CME

Acute-on-Chronic Liver Failure Clinical Guidelines

Jasmohan S. Bajaj, MD, MS, FACG[1], Jacqueline G. O'Leary, MD, MPH, FACG[2], Jennifer C. Lai, MD, MBA[3], Florence Wong, MD, FACG[4], Millie D. Long, MD, MPH, FACG (Methodologist)[5], Robert J. Wong, MD, MS, FACG (Methodologist)[6] and Patrick S. Kamath, MD[7]

In patients with cirrhosis and chronic liver disease, acute-on-chronic liver failure is emerging as a major cause of mortality. These guidelines indicate the preferred approach to the management of patients with acute-on-chronic liver failure and represent the official practice recommendations of the American College of Gastroenterology. The scientific evidence for these guidelines was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluation process. In instances where the evidence was not appropriate for Grading of Recommendations, Assessment, Development, and Evaluation, but there was consensus of significant clinical merit, key concept statements were developed using expert consensus. These guidelines are meant to be broadly applicable and should be viewed as the preferred, but not only, approach to clinical scenarios.

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INTRODUCTION

The burden of liver disease and cirrhosis is increasing worldwide. Progression of liver disease and fibrosis from fibrosis to cirrhosis and decompensation and critical illness is a major cause of mortality in this population. In patients with chronic liver disease, acute-on-chronic liver failure (ACLF), a relatively recently described entity, is diagnosed with a combination of hepatic and extrahepatic organ failures. The current definitions of ACLF vary worldwide, but despite these differences, patients with ACLF have a uniformly poor prognosis. The role of ACLF prediction, precipitating factors, individual organ failures, management strategies, and impact on liver transplantation or end-of-life care is evolving. The current guideline represents the synthesis of the current and emerging data on ACLF as a major entity in patients with chronic liver disease.

The guideline is structured in the format of statements that were considered to be clinically important by the content authors. The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) process was used to assess the quality of evidence for each statement (1). The quality of evidence is expressed as high (we are confident in the effect estimate to support a particular recommendation), moderate, low, or very low (we have very little confidence in the effect estimate to support a particular recommendation) based on the risk of bias of the studies, evidence of publication bias, heterogeneity among studies, directness of the evidence, and precision of the estimate of effect (2). A strength of recommendation is given as either strong (recommendations) or conditional (suggestions) based on the quality of evidence, risks vs benefits, feasibility, and costs taking into account perceived patient and population-based factors (3). Furthermore, a narrative evidence summary for each section provides important definitions and further details for the data supporting the statements.

The authors have also highlighted key concept statements that were not included in the GRADE assessment. Key concepts are statements that the GRADE process has not been applied to and often include definitions and epidemiological statements rather than diagnostic or management recommendations. Table 1 is a summary of recommendations, whereas Table 2 shows the key concept statements.

These guidelines are established to support clinical practice and suggest preferable approaches to a typical patient with a particular medical problem based on the currently available published literature. When exercising clinical judgment, particularly when treatments pose significant risks, healthcare providers should incorporate this guideline in addition to patient-specific medical comorbidities, health status, and preferences to arrive at a patient-centered care approach.

ACLF DEFINITION

There are 3 major definitions of ACLF depending on the part of the world.

1. Asian Pacific Association for the Study of the Liver (APASL) defines ACLF as "an acute hepatic insult manifesting as jaundice (serum bilirubin $\geq$ 5 mg/dL [85 μmol/L]) and coagulopathy (international normalized ratio [INR] $\geq$ 1.5 or prothrombin activity $<$ 40%) complicated within 4 weeks by

[1]Virginia Commonwealth University and Central Virginia Veterans Health Care System, Richmond, Virginia, USA; [2]Dallas Veterans Medical Center and University of Texas Southwestern, Dallas, Texas, USA; [3]University of California San Francisco, San Francisco, California, USA; [4]University of Toronto, Toronto, Ontario, Canada; [5]Division of Gastroenterology and Hepatology, Department of Medicine, University of North Carolina, Chapel Hill, North Carolina, USA; [6]Veterans Affairs Palo Alto Health Care System and Stanford University School of Medicine, Palo Alto, California, USA; [7]Mayo Clinic School of Medicine and Science, Rochester, Minnesota, USA. **Correspondence:** Jasmohan S. Bajaj, MD, MS, FACG.
E-mail: jasmohan.bajaj@vcuhealth.org.
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Table 1. Recommendations

Brain failure
1. In hospitalized patients with ACLF, we suggest the use of short-acting dexmedetomidine for sedation as compared to other available agents to shorten time to extubation (very low quality, conditional recommendation)
2. In patients with cirrhosis and ACLF who continue to require mechanical ventilation because of brain conditions or respiratory failure despite optimal therapy, we suggest against listing for LT to improve mortality (very low quality, conditional recommendation)
Kidney failure
1. In patients with cirrhosis and stages 2 and 3 AKI, we suggest IV albumin and vasoconstrictors as compared to albumin alone, to improve creatinine (low quality, conditional recommendation)
2. In patients with cirrhosis, we suggest against the use of biomarkers to predict the development of renal failure (very low quality, conditional recommendation)
3. In patients with cirrhosis and elevated baseline sCr who are admitted to the hospital, we suggest monitoring renal function closely because elevated baseline creatinine is associated with worse renal outcomes and 30-d survival (but no data that closer monitoring improves these outcomes) (very low quality, conditional recommendation)
4. In hospitalized patients with cirrhosis and HRS-AKI without high grade of ACLF or major cardiopulmonary or vascular disease, we suggest terlipressin (moderate quality, conditional recommendation) or norepinephrine (low quality, conditional recommendation) to improve renal function
5. In patients with cirrhosis and SBP, we recommend albumin in addition to antibiotics to prevent AKI and subsequent organ failures (high quality, strong recommendation)
6. In patients with cirrhosis and infections other than SBP, we recommend against albumin to improve renal function or mortality (high quality, strong recommendation)
Respiratory failure
1. In ventilated patients with cirrhosis, we suggest against prophylactic antibiotics to reduce mortality or duration of mechanical ventilation (very low quality, conditional recommendation)
Coagulation failure
1. In patients with cirrhosis and ACLF, we suggest against INR as a means to measure coagulation risk (very low quality, conditional recommendation)
2. In patients with cirrhosis as compared to noncirrhotic populations, we suggest there is an increased risk of VTE (low quality, conditional recommendation)
3. In patients with ACLF and altered coagulation parameters, we suggest against transfusion in the absence of bleeding or a planned procedure (low quality, conditional recommendation)
4. In patients with cirrhosis who require invasive procedures, we recommend the use of TEG or ROTEM, compared with INR, to more accurately assess transfusion needs (moderate quality, conditional recommendation)
Infections
1. In hospitalized decompensated cirrhotic patients, we recommend assessment for infection because infection is associated with the development of ACLF and increased mortality (moderate quality, strong evidence)
2. In patients with cirrhosis and suspected infection, we suggest early treatment with antibiotics to improve survival (very low quality, conditional evidence)
Nosocomial and fungal infections
1. In hospitalized patients with ACLF because of a bacterial infection who have not responded to antibiotic therapy, we suggest suspicion of a MDR organism or fungal infection to improve detection (very low quality, conditional recommendation)
Medications and prophylaxis for infection
1. In patients with cirrhosis with a history of SBP, we suggest use of antibiotics for secondary SBP prophylaxis to prevent recurrent SBP (unable to comment on specific antibiotic choice) (low quality, conditional recommendation)
2. In patients with cirrhosis in need of primary SBP prophylaxis, we suggest daily prophylactic antibiotics, although no one specific regimen is superior to another, to prevent SBP (low quality, conditional recommendation)
3. In patients with cirrhosis, we suggest avoiding PPI unless there is a clear indication because PPI increases the risk of infection (very low quality, conditional recommendation)
Alcohol-associated hepatitis
1. In patients with severe alcohol-associated hepatitis (MDF $\geq$ 32; MELD score $>$ 20) in the absence of contraindications, we recommend the use of prednisolone or prednisone (40 mg/d) orally to improve 28-d mortality (moderate quality, strong recommendation)
2. In patients with severe alcohol-associated hepatitis (MDF $\geq$ 32; MELD score $>$ 20), we suggest against the use of pentoxifylline to improve 28-d mortality (very low quality, conditional recommendation)

