungraded**).*
3. *In patients with type-1 HRS responding to vasoconstrictors and albumin with a decrease in Scr during the first days we recommend discontinuing treatment when Scr level has reached or is close to baseline. If baseline Scr is unknown, we recommend discontinuing treatment when Scr does not decrease further after 3 days of treatment. In non-responders, we recommend vasoconstrictors and albumin be stopped after a maximum of 7 days (**1D**).*
4. *We recommend that in patients with evidence of worsening AKI, worsening fluid overload with >10% total body weight despite diuretic therapy or worsening acid-base status then renal replacement therapy (RRT) should be initiated (**1D**).*

Rationale. AKI should be suspected in the presence of increased Scr or decreased UO (Fig. 1). The diagnosis of type-1 HRS is particularly important since early initiation of treatment increases the likelihood of HRS resolution and may improve survival [45]. An important step in the differential diagnosis of kidney dysfunction is to exclude parenchymal kidney disease as a cause of AKI or AKI on a background of CKD (Supplementary Fig. 1).

Plasma volume expansion is an important step not only in the treatment but also in the differential diagnosis of the cause of AKI and the type of fluid needed for resuscitation should be tailored based on the etiology of AKI (Supplementary Fig. 1). It is important to emphasize that patients with cirrhosis and AKI have reduced renal sodium and water excretion. Therefore, caution should be used with the administration of crystalloids to avoid

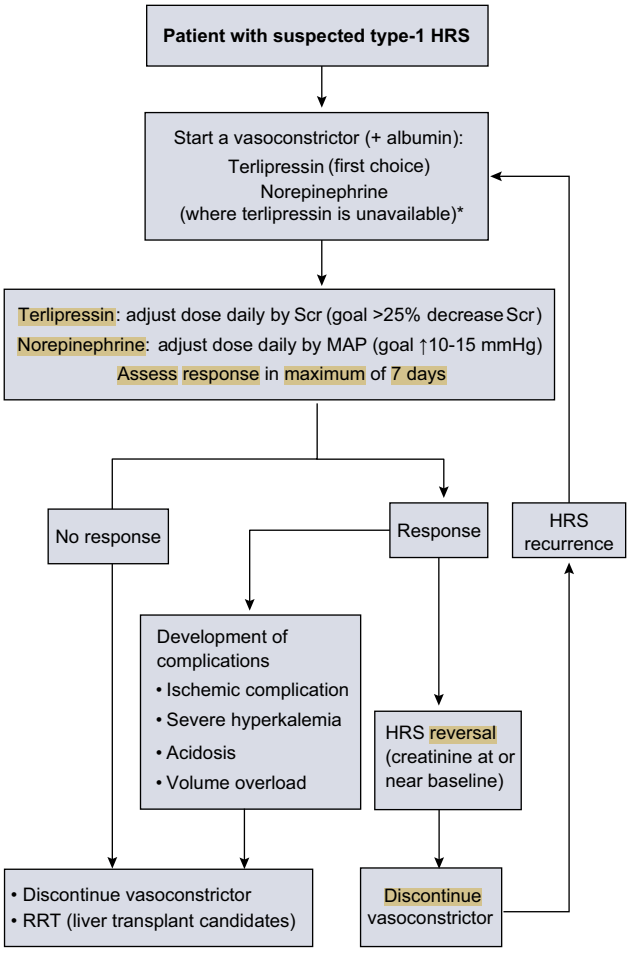

Fig. 2. Algorithm for patients with suspected type-1 HRS. HRS, hepatorenal syndrome; RRT, renal replacement therapy. *A trial of octreotide & midodrine (maximum 3 days) can be attempted prior to the initiation of norepinephrine.

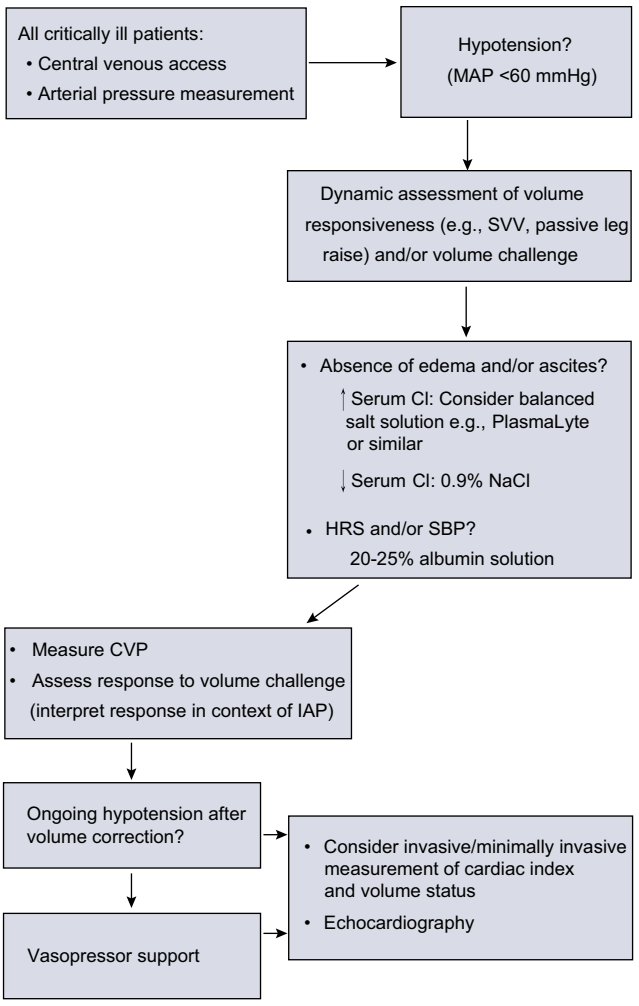

Fig. 3. Assessment and management of abnormal cardiovascular function in critically ill cirrhotic patients in shock. MAP, mean arterial pressure; CVP central venous pressure; Cl, chloride; NaCl, sodium chloride; HRS, hepatorenal syndrome; SBP, spontaneous bacterial peritonitis; IAP, intra-abdominal pressure; SVV, stroke volume variation.

development of significant fluid retention and edema. If kidney function does not improve despite a trial of plasma expansion, type-1 HRS is the most likely diagnosis but still needs to be distinguished from acute tubular necrosis (ATN). Several recent studies have shown that urine biomarkers, such as neutrophil gelatinase-associated lipocalin, interleukin-18, kidney injury molecule-1, in addition to urine microalbuminuria or fractional excretion of sodium, may be helpful in not only diagnosing AKI earlier but also shedding light on the etiology of AKI (HRS *vs.* ATN), and potentially help identify patients who are less likely to benefit from volume resuscitation and vasopressor therapy [32,46–51].