Table 1. (*continued*)

Management strategies
1. In patients with cirrhosis who are hospitalized, we suggest against the routine use of parenteral nutrition, enteral nutrition, or oral supplements to improve mortality
2. In hospitalized patients with cirrhosis, we recommend against daily infusion of albumin to maintain albumin >3 g/dL to improve mortality, prevention of renal dysfunction, or infection (moderate quality, strong recommendation)
3. In patients with cirrhosis and ACLF, we suggest against the use of G-CSF to improve mortality (very low evidence, conditional recommendation)
Transplant vs futility
1. In patients with cirrhosis and ACLF who continue to require mechanical ventilation because of ARDS or brain-related conditions despite optimal therapy, we suggest against listing for LT to improve mortality (very low evidence, conditional recommendation)
2. In patients with end-stage liver disease admitted to the hospital, we suggest early goals of care discussion and if appropriate, referral to palliative care to improve resource utilization (very low evidence, conditional recommendation)

ACLF, acute-on-chronic liver failure; AKI, acute kidney injury; ARDS, adult respiratory distress syndrome; G-CSF, granulocyte colony-stimulating factor; HRS, hepatorenal syndrome; INR, international normalized ratio; IV, intravenous; LT, liver transplant; MDF, Maddrey discriminant function; MDR, multidrug resistant; MELD, model for end-stage liver disease; PPI, proton pump inhibitor; ROTEM, rotational TEG; SBP, spontaneous bacterial peritonitis; sCr, serum creatinine; TEG, thromboelastography; VTE, venous thromboembolism.

clinical ascites and/or hepatic encephalopathy (HE) in a patient with previously diagnosed or undiagnosed chronic liver disease/cirrhosis and is associated with a high 28-day mortality." Extrahepatic organ failure is not required to make the diagnosis (4).

2. European Association for the Study of the Liver-Chronic LIver Failure (EASL-CLIF) consortium defines ACLF as a specific syndrome in patients with cirrhosis that is characterized by acute decompensation (AD), organ failure, and high short-term mortality. The development of ascites, HE, gastrointestinal hemorrhage, and/or bacterial infections defines AD; however, patients may develop ACLF without a history of AD. Organ failures include liver, kidney, brain, respiratory system, circulation, and coagulation, and they are assessed by the CLIF-consortium organ failures score (5) (https://www.efclif.com/scientific-activity/score-calculators/clif-c-aclf).
3. North American Consortium for the Study of End-Stage Liver Disease (NACSELD) defines ACLF by the presence of at least 2 severe extrahepatic organ failures including shock, grade III/IV HE, renal replacement therapy (RRT), or mechanical ventilation (www.nacseld.org) (6).

For the purposes of this document, we suggest the following definition: ACLF is a potentially reversible condition in patients with chronic liver disease with or without cirrhosis that is associated with the potential for multiple organ failure and mortality within 3 months in the absence of treatment of the underlying liver disease, liver support, or liver transplantation (7). ACLF is recognized by the presence of chronic liver disease along with elevation in the serum bilirubin and prolongation of the INR. The presence of kidney, lung, circulatory, or brain failure supports the diagnosis (Figure 1). The severity of organ failure may be assessed by the EASL-CLIF sequential organ failure assessment score or NACSELD organ failures score (Tables 3 and 4) (5). Patients with ACLF are best managed in the intensive care unit (ICU), and some may benefit from early liver transplantation.

Key concept statements

1. In patients with cirrhosis who are hospitalized, the NACSELD score is likely associated with futility, whereas the EASL-CLIF sequential organ failure assessment score is associated with 28-day prognostication.
2. None of the 3 society definitions is optimal for informing management change.

Summary of evidence

Patients with chronic liver disease may progress to cirrhosis. The onset of ascites, gastrointestinal bleeding, HE, and/or hepatorenal syndrome (HRS) defines decompensated cirrhosis. If precipitating events, such as viral hepatitis, drug-induced liver injury, and alcohol-related hepatitis, are superimposed on chronic liver disease, the result may be hepatic and extrahepatic organ failure, termed acute-on-chronic liver failure or ACLF.

EASL-CLIF and NACSELD definitions of ACLF require the presence of organ failure. Because organ failure occurs at a late stage, ACLF, as defined by these definitions, may be irreversible despite intensive therapy. Thus, current ACLF definitions may promote a passive, reactive approach to management. The multiple definitions for ACLF have also resulted in substantial confusion among multidisciplinary teams caring for these patients, especially regarding whether such patients should receive early transplantation or whether they should be excluded from transplantation. A comparison of NACSELD and EASL-CLIF ACLF criteria suggests that NACSELD criteria outperformed the EASL-CLIF ACLF classification in the prediction of 7-day mortality. There was significantly higher specificity, positive predictive value and overall accuracy and comparable sensitivity and negative predictive value. However, in predicting 90-day mortality, NACSELD criteria had lower sensitivity and negative predictive value than EASL-CLIF ACLF criteria (8). It therefore seems that the EASL-CLIF score may be used to prioritize patients for liver transplantation and the NACSELD score to exclude patients from transplantation (9). Patients without NACSELD ACLF but with EASL-CLIF ACLF are still at a

Table 2. Key concept statements

Definition of ACLF
1. In patients with cirrhosis who are hospitalized, NACSELD score is likely associated with futility, whereas EASL-CLIF score is associated with 28-day prognostication
2. None of the 3 society definitions is optimal for informing management change
Diagnostic and prognostic biomarkers for ACLF
1. Prognostic markers that predict ACLF outcome should be separate from diagnostic markers that confirm the presence of ACLF
2. Microbial composition and microbial-origin metabolites can be used as biomarkers for ACLF development and prognosis with further validation
Brain failure
1. In patients with grade 3 or 4 HE, care of the airway, evaluation of other causes of altered mental status, treatment of potential precipitating factors, and empiric HE therapy should occur simultaneously
2. Consideration for causes other than HE as the reasons for altered mental status is important, especially in patients who have not recovered after HE therapies are deployed
3. Careful monitoring of pain, delirium, and avoiding medications that prolong sedation are important in allowing for return to consciousness
4. Discussion of goals of care should ideally occur with patients before the onset of alteration in mental status and should continue afterward
5. Patients need to be monitored after they return to consciousness for critical care–related post-traumatic stress
6. Ventilation in the absence of altered mental status should not be considered brain failure
Kidney failure
1. Kidney failure is the most common organ failure in patients with ACLF, no matter how it is defined
2. AKI and CKD, as outlined by the ICA, should replace the old nomenclature of type 1 and type 2 HRS
3. The concept of renal failure in cirrhosis continues to evolve as we identify different levels of kidney dysfunction that can confer a negative prognosis. Other forms of renal dysfunction that are being recognized include AKD and acute-on-chronic kidney failure
4. Currently, there is no recommendation for the use of vasoconstrictors for stage 1 AKI
5. The pathophysiology of renal failure in cirrhosis is related to multiple factors including a combination of hemodynamic abnormalities and inflammation
6. Prevention strategies for renal failure are recommended for at-risk patients
7. Treatment options for HRS-AKI include pharmacotherapy and liver transplantation with or without intervening RRT in the appropriate patients
8. Patients with decompensated cirrhosis and ascites should be monitored regularly for changes in renal function, especially those with background CKD related to higher prevalence of conditions such as systemic hypertension or diabetes, because AKI in patients with CKD is associated with significantly worse outcomes than in patients with normal baseline renal function
9. Be vigilant for potential precipitating factors for AKI development, with bacterial infections being the most common precipitant for AKI in patients with cirrhosis and ascites
10. Prompt and judicious treatment of potential bacterial infections may avert the development of renal failure
11. LT is the definitive treatment for HRS-AKI in cirrhosis. RRT is often required while patients are waiting for LT
12. Guidelines for combined liver and kidney transplants are available, but the effectiveness of current policies regarding simultaneous liver kidney transplant needs to be evaluated
13. The use of RRT in patients with AKI should be individualized. In general, RRT is recommended for patients with HRS-AKI who are on the LT waiting list and who have failed pharmacotherapy
14. Refer for LT assessment early in the course of AKI
Respiratory failure
1. Respiratory failure is defined as PaO2/FiO2 of ≤200 or SpO2/FiO2 of ≤214 or the need for mechanical ventilation
2. Endotracheal intubation is mandatory in patients with grade 3–4 HE to facilitate airway management, prevent aspiration, and control ventilation
3. The risk of ventilation-associated pneumonia can be decreased by 30- to 45-degree head-end elevation and subglottic suction
4. Routine use of sedatives is discouraged in patients with grade 3–4 encephalopathy and may be associated with delay in extubating
5. We suggest PPIs be used in patients with cirrhosis on a ventilator
Circulatory failure
1. Higher MAP may decrease the risk of ACLF
2. Norepinephrine is the vasopressor of choice in patients with ACLF

Table 2. (*continued*)

Coagulation failure
1. Hypocoagulation found on TEG/ROTEM in ACLF is an independent marker of poor prognosis and is usually found in patients with SIRS
2. In the absence of contraindications, such as recent bleeding and significant thrombocytopenia, hospitalized cirrhotic patients should receive pharmacologic VTE prophylaxis
3. In patients with well-controlled decompensated cirrhosis, LMWH may decrease the risk of new decompensation, but inadequate data exist at this time to anticoagulate patients in the absence of thrombosis
Infections
1. Antibiotics should be de-escalated once cultures and sensitivities are available
2. First-line antibiotic therapy should be determined by the etiology and severity of the infection, how it was acquired (community-acquired, hospital-associated, or nosocomial), and local resistance patterns
3. MDR bacterial infections are on the rise and must be considered when prescribing antibiotics
4. Alterations in gut microbial composition and function are associated with infection susceptibility and ACLF
Nosocomial and fungal infections
1. Because of underlying immune changes, altered gut microbiota, multiple interventions, and admissions, patients with cirrhosis are at significant risk of nosocomial and fungal infections
2. In hospitalized patients with cirrhosis, development of a fungal infection is associated with increased risk of ACLF and increased mortality
Medications and prophylaxis for infection
1. NSBB may decrease bacterial translocation, but patients with ACLF have difficulty tolerating clinically relevant doses
2. Rifaximin may prevent complications of cirrhosis other than HE
3. Concentrating or avoiding IV medications that require large sodium loads can improve volume status in patients with ACLF
Alcohol-associated hepatitis
1. AAH leads to ACLF as a result of a combination of a severe SIRS and sepsis
Other precipitants
1. Both prescribed and nondescribed medications can cause DILI. The most common prescribed medications that cause DILI are the antimicrobials. Self-medication with CAM is common, spreading often through social media
2. Actual prevalence of ACLF related to DILI is unknown because DILI is often underreported, and most patients have an uneventful recovery
3. When DILI causes liver injury, it usually causes acute liver failure. Formal studies in patients with pre-existing liver cirrhosis are lacking. Estimated incidence in Asian countries is approximately 10%, and that in the United States is approximately 7%
4. Onset of ACLF occurs on the average 1 mo after taking the offending medication, but can be delayed for up to 3 mo
5. Mortality in DILI-related ACLF is >50%, with the ACLF grade as the only significant predictor of mortality
6. Patient education about limiting use of pharmacological agents and avoiding use of CAM is key to the prevention of DILI-associated ACLF
7. Patients with underlying liver disease should be monitored when prescribed new medication(s) with hepatotoxic potentials
8. Patients with underlying liver disease can develop ACLF if they contract any of the known viral hepatitis
9. Hepatitis B flares are a common cause of ACLF in Asian countries and may present like acute liver failure
10. This often occurs in patients either spontaneously or on abrupt stopping of their antiviral medications
11. Other viral infections that cause ACLF are hepatitis A and E infections superimposed on chronic liver disease or hepatitis D superimposed on HBV infection
12. Bacterial infections are a common trigger of ACLF in patients with viral hepatitis, which should be monitored for and treat promptly
13. Vaccinate patients with chronic liver disease against hepatitis A and hepatitis B
14. Surgery of any type in patients with cirrhosis is associated with significant risks of organ failure and ACLF development when compared with patients without cirrhosis
15. Both the Mayo Clinic score and the VOCAL PENN score are available on-line for calculating the risks of mortality with surgery for patients with cirrhosis contemplating surgery
16. Acute hepatic decompensation and the presence of infection are significant risk factors for the development of ACLF after surgery
17. The development of ACLF after surgery is associated with significantly reduced survival compared with patients without ACLF
18. Patients with cirrhosis who require surgery should be carefully selected because perioperative management of such patients also impacts survival
19. Nonsurgical interventions can also precipitate ACLF, but the exact incidence is unknown

Table 2. (*continued*)