Type-1 HRS treatment. Patients in whom other causes of AKI have been ruled out should receive treatment for type-1 HRS with vasoconstrictors (Supplementary Table 2), which in conjunction with albumin, constitutes the main therapy for type-1 HRS (Fig. 2) [45]. Until now, vasoconstrictors have been typically initiated only when Scr reaches a threshold level of >2.5 mg/dl, however, type-1 HRS reversal and survival rates may improve with earlier institution of vasoconstrictor therapy [52]. Countries where terlipressin is not available, the combination of octreotide/midodrine can be initiated, and if there is no decline in Scr within a maximum of 3 days then the patient should be transferred to the ICU for a trial of norepinephrine [53,54]. All patients receiving vasoconstrictors should be monitored for ischemic and cardiovascular complications. Vasoconstrictors are not recommended in patients with pre-existing ischemic heart disease, cerebrovascular disease, peripheral arterial disease, hypertension or asthma.

Renal replacement therapy. The initiation of RRT should be made on clinical grounds, including volume overload, metabolic acidosis, hyperkalemia and hyponatremia not responding to medical management, and diuretic intolerance/resistance. RRT should be considered even in nonoliguric patients if the daily fluid balance cannot be maintained as even or negative (Supplementary Fig. 2). Continuous renal replacement therapy (CRRT) allows the option of adjusting dialysate and replacement solution flow rates or composition to allow for the slower correction of serum sodium in patients with hyponatremia and provides greater cardiovascular stability compared to standard intermittent hemodialysis [55,56].

Seminar

Table 3. Methods to assess volume status in patients with cirrhosis and their limitations.

Methods	Possible limitations
Clinical	
Weight changes	Biased by ascites and edema
Arterial pressure	Lower in average during cirrhosis
Pulse	Lower in patients receiving beta blockers
Physical examination	Possible edema at baseline
Urine output	Lower in patients with renal vasoconstriction (HRS)
Chest radiogram	Abnormalities due to ascites/pleural effusion
Clinical history (recent diuretic use, diarrhea, etc.)	
Laboratory variables	
Blood lactate	Decreased blood lactate clearance
Central/mixed venous oxygen saturation	Not validated in cirrhosis
Urinary biochemistry	Decreased sodium excretion in patients with activation of the renin-angiotensin-aldosterone system
Static hemodynamic variables	
Central venous pressure	Invasive. Poor correlation with fluid responsiveness
Pulmonary artery measurements	Invasive
Echocardiographic variables	Single measurement. Not useful for continuous monitoring
Dynamic hemodynamic variables	
Passive leg raising	Unreliable in setting of intrabdominal hypertension
Stroke volume/pulse pressure variations	Not validated in cirrhosis
Pulmonary artery occlusive pressure	Invasive
Vena cava diameter	Not accurate in setting of ascites. Not validated in cirrhosis

Cardio-pulmonary dysfunction

Circulatory changes in cirrhotic patients are characterized by increased cardiac output, peripheral vasodilatation, decreased systemic vascular resistance (SVR) and decreased oxygen extraction. Circulatory failure in cirrhotic patients with ACLF is distributive in nature and characterized by a greater decrease in arterial pressure associated with signs of impaired tissue perfusion. Marked splanchnic vasodilatation results in a state of effective hypovolemia with water and sodium retention [11]. The activation of the renin-angiotensin system and other vasoconstriction systems results in renal vasoconstriction. This leads to impaired renal function, which can be further exacerbated by abdominal compartment syndrome in patients with tense ascites. Circulatory shock leads to further deterioration in liver function in patients with cirrhosis and contributes significantly to prognosis [57,58].

Goals of resuscitation

Recommendations

1. *Achieve a mean arterial pressure that ensures organ perfusion (**ungraded**). We recommend individualizing the mean arterial pressure goal; in a cirrhotic patient in shock, a mean arterial pressure ⩾60 mmHg is usually appropriate (**1D**).*
2. *We do not suggest the use of a specific goal for blood lactate or venous oxygen saturation ($ScvO_2$) during fluid resuscitation (**2C**).*
3. *We recommend therapeutic paracentesis in patients with tense ascites (**1A**).*
4. *We recommend careful attention and monitoring of patients, preferably with a pulmonary artery catheter (PAC) or echocardiography, during fluid resuscitation to avoid development of fluid overload (**1D**).*

Rationale. In septic shock, the first goal is to achieve a mean arterial pressure of 60 mmHg or more [59]. No specific target for ventricular filling pressure, or volume, lactate, $ScvO_2$, can be recommended [60]. Trends are more informative than absolute values. A growing body of evidence suggests that over-zealous fluid administration with increases in tissue edema and total body water may lead to organ dysfunction and poor outcomes and thus, careful attention to fluid resuscitation is mandatory [61–65]. Cirrhotic patients are particularly susceptible to the development of extracellular edema, ascites and pulmonary edema with aggressive fluid administration. Increased edema formation and ascites can worsen intra-abdominal hypertension with resultant intra-abdominal compartment syndrome with decreases in respiratory compliance and impaired renal and cardiac function [66]. Systematic measurement of intra-abdominal pressure is not recommended in patients with ascites however, in critically ill cirrhotic patients with tense ascites and clinical suspicion of abdominal hypertension, therapeutic paracentesis is recommended with albumin replacement as described below.

Monitoring of circulatory status

Recommendations

1. *We recommend placement of arterial catheters to guide therapy patients with circulatory shock receiving ongoing resuscitation (**1D**).*
2. *We recommend ensuring adequate venous access for fluids in patients with circulatory shock receiving ongoing resuscitation (**1D**); this will often require central venous access.*
3. *We recommend the use of echocardiography as a first line option for initial evaluation of circulatory failure (**1C**).*
4. *We recommend repeated measurements of blood lactate levels even though the interpretation may be complicated by the impaired clearance in cirrhosis (**1A**).*
5. *We suggest the use of pulmonary artery catheter (PAC) for monitoring in patients with respiratory failure and/or persistent hemodynamic instability (**2D**).*

Rationale. In patients with circulatory shock, central venous and arterial lines should be routinely inserted (Fig. 3). Detailed hemodynamic monitoring may be needed, thus the first objective is to characterize the type of shock even though distributive shock is by far the most common pattern. Thereafter, secondary objectives are to assess myocardial function, to ensure venous return is adequate, vascular tone is restored, tissue oxygenation is optimized and to evaluate response to therapy [60].

The complex circulatory alterations in cirrhosis, especially patients with ACLF, complicate assessment of hemodynamics. Minimally invasive methods of assessing hemodynamic parame-

Table 4. Considerations for management and relisting patients for liver transplantation after common bacterial and fungal infections.