20. It seems that patients with more severe liver dysfunction are at higher risk of the development of ACLF with ERCP
21. For every nonsurgical intervention proposed for cirrhotic patients, it is imperative to weigh out the risks and benefits and the potential for ACLF development
22. Patients need to be closely monitored in the postprocedure period for the development of ACLF
Critical care management:
1. Management of the ACLF patient is best accomplished by a multidisciplinary team approach including expertise in critical care and transplant hepatology
2. The goal of treatment is reversal of the precipitating cause, treatment of sepsis, support of the failing organ, and liver transplantation in selected patients
Management strategies
1. Caution is advised when using enteral nutritional support in those at high risk of aspiration, such as those with HE
2. Albumin has several potential benefits beyond the oncotic effect
3. IV albumin is recommended to prevent AKI and subsequent organ failures in patients diagnosed with SBP
4. IV albumin is not recommended to prevent organ failures in patients with cirrhosis who have infections other than SBP
5. Five-percent albumin is often used for rapid volume resuscitation, whereas for more sustained volume expansion, we recommend 25% albumin
6. Artificial liver support systems, with or without a biological component, theoretically can take over some of the functions of the liver, but whether they provide any clinical benefit is still unclear
7. Plasma exchange has been shown to improve survival in patients with acute liver failure. Whether the same results could be observed in patients with ACLF is unknown
8. In patients with ACLF, administration of G-CSF has been shown to reduce short-term mortality in adult cohorts in Asia but not in Western cohorts or in children, suggesting that the impact of G-CSF may vary according to precipitating ACLF factors or other unmeasured confounders
9. Stem cell therapy represents a novel and promising therapeutic strategy to bridge patients with ACLF to more definitive therapy (e.g., control of acute infection and liver transplantation), but evidence to support its use in routine clinical practice is currently insufficient

AAH, alcohol-associated hepatitis; ACLF, acute-on-chronic liver failure; AKD, acute kidney disease; AKI, acute kidney injury; CAM, complementary and alternative medicine; CKD, chronic kidney disease; DILI, drug-induced liver injury; EASL-CLIF, European Association for the Study of the Liver-Chronic LIver Failure; ERCP, endoscopic retrograde cholangiopancreatography; G-CSF, granulocyte colony-stimulating factor; HBV, hepatitis B viral; HE, hepatic encephalopathy; HRS, hepatorenal syndrome; ICA, International Club of Ascites; IV, intravenous; LMWH, low-molecular-weight heparin; LT, liver transplant; MAP, mean arterial blood pressure; MDR, multidrug-resistant; NACSELD, North American Consortium for the Study of End-Stage Liver Disease; NSBB, nonselective beta-blockers; PPI, proton pump inhibitor; ROTEM, rotational TEG; RRT, renal replacement therapy; SBP, spontaneous bacterial peritonitis; SIRS, systemic inflammatory response syndrome; TEG, thromboelastography; VTE, venous thromboembolism.

relatively high risk of short-term mortality and therefore still deserve intensive management and consideration for early liver transplantation if available. Certainly, some patients with higher grades of ACLF (3 or more organ failures) may be considered for palliative care alone. Recent evidence suggests that continuing intensive care when the CLIF-C ACLF score is ≥70 despite 48 hours of intensive care may be futile (10). The common features in all current definitions of ACLF include rapid worsening of chronic

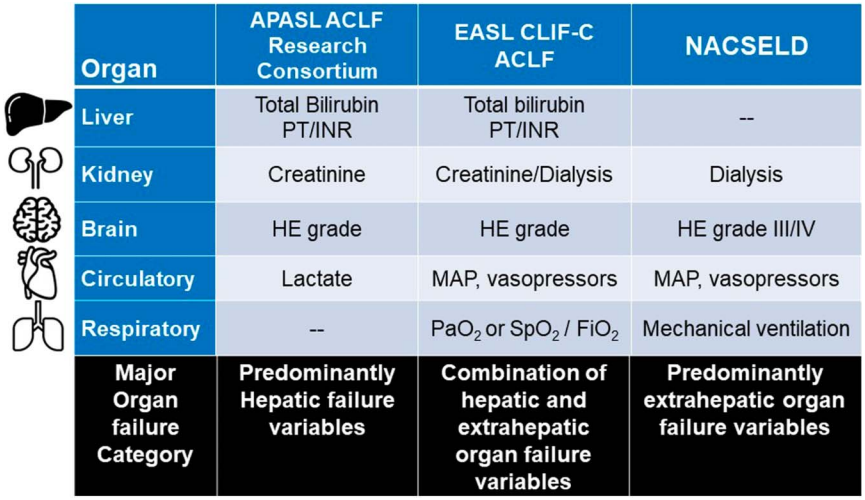

Figure 1. Outlines of the 3 major ACLF definitions. ACLF, acute-on-chronic liver failure; APASL, Asian Pacific Association for the Study of the Liver; EASL CLIF-C, European Association for the Study of the Liver-Chronic LIver Failure consortium; HE, hepatic encephalopathy; INR, international normalized ratio; MAP, mean arterial blood pressure; NACSELD, North American Consortium for the Study of End-Stage Liver Disease.

Table 3. Comparison of the definitions for ACLF

	APASL	EASL-CLIF	NACSELD	WGO proposal
Derivation	Consensus and observational	Prospective, observational study	Prospective study in patients with cirrhosis with and without infection	Consensus
Patient population inclusion	Chronic liver disease Compensated cirrhosis	Compensated and decompensated cirrhosis	Decompensated cirrhosis by implication	Noncirrhotic chronic liver disease; compensated and decompensated cirrhosis
Exclusion	Infection, previous hepatic decompensation	HCC outside Milan criteria HIV infection Significant comorbidity	HIV infection Previous organ transplantation Untreated malignancies	Not stated
Severity score	Liver failure defined as jaundice (serum bilirubin ≥5 mg/dL) and coagulopathy (INR of ≥1.5 or prothrombin activity of ≤40%). Ascites or encephalopathy develops within 4 wk	Hepatic and extrahepatic organ failure	Extrahepatic organ failure	Not stated
Comments	Diagnosis can be made early enough for intervention to alter disease course Diagnosis is sensitive but not specific for early mortality	Diagnosis of ACLF may be made too late to impact disease outcome	Diagnosis of ACLF may be made too late to impact disease outcome	Working definition for data collection to ultimately arrive at a validated definition

ACLF, acute-on-chronic liver failure; APASL, Asian Pacific Association for the Study of the Liver; EASL-CLIF, European Association for the Study of the Liver-Chronic LIver Failure; HCC, hepatocellular carcinoma; INR, international normalized ratio; NACSELD, North American Consortium for the Study of End-Stage Liver Disease; WGO, World Gastroenterology Organization.

liver disease and high risk of mortality. These definitions, however, do not serve to define the disease but rather reflect prognosis of the condition. Moreover, none of the definitions requires the potential for reversibility of liver failure, which is the hallmark of an "acute-on-chronic" condition as opposed to chronic end-stage disease. In kidney and heart failure, the criteria for organ failure (kidney or heart) remain the same whether the condition is acute, chronic, or acute-on-chronic. On the other hand, acute liver failure requires coagulopathy, HE, and hepatic failure for diagnosis, whereas in ACLF, especially with the CLIF definition, the diagnosis can be made in the absence of coagulopathy, HE, and hepatic failure. An additional reason for current disagreements between the various definitions is the presence of diagnostic or prognostic criteria vs defining criteria (ascites and jaundice in

Table 4. Variability in definitions of organ failure[a]

Type of organ failure	APASL organ failure definitions	EASL-CLIF organ failure definitions	NACSELD organ failure definition
Liver	Total bilirubin ≥5 mg/dL and INR ≥1.5	Bilirubin level >12 mg/dL	—
Kidney	AKI Network criteria	Creatinine level of ≥2.0 mg/dL or RRT	Need for dialysis or other forms of RRT
Brain	West-Haven HE grade 3–4	West-Haven HE grade 3–4	West-Haven HE grade 3–4
Coagulation	INR ≥ 1.5	INR ≥ 2.5	
Circulation		Use of vasopressor (terlipressin and/or catecholamines)	Presence of shock defined by mean arterial pressure <60 mm Hg or a reduction of 40 mm Hg in systolic blood pressure from baseline, despite adequate fluid resuscitation and cardiac output
Respiration		PaO_2/FiO_2 of ≤200 or SpO_2/FiO_2 of ≤214 or need for mechanical ventilation (note: accepted ratio is ≤300 for ALI or ≤200 for ARDS)	Need for mechanical ventilation

AKI, acute kidney injury; ALI, acute lung injury; APASL, Asian Pacific Association for the Study of the Liver; ARDS, adult respiratory distress syndrome; EASL-CLIF, European Association for the Study of Liver-Chronic Liver Failure; FiO_2, fraction of inspired oxygen; HE, hepatic encephalopathy; INR, international normalized ratio; NACSELD, North American Consortium for the Study of End-Stage Liver Disease; PaO_2, partial pressure of arterial oxygen; RRT, renal replacement therapy; SpO_2, pulse oximetric saturation.
[a]World Gastroenterology Organization did not define organ failures.

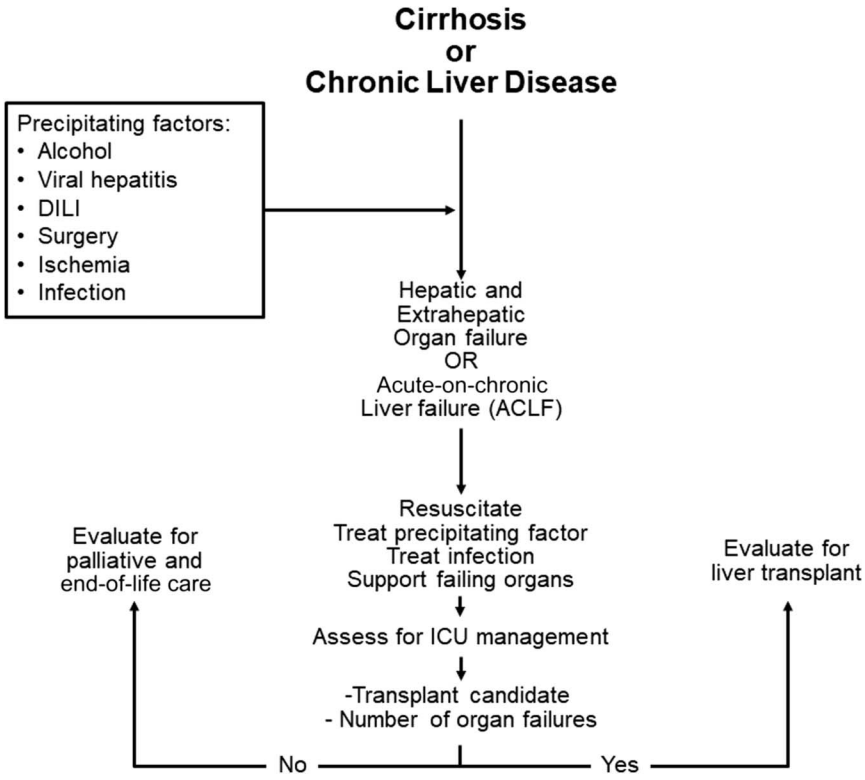

Figure 2. Course of ACLF. ACLF, acute-on-chronic liver failure; DILI, drug-induced liver injury; ICU, intensive care unit.

the Asian Pacific definition and organ failure in CLIF and NACSELD definitions) (11).

The pathophysiology of ACLF has also not been clearly defined. Although several lines of evidence suggest the role of inflammation (12), it is unclear whether inflammation is specific to ACLF or results from alcohol-associated hepatitis or occurs as a result of infection (13,14). A disease is easiest to define when there is a singular cause and it is known. Diseases related to genetic mutations are also easy to define. Diseases may be classified according to pathophysiology, or based on the organ involved, although characterizing the disease is often difficult because many diseases affect more than one organ. Liver failure is one such condition, which involves multiple organs outside the liver. The variability in precipitating events (alcohol-associated hepatitis [AAH] vs drugs or viral hepatitis) and underlying etiology of chronic liver disease in different parts of the world (viral vs alcohol-related vs metabolic fatty liver disease) may give rise to different phenotypes. This factor may also account for the difficulty in developing a uniform definition. Until the time when the pathogenesis of ACLF is clearly understood, diagnosis of ACLF should rely on a set of symptoms, signs, and laboratory tests. That is, ACLF is best considered a syndrome at this time (Figure 2). Identification of specific diagnostic signs or symptoms, or a confirmatory test is key to further defining the entity such that the diagnosis can be made early and will warrant management changes. The current definitions should be considered only interim and for the purposes of collecting data until such time, a validated definition is achieved. It is mandatory that any definition be widely validated based on a distinct pathophysiology and includes specific diagnostic signs or symptoms and a confirmatory test.

DIAGNOSTIC AND PROGNOSTIC BIOMARKERS FOR ACLF

Key concept statements

1. Prognostic markers that predict ACLF outcome should be separate from diagnostic markers that confirm the presence of ACLF.
2. Microbial composition and microbial-origin metabolites can be used as biomarkers for ACLF development and prognosis with further validation.

Summary of evidence

It is desirable to have admission biomarkers that are diagnostic and prognostic. These biomarkers should help in identifying which patients will benefit from intensive care, require early transplantation, respond to regenerative therapies, or derive benefit from bioartificial liver support, as well identify patients for whom such aggressive medical interventions are futile. Current diagnostic parameters for ACLF point toward self-evident organ failures, which has led to considerable confusion in the general clinical community about the differentiation from AD in cirrhosis (11). The lack of objective biomarkers has hampered the diagnosis of ACLF beyond organ failures, which occur too late in the natural history of disease (7). Studies in inflammation and metabolomics of the serum have found that there are differences between patients with AD and ACLF, but there remains a significant overlap between the groups (12,15). There is a growing body of evidence that patients with ACLF have an altered gut microbiota compared with those without ACLF, but the overlaps and confounders and lack of differentiation between other patients who need critical care remain an issue (16,17). A recent study also demonstrated that