Infection	Characteristics	Recommendations
Urine	Asymptomatic bacteriuria	Not a contraindication; antibiotic therapy peri-transplant (**1D**)
	Asymptomatic candiduria	Not a contraindication (**1D**)
	UTI with negative blood cultures	Not a contraindication; antibiotic treatment peri-transplant (**1D**)
SBP	Bacterial SBP*	5 days of treatment (**1B**) Reactivate if repeat tap shows a >25% decrease in PMN count ≥48 hours after treatment initiation (**2D**) and other clinical parameters document improvement
	Fungal SBP	Requires a full course of therapy and a PMN count <250 cells/mm^3 off treatment. Always rule out secondary cause (**2D**)**
Pneumonia	Pneumonia	Reactivate floor patients after ≥7 days of therapy when clinical improvement is documented (**1D**)
		Imaging lags behind clinical improvement; is needed only in patients without clinical improvement (**2D**)
		Patients on ventilator may benefit from a tracheal aspirate to guide treatment (**2D**)
		ICU patients: clinical improvement is required to achieve oxygen levels above local standards (**2D**)
		Pleural effusion requires a thoracentesis. Parapneumonic effusion requires no additional intervention (**1D**)
		Empyema requires drainage; complete course of antibiotics, VATS is sometimes required (**2D**)
Bacteremia	Central Line	Follow infectious disease guidelines [118] (Supplementary Fig. 3)
	Spontaneous	Antibiotics for 7-14 days (**1C**) Likely source: bacterial translocation or skin. Reactivation can be considered before completion of antibiotics if patient has documented rapid clinical improvement with negative repeat blood cultures for ≥48 hours (**2D**)
	Fungemia	Completion of a course of treatment with repeat negative blood cultures off therapy is required in addition to exclusion of a secondary source (**2D**)
C. Difficile	Diarrhea and repeat *C. difficile* toxin and PCR are not good assessment tools	Therapy for at least 7 days is required, in addition to clinical improvement and normalization of WBC prior to reactivation. When uncertain, a flex sig can be performed to assess mucosal healing (**2D**)
		Consider fidaxomicin therapy as initial therapy to decrease relapse rate (**1B**) and VRE colonization (**2D**)
Cholecystitis	Operative candidates	Surgical intervention (**1A**)
	Non-operative candidates	IV antibiotics are first line therapy (**1D**). C-tube placement should be considered in those without a clinical response. Endoscopic gallbladder stenting or aspiration should only be considered when C-tube placement is absolutely contraindication and IV antibiotics are failing. Transplant reactivation should occur after an adequate clinical response (**2D**)

*Spontaneous bacterial infection of pleural fluid (spontaneous bacterial empyema) should be treated as SBP unless loculated (Level D1).
**Fungi rarely cause a SBP. A secondary peritonitis is very likely when at least two of the following parameters are present in ascites: glucose levels <50 mg/dl, protein concentration >10 g/L, LDH concentration >normal serum levels (Runyon's criteria). Patients with gastrointestinal perforation also present high levels of amylase and bilirubin in ascitic fluid. Prompt abdominal CT must be performed to exclude secondary peritonitis.
UTI, urinary tract infection; SBP, spontaneous bacterial peritonitis; PMN, polymorphonuclear; VATS, video-assisted thoracic surgery; ICU, intensive care unit; PCR, polymerase chain reaction; WBC, white blood cell count; VRE, vancomycin-resistant enterococci.

ters such as stroke volume variation (SVV) and pulse pressure variation (PPV) have gained popularity in the ICU, however in patients who are spontaneously breathing, these methods have limited utility (Table 3) [67,68]. Such monitors have failed to demonstrate acceptable accuracy in cirrhotic patients undergoing liver transplantation, which further questions their role in the ICU [69].

Dynamic assessments of circulatory function including echocardiography are superior to static measures [70]. Changes in central venous pressure (CVP) in response to volume challenge is more instructive than a single measurement and, when properly applied, passive leg raise may be used to assess volume responsiveness [68]. Increased intra-abdominal pressure may result in increased CVP without improving cardiac preload. In patients with suspected right ventricular dysfunction or in patients with pulmonary hypertension, a PAC may be indicated to guide resuscitation. PAC may also be useful in the management of complex cases in which fluid management is critical such as patients with respiratory failure or when clinical or radiologic findings do not allow differentiation of high pressure *vs.* low pressure pulmonary edema and pulmonary infection.

Indirect markers of circulatory/tissue oxygenation status should be interpreted with caution in the context of cirrhosis; the levels in circulatory failure are higher in patients with cirrhosis as compared to patients without cirrhosis due to impaired liver function resulting in decreased lactate clearance [71]. Thus, trends in serum lactate may be more informative than absolute values. A substantial part of fluid administered goes to the splanchnic circulation without restoring central effective volume. Worsening of tissue oxygen saturation (StO_2), measured by near

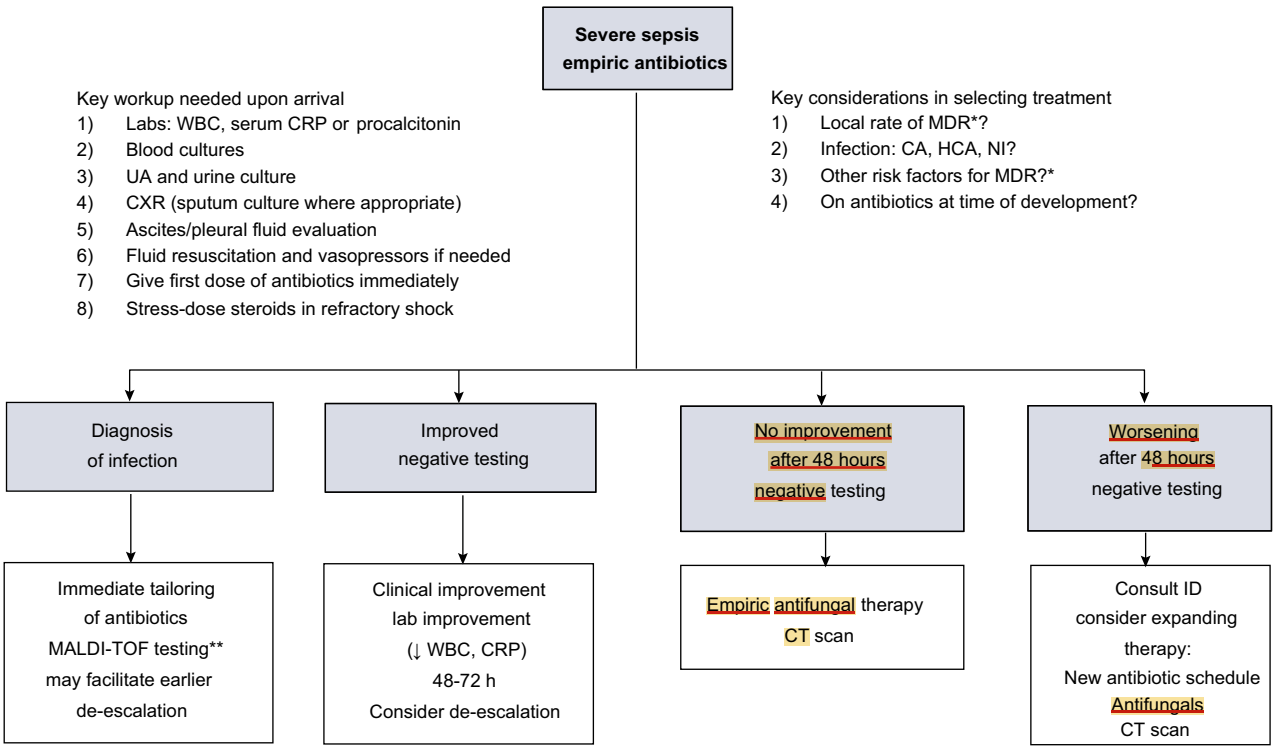

Fig. 4. Algorithm for workup of patients with severe sepsis. *Risk factors for MDR: long-term SBP prophylaxis, recent use of beta-lactams (last 3 months), infection by MDR bacteria in the last 6 months. **MALDI-TOF testing is not commercially available in the U.S. at this time, but once available will likely be incorporated into routine culture analysis. WBC, white blood cell count; CRP, C-reactive protein; UA, urine analysis; CXR, chest x-ray; MDR, multi-drug resistant; CA, community acquired; HCA, healthcare associated; NI, nosocomial infection; MALDI-TOF, matrix-assisted laser desorption ionization time-of-flight; ID, infectious disease.