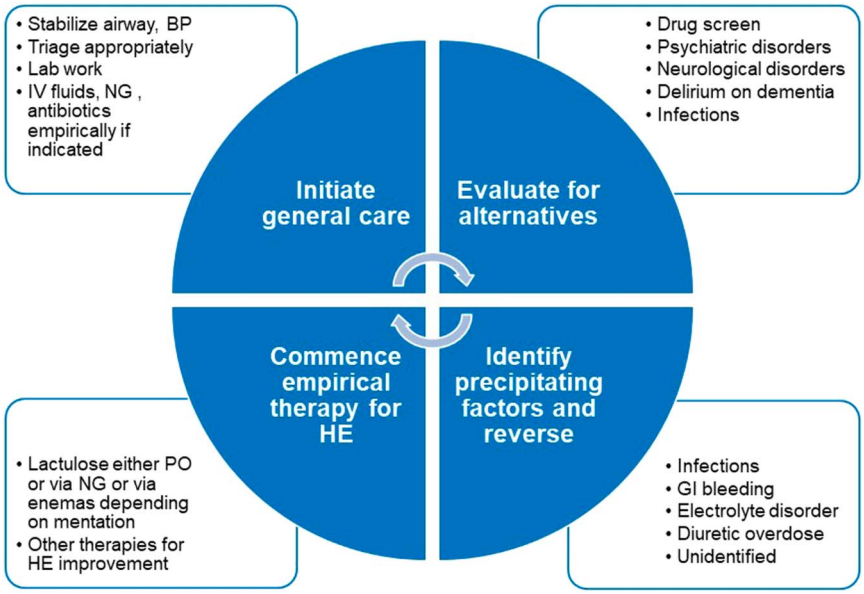

Figure 3. Four principles to approach patients with cirrhosis and altered mentation; Adapted from Acharya et al. Am J Gastroenterol 2018. BP, blood pressure; GI, gastrointestinal; HE, hepatic encephalopathy; IV, intravenous; NG, nasogastric; PO, per oral.

prognosis of patients with cirrhosis and ACLF is similar to those admitted with similar level of critical illness in the absence of cirrhosis (18). Therefore, unique diagnostic biomarkers for ACLF are needed that are (i) objective, (ii) reliable, (iii) specific to ACLF and distinct from AD and from other patients without cirrhosis requiring critical care, (iv) easily translatable into clinical practice, and (v) determine who is a good candidate for liver transplantation.

Because the prognosis of ACLF that has already developed is relatively poor, biomarkers that help clinicians predict its development will best guide therapies or interventions that improve prognosis. In patients who do not have ACLF on admission, there are few studies that address clinical characteristics and biomarkers that predict its development. Single-center studies have identified gut and circulating microbial composition that independently predict the development of ACLF, albeit defined differently (16,17,19). When these observations were extended into a multicenter study, gut microbial composition on admission predicted outcomes (20). Another multicenter experience has shown that serum metabolites focused on microbial function and estrogens collected on admission can also independently predict ACLF development (21). However, further studies are needed to validate and operationalize these biomarkers to determine whether interventions can alter the outcome.

INDIVIDUAL ORGAN FAILURE–RELATED QUESTIONS

Brain

Recommendations

1. In hospitalized patients with ACLF, we suggest the use of short-acting dexmedetomidine for sedation as compared to other available agents to shorten time to extubation (very low quality, conditional recommendation).
2. In patients with cirrhosis and ACLF who continue to require mechanical ventilation because of brain conditions or respiratory failure despite optimal therapy, we suggest against listing for liver transplant (LT) to improve mortality (very low quality, conditional recommendation).

Key concept statements

1. In patients with grade 3 or 4 HE, care of the airway, evaluation of other causes of altered mental status, treatment of potential precipitating factors, and empiric HE therapy should occur simultaneously.
2. Consideration for causes other than HE as the reasons for altered mental status is important, especially in patients who have not recovered after HE therapies are deployed.
3. Careful monitoring of pain, delirium, and avoiding medications that prolong sedation are important in promoting a return to consciousness.
4. Discussion of goals of care should ideally occur with patients before the onset of alteration in mental status and should continue afterward.
5. Patients need to be monitored after they return to consciousness for critical care–related post-traumatic stress.
6. Ventilation in the absence of altered mental status should not be considered brain failure.

Summary of evidence

Brain failure is the only consistently defined organ failure by EASL-CLIF, NACSELD, and APASL and is defined as grade 3 or 4 HE. Studies on ACLF focused on grade III/IV HE from Europe and North America showed that patients with HE as part of the ACLF syndrome had a worse prognosis than patients with HE but without ACLF (22,23). In addition, the larger North American study also showed that grade III/IV HE, regardless of other organ failures, was independently associated with mortality (18). This demonstrates that brain failure is an independent prognostic marker in hospitalized patients with cirrhosis (23). The pathogenesis of HE is related to hyperammonemia, systemic inflammation, and gut microbial dysbiosis in the setting of precipitating factors (24). These factors are often worsened by concomitant medications such as opioids, benzodiazepines, and proton pump inhibitors (PPIs) and by infections (25,26). Despite the preponderance of HE as the cause

of altered mental status, patients with cirrhosis are also prone to changes in mentation related to the medications above, infections, altered electrolytes, alcohol and illicit drugs, and strokes (27). These alternative or synergistic causes of altered mental status are important to exclude before assuming that all mental status alteration in patients with cirrhosis is HE (28).

For any patient with cirrhosis admitted with altered mental status, the following 4 steps need to be undertaken concurrently (Figure 3): (i) airway management to prevent aspiration pneumonia; (ii) confirmation whether the condition is HE (or search for alternative causes as necessary); (iii) management of precipitating factors; and (iv) empirical therapy for HE (27,29).

Patients with persistent alterations in mental status despite HE therapy should be thoroughly investigated for alternative causes of confusion, undiagnosed or incompletely treated precipitating factors or persistent portosystemic shunts that warrant occlusion (30). Brain failure can be difficult to assess in intubated patients, and an evaluation for causes other than HE should be deferred until the patient is extubated. Given the impaired hepatic metabolism in the setting of cirrhosis, short-acting medications such as dexmedetomidine are preferred to benzodiazepines and short parenteral boluses rather than infusions are preferable (31). It can be challenging to make decisions pertaining to end-of-life measures and evaluating patients for LT when they are comatose (32,33). This is especially relevant if patients still do not recover despite the measures instituted above. Therefore, every attempt should be made to discuss goals of care with the patient before the onset of encephalopathy whenever possible.

After patients recover, they can often suffer from post-traumatic stress from their critical care experience (34). This needs to be recognized as a potential sequela and managed appropriately once the patient has recovered.

Kidney

Recommendations

1. In patients with cirrhosis and stages 2 and 3 acute kidney injury (AKI), we suggest intravenous (IV) albumin and vasoconstrictors as compared to albumin alone, to improve creatinine (low quality, conditional recommendation).
2. In patients with cirrhosis, we suggest against the use of biomarkers to predict the development of renal failure (very low quality, conditional recommendation).
3. In patients with cirrhosis and elevated baseline serum creatinine (sCr) who are admitted to the hospital, we suggest monitoring renal function closely because elevated baseline creatinine is associated with worse renal outcomes and 30-day survival
(but no data that closer monitoring improves these outcomes) (very low quality, conditional recommendation).
4. In hospitalized patients with cirrhosis and HRS-AKI without high grade of ACLF or disease, we suggest terlipressin (moderate quality, conditional recommendation) or norepinephrine (low quality, conditional recommendation) to improve renal function.
5. In patients with cirrhosis and spontaneous bacterial peritonitis (SBP), we recommend albumin in addition to antibiotics to prevent AKI and subsequent organ failures (high quality, strong recommendation).
6. In patients with cirrhosis and infections other than SBP, we recommend against albumin to improve renal function or mortality (high quality, strong recommendation).

Key concept statements

1. Kidney failure is the most common organ failure in patients with ACLF, no matter how it is defined.
2. AKI and chronic kidney disease (CKD), as outlined by the International Club of Ascites (ICA), should replace the old nomenclature of type 1 and type 2 HRS.
3. The concept of renal failure in cirrhosis continues to evolve as we identify different levels of kidney function that can confer a negative prognosis. Other forms of renal dysfunction that are being recognized include acute kidney disease and acute-on-chronic kidney failure.
4. Currently, there is no recommendation for the use of vasoconstrictors for stage 1 AKI.
5. The pathophysiology of renal failure in cirrhosis is related to multiple factors including a combination of hemodynamic abnormalities and inflammation.
6. Prevention strategies for renal failure are recommended for at-risk patients.
7. Treatment options for HRS-AKI include pharmacotherapy and liver transplantation with or without intervening RRT in the appropriate patients.
8. Patients with decompensated cirrhosis and ascites should be monitored regularly for changes in renal function, especially those with background CKD related to higher prevalence of conditions such as systemic hypertension or diabetes, because AKI in patients with CKD is associated with significantly worse outcomes than in patients with normal baseline renal function.
9. Be vigilant for potential precipitating factors for AKI development, with bacterial infections being the most common precipitant for AKI in patients with cirrhosis and ascites.
10. Prompt and judicious treatment of potential bacterial infections may avert the development of renal failure.
11. LT is the definitive treatment for HRS-AKI in cirrhosis. RRT is often required while patients are waiting for LT.
12. Guidelines for combined liver and kidney transplants are available, but the effectiveness of current policies regarding simultaneous liver kidney transplant needs to be evaluated.
13. The use of RRT in patients with AKI should be individualized. In general, RRT is recommended for patients with HRS-AKI who are on the LT waiting list and who have failed pharmacotherapy.
14. Refer for LT assessment early in the course of AKI.

Summary of evidence

Definitions. The definition of renal dysfunction in cirrhosis has undergone significant recent changes. The ICA has proposed that renal dysfunction be divided into acute and chronic types (Table 5). Acute renal dysfunction is now renamed as AKI and is defined as acute increase of sCr by $\geq$0.3 mg/dL in $<$48 hours or a 50% increase in sCr from a stable baseline sCr with the increase presumably to have occurred in the past 7 days (Table 5) (30). The severity of AKI is defined by stages. Acute renal failure is defined by the ICA as $\geq$stage 2 AKI. The previously known acute or type 1 HRS in cirrhosis is a special form of functional stage 2 AKI (now known as HRS-AKI) that also fulfills all the

Table 5. Definition of AKI and HRS-AKI

Definition of AKI	Definition
Baseline sCr	1. Stable SCr ≤3 mo 2. If not available, a stable SCr closest to the current one 3. If no previous sCr, use admission sCr
Definition of AKI	Increase in sCr 0.3 mg/dL (≥26.5 μmol/L) ≤48 hr or 50% increase from baseline
Staging	Stage 1: increase in sCr 0.3 mg/dL or (≥26.5 μmol/L) in ≤48 hr OR increase in sCr ≥ 1.5–2.0 times from baseline Stage 2: increase in sCr ≥ 2.0–3.0 times from baseline Stage 3: increase in sCr ≥ 3.0 times from baseline OR sCr 4.0 mg/dL (≥352 μmol/L) with an acute increase of 0.3 mg/dL (≥26.5 μmol/L) OR initiation of RRT
HRS-AKI	
Diagnostic criteria	1. Cirrhosis and ascites; 2. Stage 2 or 3 AKI; 3. No improvement of sCr (decrease of creatinine ≤ 0.3 mg/dL of baseline) after at least 48 hr of diuretic withdrawal and volume expansion with albumin (1-g/kg body weight/day for 2 d); 4. Absence of hypovolemic shock or severe infection requiring vasoactive drugs to maintain arterial pressure; 5. No current or recent treatment with nephrotoxic drugs; 6. Proteinuria <500 mg/d and no microhematuria (<50 RBCs/mL).

AKI, acute kidney injury; HRS, hepatorenal syndrome; RBC, red blood cell; RRT, renal replacement therapy; sCr, serum creatinine.

other previous diagnostic criteria of type 1 HRS (35). EASL-CLIF defines renal failure as an sCr ≥2 mg/dL (36), whereas NACSELD defines renal failure in the context of ACLF as any patient with renal dysfunction that requires RRT (6).

The ICA's definition of AKI is becoming more widely used in daily practice in the assessment of renal dysfunction in patient with cirrhosis because there are algorithms designed for treatment of renal dysfunction in cirrhosis based on the ICA definition (Figure 4).

CKD is defined as persistent reduction of glomerular filtration rate to <60 mL/min for ≥3 months (37). CKD can be either functional, observed mostly in patients with refractory ascites and would be equivalent to what used to be known as HRS type 2, or related to structural renal diseases such as diabetic nephropathy. The prevalence of CKD in cirrhosis is rising, related to non-alcoholic steatohepatitis being an increasingly common etiology of cirrhosis, with diabetes or systemic hypertension as comorbid conditions. It should be noted that patients with CKD with a higher baseline sCr have a more severe course of AKI (38).

Patients with CKD can also develop an acute deterioration in renal function with prerenal azotemia or with the development of a bacterial infection. Such a change in renal function is known as acute-on-CKD, defined as a rise in sCr of ≥50% from baseline or a rise of sCr by ≥0.3 mg/dL (≥26.4 μmol/L) in <48 hours in a patient with cirrhosis whose glomerular filtration rate is <60 mL/min for >3 months calculated using the 6-parameter modification of diet in renal disease formula (37).

Finally, it has been proposed that a lesser degree of acute deterioration in renal function in cirrhosis should be recognized, and it has been proposed to be named acute kidney disease because even this seemingly minor deterioration of renal function may have prognostic implications (39).

Pathophysiology. The pathophysiology of renal failure in cirrhosis involves both hemodynamic changes leading to renal vasoconstriction and intense inflammation leading to renal microcirculatory changes as well as tubular damage (40). Therefore, correcting the pathophysiological changes should lead to an improvement in renal function.