infrared spectroscopy, was recently shown to be associated with a poor prognosis in patients with cirrhosis [72]. Whether StO_2 as well as $ScvO_2$ could be useful for monitoring is unknown.

Choice of fluid therapy

Recommendations

1. *We recommend use of crystalloid solutions as the initial fluid of choice in volume depleted patients (10–20 ml/kg) (**1C**).*
2. *We recommend use of albumin (8 g/L of ascites removed) following large volume paracentesis (>5 L) (**1B**).*
3. *We recommend patients with spontaneous bacterial peritonitis (SBP) should receive concentrated albumin (1.5 g/kg on day one followed by 1 g/kg on day 3) (**1B**).*
4. *We suggest that in patients with suspected bacterial infection fluid resuscitation with crystalloids and a proportion of 4–5% albumin may be an option (**2D**).*
5. *We recommend against the use of hydroxyethyl starch (HES) (**1B**).*

Rationale. In volume depleted patients with distributive shock, crystalloids (normal 0.9% saline) are recommended at an initial dose of 10–20 ml/kg [73]. However, balanced salt solutions (such as PlasmaLyte®) may be preferred to than normal saline in patients with hyperchloremic acidosis [74] and in patients with relative hyperchloremia (e.g. those with "normal" chloride in the setting of low serum sodium). In patients with evidence of fluid overload (tense ascites, generalized edema, CVP >12 mmHg) fluid administration should be discontinued.

There are theoretical benefits to the use of albumin in patients with cirrhosis beyond simple volume expansion based on its numerous biological properties [75]. Patients with cirrhosis should receive albumin in three specific situations: SBP, large volume paracentesis and type-1 HRS [76]. A randomized controlled trial has shown that in patients with SBP, antibiotics plus albumin are superior to antibiotics alone in prevention of the occurrence of type-1 HRS [45,77]. Albumin is also recommended in patients with large volume paracentesis as it is superior to crystalloids in preventing post-paracentesis circulatory dysfunction [78–80]. In cirrhotic patients with infections other than SBP, two controlled trials showed that the administration of albumin in combination with antibiotics did not improve survival, however the incidence of AKI was significantly lower with albumin [81,82].

HES solutions may have harmful effects in patients with sepsis and should be avoided due to potential nephrotoxicity [83,84].

Pharmacological management of persistent shock

Recommendations

1. *We recommend the use of norepinephrine as the first line vasopressor agent (**1A**). Vasopressin or terlipressin are appropriate second line agents for persistent hypotension (**1B**).*

2. *A trial of hydrocortisone 200–300 mg/day in divided doses in patients with refractory hypotension should be started and stopped following improvement in hemodynamics (**1C**).*

Rationale. Norepinephrine is the first line agent as it is associated with fewer adverse events [85]. Vasopressin or terlipressin may be used as second line agents and have demonstrated improvements in hemodynamics and norepinephrine sparing in patients with cirrhosis [53,86–89].

Adrenal insufficiency is common in critically ill patients with cirrhosis, however, it could also be a feature of liver disease *per se* and not simply related to critical illness [90–93]. So far, there has not been a consensus about the appropriate method for the precise adrenal insufficiency diagnosis in patients with cirrhosis. The use of corticosteroids in critically ill patients with cirrhosis has been associated with a significant reduction in vasopressor doses and a higher rate of shock reversal [94–96]. Survival benefit however, was demonstrated in some [91,95] but not all studies [94,96]. In patients with increasing vasopressor requirements, hydrocortisone 200–300 mg/day in divided doses should be administered [93,97].

Prevention and management of infections

Patients with advanced cirrhosis are at an increased risk for bacterial and fungal infections because of several key factors: 1) dysbiosis (i.e. alterations of the gut microbiome); 2) small intestinal bacterial overgrowth; 3) increased bacterial translocation; 4) immunocompromised state; and 5) increased rate of resistant organism colonization [2,10,98–103]. Once infection occurs and leads to ACLF [10,23], the compensatory anti-inflammatory response increases the risk for subsequent infections with further worsening in prognosis [3,104]. Following an episode of infection, the decision to reactivate a patient for transplant should balance the benefit of transplant with the risk of post-operative infectious complications (Table 4).

Antibiotic prophylaxis
Following gastrointestinal bleeding

Recommendations

1. *We recommend immediate antibiotic prophylaxis for 7 days following GIB (**1A**), although the absolute benefit and required duration are not clear in patients with compensated cirrhosis after rapid control of bleeding (**2D**).*
2. *We recommend intravenous ceftriaxone for GIB prophylaxis in patients with severely decompensated cirrhosis with active bleeding who are on a quinolone at admission or have a history of quinolone resistant infection. Quinolones are recommended in the remaining patients (**1A**).*

Rationale. Following an episode of GIB, antibiotic prophylaxis is currently recommended [105] as it decreases the risk of infection, rebleeding, infection-related and all-cause mortality [106,107]. Most studies evaluated 7 days of antibiotic therapy, but in patients with rapid control of bleeding and less severe liver disease, shorter course therapy may be acceptable. Controversy remains regarding the necessity of antibiotic prophylaxis in compensated cirrhosis. When administering antibiotic prophylaxis after GIB, the majority of studies utilized norfloxacin 400 mg orally twice daily or ceftriaxone 1 g intravenously daily [106,108]. Oral ciprofloxacin has limited data on its efficacy, but would be the preferred alternative where norfloxacin is unavailable. In patients with more advanced liver disease with at least two of the following: ascites, hepatic encephalopathy (HE), jaundice, or severe malnutrition, superior results were achieved with intravenous ceftriaxone [95,109]. Intravenous ceftriaxone should also be considered in patients with active GIB, on a quinolone at admission, with a history of a quinolone resistant infection, or who live in regions with a high prevalence ($\geqslant$20%) of quinolone resistance.

Spontaneous bacterial peritonitis

Recommendations

1. *We recommend primary SBP prophylaxis only in patients with low protein ascites (<1.5 g/dl) and renal and/or liver impairment and secondary SBP prophylaxis in all patients (**1A**).*
2. *We recommend SBP prophylaxis with norfloxacin 400 mg daily. Ciprofloxacin 500 mg or trimethoprim/sulfamethoxazole (TMP-SMX) 160/800 mg daily can be used if norfloxacin is unavailable (**1A**).*
3. *We do not recommend weekly quinolones (**1C**), nor probiotics alone (**2C**) or in combination with antibiotics (**2D**) for SBP prophylaxis.*
4. *Resistant infections can occur in patients on SBP prophylaxis, after which the ideal antibiotic prophylactic strategy is not known (**2D**).*

Rationale. Current guidelines only recommend primary SBP prophylaxis in highly selected patients: ascitic fluid total protein <1.5 g/dl and renal impairment (Scr $\geqslant$1.2 mg/dl, BUN $\geqslant$25 mg/dl or serum Na $\leqslant$130 mEq/L) or Child-Pugh Turcotte $\geqslant$9 with serum bilirubin $\geqslant$3 mg/dl. A meta-analysis confirmed improved outcomes in patients receiving primary prophylaxis with a decrease in serious infections, SBP and mortality [110], however, development of resistant infections is the major concern with this approach.

When choosing an antibiotic for prophylaxis, norfloxacin 400 mg/day is the best studied [111–113]. In areas where norfloxacin is unavailable ciprofloxacin 500 mg or TMP-SMX 160/800 mg daily can be used [114]. Weekly quinolone therapy is not recommended because of inferior efficacy and increased risk of resistance. Limited data has not shown reduced risk of SBP with probiotic administration alone or in combination with antibiotics [115]. Since no clinical studies have been performed, SBP prophylaxis in patients with prior antibiotic-resistant bacteria is a critical area of research required.

Other antibiotic prophylactic strategies

Recommendations

1. *We suggest universal decontamination with intranasal mupirocin and chlorhexidine baths of ICU patients as part of a hospital wide plan to decrease bloodstream infections (**2B**).*
2. *We recommend antibiotic-impregnated catheters only when a comprehensive strategy to reduce the rate of central line associ-*

Seminar

*ated blood stream infections has failed and the line will remain >5 days (**1A**).*

Rationale. Universal decontamination of patients, using twice daily intranasal mupirocin and daily chlorhexidine baths, is associated with a statistically significant decrease in bloodstream infections [116]. While studies of this intervention included few cirrhotic patients, the results likely apply to this population.

The best approach to prevent catheter-associated infections is to avoid unnecessary catheterizations and to remove them when no longer necessary [117]. Foley catheters should only be inserted when clinically indicated to decrease the risk of bacteriuria (5–10%/day ⩾2 days after insertion) and infection. In patients with long-term indwelling catheters, antibiotic coated catheters could be considered, without definitive evidence that they reduce infections. However, use of antibiotic-impregnated catheters in those expected to remain >5 days could be recommended only if a comprehensive strategy to reduce the rate of central line associated blood stream infections has been implemented without success. Replacement of central lines in the absence of infection is not recommended [118].

Treatment of infectious complications

Recommendation

1. *We recommend that antibiotic therapy should be tailored to the specific pathogen once identified. If a pathogen is not identified, ongoing therapy and evaluation should be determined by the patient's clinical course (**1B**).*

Rationale. Discussing specific infection treatment algorithms is outside the scope of this manuscript [119]; however, since severe sepsis is a common complication of cirrhotic patients with acute decompensation [120], important diagnostic and management strategies are highlighted in Fig. 4. When working up a patient with suspected infection, inflammatory biomarkers such as serum C-reactive protein (CRP) or procalcitonin can be useful; one is not superior to the other (Supplementary Table 3) [121]. Serum CRP levels increase to a lesser extent during infection in patients with more advanced liver disease, but can still be used to identify infection and improvement.

Once severe sepsis is suspected, a thorough evaluation should be promptly followed by antibiotic administration, since each hour delay impairs outcome [122]. In patients with clinical improvement within 48–72 h and a known pathogen, immediate tailoring of antibiotics is recommended; matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) testing [123] in countries where it is commercially available (currently unavailable in the U.S.) may facilitate de-escalation. In patients without clinical improvement empiric antifungal therapy and CT scan should be considered [124].

Fungal infections

Recommendations

1. *We do not recommend treatment in patients with asymptomatic candiduria (**1D**).*
2. *We recommend antifungal therapy in intubated patients with yeast in sputum or bronchial lavages (BAL) with an additional positive fungal culture at another sterile site (**1B**).*
3. *We recommend antifungal therapy in ICU patients without clinical improvement after 48 h and in high prevalence (>5%) regions or with risk factors for development of invasive fungal infections (**1D**).*

Rationale. In addition to having an increased susceptibility to bacterial infections, patients with advanced liver disease are at a higher risk of fungal infections likely due to significant immunologic impairment, increased intestinal permeability, frequent use of corticosteroids, malnutrition and performance of invasive procedures [125,126].

In patients with multifocal candida colonization with clinical risk factors for infection but who remain in stable condition, preemptive therapy is not indicated. BAL candida isolation generally indicates colonization but not infection [127]. Initial therapy for candiduria should include Foley catheter removal or exchange. Although amphotericin bladder washes are generally not recommended, it may be useful for treatment of patients with refractory cystitis due to fluconazole-resistant candida species such as candida glabrata and krusei [128,129]. Antifungal therapy should be considered in patients with two positive cultures from different sites, isolated positive blood culture and in septic patients without improvement for 48 h (Fig. 4) [129]. As recommended in the general population, critically ill cirrhotic patients should receive echinocandins as first line therapy [129,130]. Azoles should be used during de-escalation after susceptibility has been confirmed.

Antifungal prophylaxis may be used in ICU patients without clinical improvement in high prevalence areas or in those with multiple risk factors for infection (corticosteroid use, prolonged microbial use, central venous catheter, total parenteral nutrition, high APACHE score, RRT, or malnutrition) [131].

Alterations in hemostasis

Patients with acute decompensation of cirrhosis, especially those with ACLF, are in a fragile continuum between ineffective hemostasis and excessive coagulation. Alterations in primary hemostasis, secondary hemostasis and fibrinolysis results in dis-

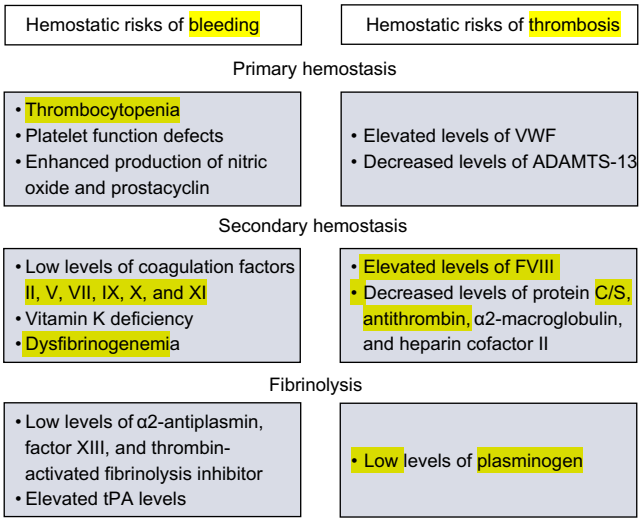

Fig. 5. Hemostasis balance in patients with liver disease. Modified from Lisman and Porte, blood 2010 [217].

turbance of this balance, which leads to either bleeding or thrombotic episodes (Fig. 5) [132–135]. Pathophysiological conditions of ACLF that may further disturb cirrhotic hemostatic imbalance include hemodynamic instability [133,136], endothelial dysfunction [133], development of endogenous heparin-like substances due to infection [133,136] and renal dysfunction [137].

Clinical and laboratory tests to assess the risk of bleeding and thrombosis

Recommendations

1. *INR does not provide an adequate assessment of hemostasis in cirrhosis (**2B**).*
2. *We recommend against routine prophylactic use of fresh frozen plasma (FFP) (**1B**).*
3. *We suggest maintaining platelet counts above 50×10^9/L in the presence of active bleeding (**2C**).*
4. *We recommend a hemoglobin transfusion trigger of 7 mg/dl (**1A**). Erythropoietin supplementation does not have a role in the absence of chronic kidney disease (**1B**).*
5. *Viscoelastic testing should be considered during liver transplantation and other major surgery (cardiac, major trauma). Its role in the ICU setting or prior to invasive procedures requires further evaluation (**2C**).*
6. *We suggest anticoagulation with unfractionated/low molecular weight heparin in patients with occlusive portal vein thrombosis in the absence of bleeding risk factors (**2C**).*

Rationale. *Internationalized ratio (INR)/prothrombin time (PT).* The INR is based on the PT which itself depends on the level of procoagulant factors I, II, V, VII, and X. It does not account for deficiencies of the anticoagulation system (especially low protein C), which may result in a hypercoagulable state not reflected in prolongation of the INR. Together with elevated endothelial-derived factor VIII, the low protein C causes thrombin generation to be normal or even high in cirrhosis [132]. Inter-laboratory variation in the INR in cirrhosis (due to absence of normalization of thromboplastins to a standard based on liver disease) makes INR 'cut-off' values of little value [138]. Furthermore, thrombin production does not improve when normal plasma is transfused despite improvements in INR [139]. Standard doses of FFP rarely correct coagulopathy of cirrhosis [133,140], and can be harmful due to increases in portal pressure during variceal bleeding [141].

Platelet count. Despite thrombocytopenia in cirrhosis, platelet adhesion *in vitro* is preserved by increased levels of von Willebrand factor (decreased ADAMTS13) [133]. Using thrombin (factor II) production as a surrogate for clot formation, platelet counts exceeding 50×10^9/L are associated with adequate thrombin formation, making this a practical clinical target in the setting of active bleeding or as prophylaxis prior to procedures [133,142]. However, prophylactic transfusion of a single adult platelet unit is of marginal benefit in increasing the platelet count to target levels [143]. Despite laboratory data, there is no clinical evidence of a definitive threshold that correlates with increase bleeding risk during surgery (i.e. liver transplant) or invasive procedures (including liver biopsy).

Hemoglobin targets. A recent study showed that a restrictive hemoglobin transfusion target (7 mg/dl) was not inferior to a liberal strategy (9 mg/dl), and may have benefits in patients with Child-Pugh A and B [144]. Endogenous erythropoetin levels are elevated in cirrhotic patients and correlate with the severity of portal hypertension [145]. Exogenous erythropoetin stimulates increased thrombopoiesis and platelet reactivity possibly exacerbating the risk of thrombosis [146].

Viscoelastic tests of whole blood coagulation. Viscoelastic tests, which include thromboelastography (TEG), thromboelastometry (ROTEM) and sonorheometry, offer a means of assessing the activity of pro- and anticoagulant pathways as well as providing a means of recognizing hyperfibrinolysis or premature clot dissolution [147]. The tests are *in vitro* assays and do not account for the *in vivo* contributions of the endothelium and blood flow. Assessment of clotting can be performed in 10–20 min; however, assessment of fibrinolysis takes 30–60 min [148]. Viscoelastic testing suggests that hypercoagulability is more prevalent in patients with cholestatic liver disease, acute liver failure and non-alcoholic steatohepatitis [149,150]. The management of patients with hypercoagulability on viscoelastic testing is not clear; however, pro-coagulants and antifibrinolytics should be used cautiously in these patients.

Venous thromboembolic disease and anticoagulant therapy. Increased risks of venous thromboembolic disease (0.5–2% absolute risks) have been demonstrated in cirrhotic patients, especially in those patients with hypoalbuminemia [151,152]. Rates of portal vein thrombosis have been reported as approximately 8% per year with morbidity and mortality at one year impacted by prophylactic anticoagulation [153,154]. Anticoagulation demonstrates the most utility in patients with more extensive portal vein and mesenteric thrombosis in the absence of other risk factors for bleeding [153,155]. Low molecular weight heparin does not appear to increase risk of variceal bleeding [156] and is likely the safest choice. However it should be considered that it has an increased clinical effect despite decreased antithrombin III levels in cirrhotic patients [157].

Bleeding risks for minimally invasive and surgical procedures

Recommendations

1. *We suggest transfusion to a platelet count above 50×10^9/L prior to minimally invasive procedures (**2C**).*
2. *During surgical procedures, viscoelastic testing should be considered to guide coagulation management (**2C**).*
3. *We suggest maintaining fibrinogen levels >1.5 g/L in patients with significant bleeding or during invasive/surgical procedures (**2C**).*

Rationale. Bleeding rates after minimally invasive procedures in cirrhotic patients have been demonstrated to be low for paracentesis (0–3.3%) and thoracentesis (2%) [158]. Bleeding does not appear to correlate with platelet count or INR. Reported incidence of major bleeding complications after liver biopsy was between 0.22 and 0.58% with a 0.1% mortality. Bleeding rates were higher in patients with advanced hepatic fibrosis and platelet count $\leqslant 60 \times 10^9$/L [159,160]. Transjugular liver biopsy has been shown to be relatively safe even in those patients with decreased platelet count or prolonged INR [161]. Risk of bleeding after liver surgery has been shown to correlate with surgical and hemostatic techniques rather than coagulation parameters [162]. Although the optimal fibrinogen level is uncertain (normal 2–4.5 g/L), in bleeding/surgical patients, fibrinogen levels of >1 g/L are recommended [163,164]. More recent guidelines suggest higher levels (>1.5–2.0 g/L) are bene-

ficial in major trauma with significant bleeding, a recommendation which aligns with *in vitro* levels required for optimal clot formation time on viscoelastic testing [165,166]. The routine use of viscoelastic testing during liver transplantation appears well established as a means to determine global coagulation status [167].

Role of novel coagulation agents/complexes

Recommendations

1. *We suggest prothrombin complex concentrates before invasive procedures preferably guided by viscoelastic testing (**2D**).*
2. *We recommend against routine use of thrombopoeitin receptor agonists (**1B**).*
3. *We suggest antifibrinolytic therapy (tranexamic acid or ε-aminocaproic acid) use in decompensated cirrhosis with bleeding when hyperfibrinolysis is suspected or proven. Although safe, its clinical efficacy has not been established (**2C**).*

Rationale. *Prothrombin complexes.* Prothrombin complex concentrates (PCC) are available as 3-factor (FII, IX, X) and 4-factor products (same factors plus FVII). Some contain endogenous anticoagulants (protein C, protein S, antithrombin III) with or without heparin in an attempt to lessen the thrombotic risk [168]. Thrombotic complications in ACLF patients may be reduced by limiting repeat dosing of PCCs. Factor II and X have long half-lives (60 and 30 h, respectively) and may accumulate during repeated administration. Thromboelastometry-guided PCC administration, when compared to FFP transfusion for massive trauma, resulted in a higher likelihood of avoidance of red blood cell and platelet transfusion [169].

Thrombopoetin receptor agonists. In trials, the oral thrombopoetin receptor agonist eltrombopag increased platelet count in thrombocytopenic hepatitis C virus (HCV) patients, improving tolerance of anti-HCV therapy [170]. However, in the ELEVATE study, 6 eltrombopag-treated patients developed portal vein thrombosis [171]. Nplate® (romiplostim), administered to thrombocytopenic HCV patients prior to procedures, improved platelet counts and facilitated interventions without experiencing procedural bleeding or thrombosis [172]. However, other reports suggest increased thrombotic risk, particularly in patients with platelet counts over 200 $\times$ 10^9/L [173].

Antifibrinolytics. Aprotinin, the most extensively studied antifibrinolytic, is efficacious for reducing transfusion requirements during transplant [174,175]. Aprotinin has been controversial and was withdrawn from the market in the wake of a cardiac surgery trial showing increased mortality [176]. In an uncontrolled study, ε-aminocaproic acid (Amicar®) was deemed effective and safe for treatment of hyperfibrinolysis in patients with cirrhosis [177]. Viscoelastic testing during antifibrinolytic therapy is recommended.

Neurologic dysfunction

Mechanisms behind neurological dysfunction, mostly which is caused by HE in hospitalized cirrhotic patients, are varied and are often overlapping with concurrent or precipitating illnesses such as infections and electrolyte abnormalities [178]. Studies of the brain have demonstrated alterations in ammonia metabolism, brain and systemic inflammation, and changes in cerebral blood flow and oxygenation [179].

Diagnosis of hepatic encephalopathy

Recommendations

1. *We suggest brain imaging only be used for overt HE at its first occurrence if: a) the onset of the symptoms is abrupt and severe; b) there are focal neurological signs; or c) there is limited or no response to treatment of the precipitating factor and/or to ammonia lowering strategies. Electroencephalogram (EEG) can be used to exclude other causes of altered mental status (**2D**).*
2. *Measurement of fasting ammonia levels can be informative only if it is normal in a confused, disorientated or comatose patient with cirrhosis (**2D**).*

Rationale. The differential diagnosis of HE is vast and should be rigorously investigated (Table 5) [10,23,179,180]. EEG changes, are non-specific and of limited value in the diagnosis of HE, nevertheless they can assess HE severity and exclude other causes of altered mental status [181]. The risk of intra-cerebral hemorrhage is increased in cirrhotic patients and thus, brain imaging could be useful to exclude other causes of altered mental status [182].

To differentiate HE from other conditions, fasting ammonia levels can be relevant since, in a confused, disorientated or comatose cirrhotic patient, the finding of normal plasma ammonia levels suggests an alternative cause of neuropsychiatric abnormalities [179]. Nevertheless, one should be warned against the use of high ammonia levels alone for the purpose of diagnosing HE since false positive results are frequent.

Grading hepatic encephalopathy

Recommendations

1. *We recommend the use of West-Haven criteria (WHC) for clinical use provided it is refined using tools such as clinical HE staging scale (CHESS), HE scoring algorithm (HESA) or modified orientation log (MO-log) (**1C**).*
2. *We recommend the Glasgow coma scale (GCS) for clinical use and to guide the need for airway protection (**1B**).*
3. *We suggest head imaging studies and EEG only to exclude other causes especially when there is lack of response to therapy (**2D**).*

Table 5. Differential diagnosis for hepatic encephalopathy.

Diabetic (hypoglycemia, ketoacidosis, hyperosmolar, lactic acidosis)
Alcohol (intoxication, withdrawal, Wernicke)
Drugs (benzodiazepines, neuroleptics, opioids)
Renal dysfunction
Electrolyte disorders (hyponatraemia and hypercalcemia)
Neurological infections
Non-convulsive epilepsy
Psychiatric disorders
Intracranial bleeding and stroke
Severe medical stressful events (organ failure and inflammation)

Rationale. Grading of mental status is important to assess and document the progression of disease and the impact of treatment. Currently there are no available tools that reliably distinguish HE from other etiologies of metabolic encephalopathy. Although simplicity and familiarity favor usage of the WHC to grade and monitor HE for clinical purposes, these criteria are not reliable in the earlier stages and therefore other questionnaires have been studied to refine the assessment (Supplementary Table 4) [183–187]. Use of HESA, MO-log or CHESS may be considered for clinical research or practice where the outcome of interest is the presence, absence or change in HE. The GCS is a simple and widely utilized tool for characterizing neurologic dysfunction after traumatic brain injury [188] that has been applied to metabolic encephalopathy [189]. Its greatest utility is defining the threshold (<8) below which airway protection may be required. Serial brain imaging and EEG assessments beyond exclusion of other causes and investigation of lack of improvement have not been shown to be clinically useful.

Therapy for hepatic encephalopathy

Recommendations

1. *We recommend the use of lactulose as the initial therapy for HE with close monitoring of electrolytes and the development of ileus (**1C**).*
2. *We do not recommend the use of neomycin, LOLA, intravenous albumin or other laxatives for the treatment of HE (**1D**).*
3. *We suggest albumin dialysis in patients with encephalopathy that is refractory to medical therapy (**2C**).*
4. *We recommend HE-specific therapies such as lactulose and rifaximin to be started to prevent recurrent episodes (**1A**).*

Rationale. In patients with altered mental status, specific therapies for HE is often initiated along with treatment of the precipitating factors such as GIB, electrolyte disorders, renal dysfunction, medications (Fig. 6). Recurrence of HE has emerged as one of the leading causes for re-admission in cirrhotic patients [190]. Lactulose, rifaximin and the probiotic VSL#3 have been shown to prevent HE recurrence [191–193].

Lactulose: The use of lactulose in hospitalized cirrhotic patients is hampered by trials with low sample sizes [194]. Nevertheless, it continues to be used as a first line therapy for HE. The specific mode of administration is critical to prevent aspiration, especially in advanced stages of HE and over-administration can result in HE recurrence [195]. The oral dose is 20 ml per hour until at least one bowel movement and then reduced to 20–30 ml twice daily to three times daily titrated to 2–3 soft bowel movements per day [179]. Following an episode of acute variceal bleeding, studies have shown that mental status significantly improved after lactulose compared to no treatment and there was an equivalent improvement with lactulose compared to rifaximin [196,197]. Studies comparing simple laxatives (polyethylene glycol (PEG) orally, saline enemas) to acidifying enemas or laxatives such as lactulose, lactitol and lactose, have shown a significant benefit of the "acidifying" enemas on mental status [198]. In contrast a recent study showed superiority of PEG compared to lactulose in mental status improvement [199]. Given the small number of patients in both studies further large-scale studies are needed to find out the differences between laxatives and potential acidifying agents.

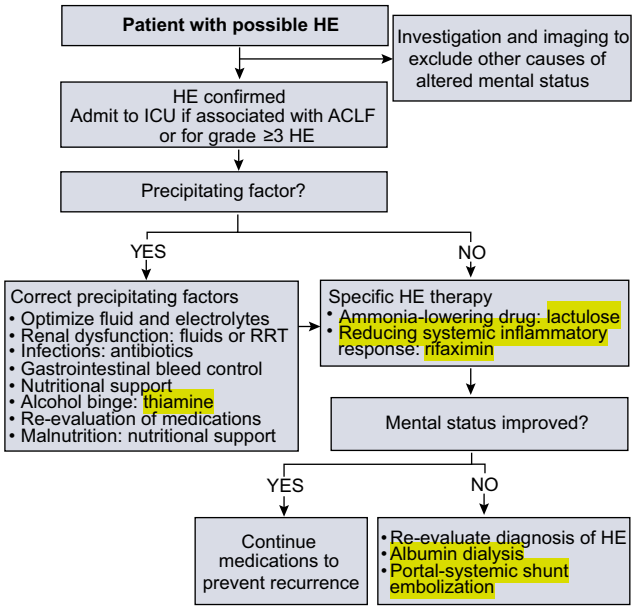

Fig. 6. Algorithm for the management of hepatic encephalopathy (HE). RRT, renal replacement therapy; ACLF, acute on chronic liver failure.

Rifaximin: Current standard of care does not include rifaximin in the treatment of a HE episode but does not call for discontinuation if the patient was already taking it as an outpatient [200]. Mas *et al.* demonstrated equivalent global recovery, (despite greater improvement in ammonia and EEG in rifaximin) with rifaximin when it was directly compared to lactitol in patients with an episode of HE [201]. This was followed by a study in which combined rifaximin and lactulose showed superior efficacy over lactulose alone [202]. These two studies used different comparators and need to be replicated before routine rifaximin use can be recommended.

Albumin and albumin dialysis: Although in one controlled trial, treatment with albumin improved HE in patients with diuretic-related HE [203], in a randomized control trial, the primary endpoint of HE resolution was not reached but there was a survival benefit [179]. Several studies have found a significant improvement in HE using albumin dialysis compared to standard medical therapy [204–207]. However, only a few small studies have shown overall survival benefit [208–210]. While the role of these therapies is being debated, their use as a bridge to liver transplant by providing temporary support of organ failure (liver, kidney and brain) is a potentially important goal in this situation.

Neomycin: Neomycin was the first drug approved for HE treatment in the U.S. and was the standard to which lactulose was compared. Several underpowered studies with lactulose and neomycin demonstrated similar outcomes regarding mental status [179]. However due to several adverse effects (nephro/oto-toxicity), the use of neomycin has fallen out of favor.

L-ornithine L-aspartate (LOLA): Intravenous LOLA has been shown to improve mental status in one high quality German trial, which has been replicated at least once in other countries. However, this drug is not available in the U.S. [211].

Intubation and sedation

Recommendations

1. *We recommend intubation in patients with GCS <8 (**1D**).*
2. *We recommend sedation with short-acting agents and avoidance of benzodiazepines (**1D**).*

Rationale. All patients with HE WHC grade 3 or 4 and GCS <8 should be considered for intubation for airway protection [180]. Short-acting drugs such as propofol or dexmedetomidine should be used, with caution paid to hemodynamic side effects [212]. Dexmedetomidine is associated with preservation of cognitive function [213] and reduced duration of mechanical ventilation in ICU patients [214] and may be used for the management of alcohol withdrawal, which may allow decreased benzodiazepine administration [215]. Both dexmedetomidine and propofol are associated with similar hemodynamic side effects [216].

Conclusion

ACLF is a recently recognized syndrome associated with multi-organ/system failure(s) (liver, kidney, brain, coagulation, circulation and/or respiration) and with an extremely poor survival. These patients often require ICU care. The optimum treatment of patients with ACLF is evolving and further programmatic clinical research are essential to determine the mechanisms of organ failure in ACLF and to help develop effective methods that can bridge patients with ACLF to liver transplantation.

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Conflict of interest

MKN is a consultant for Ikaria and Baxter and an Advisor and on the Data and Safety Monitoring board for La Jolla Pharmaceutical Company. FD is a consultant for Astellas, Novartis, Gilead and Bristol-Myers Squibb and has received research funding from Gilead and Astellas Pharma. JAK is a consultant for Fresenius, Baxter, Grifols, Astute Medical, Alere, AM Pharma, Spectral, Cytosorbents, Alung, Atox Bio and Bard, has received grant support from Gambro, Baxter, Bard, Astute Medical, Alere, Spectral, Grifols, Cytosorbents, Kaneka, Atox Bio and has licensing agreement with Astute Medical, Spectral and Cytosorbents. JGO is a consultant for Grifols, Gilead, Abbvie, Novartis, Astellas, Fisher Scientific and has received grant support from Grifols. PG is a consultant and on the advisory board for Ferring Pharmaceuticals and Ikaria and has research funding from Grifols and Sequana Medical. JSB is a consultant for Salix, Norgine and Grifols. RJ has received research funding from Vital Therapies, has served on Scientific Advisory Board for Conatus Pharma, received lecture fees from Gambro, has ongoing research collaboration with Gambro, Grifols, is the Principal Investigator of an Industry sponsored study (Sequana Medical), inventor for a drug, L-ornithine phenyl acetate which UCL has licensed to Ocera Therapeutics and the founder of UCL spin-out company Yaqrit ltd. and Cyberliver ltd. SHC is a consultant and has received research funding from Vital Therapies. MGI has research support from Anolinx, Chimerix, Gilead, Glaxo Smith Klein, Viro Pharma, is a consultant for Biota, Chimerix, Farmark, Genentech/Roche, Shionogi, Adamas, BioCryst, Cellex, Clarassance, Glaxo Smith Klein, GenMarkDx, Romark, Toyama/MediVector, NexBio, Theraclone, Vertex and on the Data and Safety Monitoring Board for Abbott, Jansen/Vertex. JCO is a consultant for Baxter. YSG is a consultant for Baxter.

The rest of the authors have disclosed no conflict of interest with any company.

Authors' contribution

All authors contributed to the literature review, figure and table development and manuscript preparation as it pertained to their working group. The organizing committee edited the final version of the manuscript. All authors reviewed and approved the final manuscript.

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Supplementary data

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