Management of renal dysfunction in inpatients with cirrhosis: Patients with ≥stage 2 AKI are usually inpatients because they not only have significant renal dysfunction, but frequently, the precipitating event that leads to AKI also needs treatment. The current treatment options for stage 2 AKI are mostly reserved for HRS-AKI because that is the most studied phenotype of stage 2 AKI. Albumin alone has not been shown to be effective for the treatment of HRS-AKI but is recommended as the adjunct therapy for HRS-AKI, both for its volume expanding and anti-inflammatory properties (41–43). Vasoconstrictors are used to improve splanchnic and systemic hemodynamics, so to improve renal perfusion and function. All studies on pharmacotherapy for HRS-AKI were performed on patients who fulfilled the traditional definition of type 1 HRS (HRS-1), rather than the more recent definition of HRS-AKI. The most commonly used vasoconstrictor worldwide for HRS-1 is terlipressin, associated with a response rate of up to 44% (44,45). The response rate is dependent on the severity of the associated ACLF, being significantly reduced with higher grades of ACLF (46). Current studies have used protocols that provide vasoconstrictor treatment for up to 14 days under which treatment could be stopped earlier if there is no response to treatment on day 4 (less than 25% reduction in sCr with vasoconstrictor) (45). Terlipressin is not currently US Food and Drug Administration–approved but is expected to be approved in the near future. Side effects include ischemic events in patients with underlying coronary artery disease or peripheral vascular disease, and the benefits of terlipressin use should be weighed against the risks of ischemia in patients with these underlying conditions. Emerging data show that terlipressin may be associated with respiratory failure in patients with underlying respiratory comorbidities (45), especially in those with grade 3 ACLF, and therefore, caution should be exercised when used in these patients (47). Responders to terlipressin have improved survival, and this includes responders who do not have complete HRS-AKI reversal (47,48). Patients who do not respond to vasoconstrictors will need LT if eligible as a definitive treatment for their renal dysfunction, with RRT as a bridging treatment, or be referred for palliative care if they are not transplant candidates (49). LT referral should not be delayed as the strongest predictor for nonrecovery of renal function after transplant is the duration of pretransplant RRT, with 14 days of pretransplant RRT being the cutoff duration for predicting nonrecovery of renal function after LT (50). Combined liver kidney transplant is recommended for patients with a prolonged history of AKI, those requiring RRT for >90 days before LT, those older than 60 years, those with underlying CKD, or those with hereditary renal conditions (51–53).

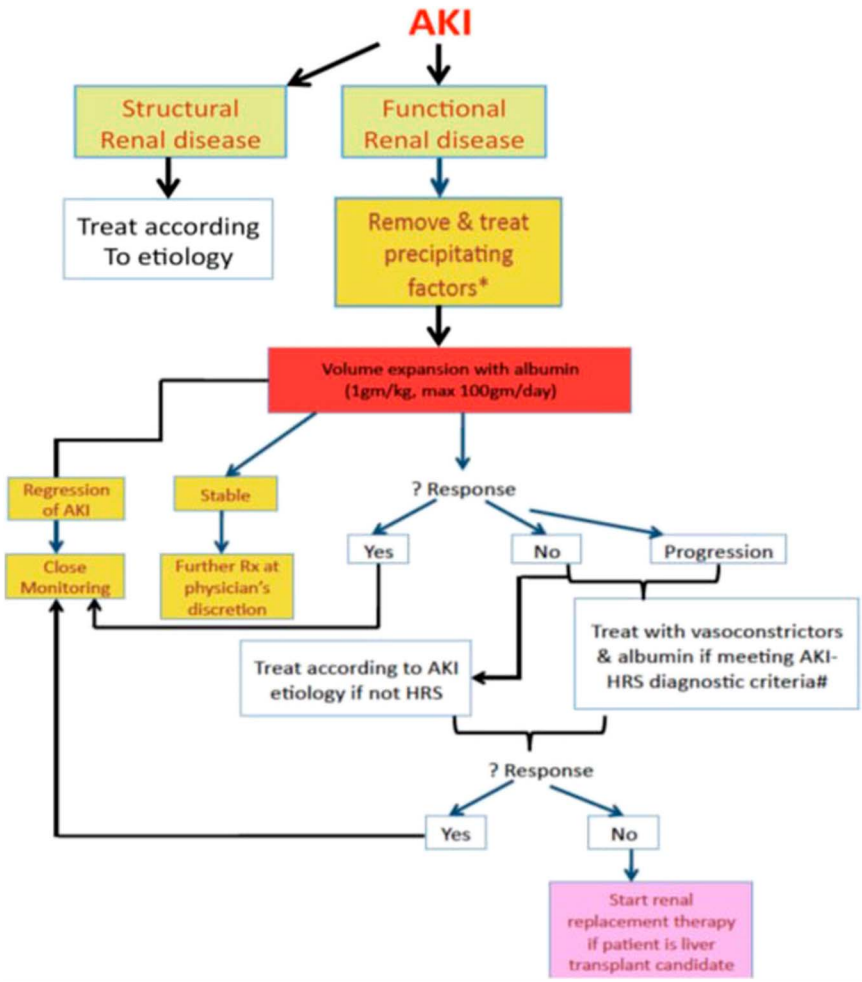

Figure 4. Suggested algorithm for the management of AKI in cirrhosis; Adapted from Wong F. Acute Kidney in Cirrhosis, in Encyclopedia of Gastroenterology, 2nd Edition, Editor-in-Chief: Ernst J. Kuipers, 2019. AKI, acute kidney injury; HRS, hepatorenal syndrome.

Prevention. Because bacterial infections are a common precipitant of AKI, early diagnosis and treatment of bacterial infections are key to prevent AKI development. The use of albumin in addition to antibiotics is recommended in patients with SBP to prevent HRS-AKI and subsequent organ failures but not recommended in non-SBP infections (54,55). Other measures include (i) judicious use of laxatives and diuretics; (ii) albumin infusions with large-volume paracentesis; (iii) prompt treatment of gastrointestinal bleeds and use of antibiotic prophylaxis in patients with established gastrointestinal bleeds; (iv) avoidance of nephrotoxic drugs or radiographic dye; and (v) primary prophylaxis against SBP in high-risk individuals and secondary prophylaxis for patients after the first episode of SBP. Recent data suggest that despite prophylactic antibiotics, 10% of patients on primary prophylaxis and 22% of patients on secondary prophylaxis still developed SBP with negative outcomes (56). The presence of CKD predisposes the patient to other organ failures, which in turn makes reversal of superimposed AKI much more difficult (38). Because repeated episodes of AKI can lead to the development of CKD, and the presence of CKD predisposes the patient to AKI episodes, it is important to treat the causes of CKD to break the AKI/CKD vicious cycle (57,58).

Lung

Recommendation

1. In ventilated patients with cirrhosis, we suggest against prophylactic antibiotics to reduce mortality or duration of mechanical ventilation (very low quality, conditional recommendation).

Key concept statements

1. Respiratory failure is defined as PaO2/FiO2 of ≤200 or SpO2/FiO2 of ≤214 or the need for mechanical ventilation.
2. Endotracheal intubation is mandatory in patients with grade 3–4 HE to facilitate airway management, prevent aspiration, and control ventilation.
3. The risk of ventilation-associated pneumonia can be decreased by 30- to 45-degree head-end elevation and subglottic suction.
4. Routine use of sedatives is discouraged in patients with grade 3–4 encephalopathy and may be associated with delay in extubating.
5. We suggest PPIs be used in patients with cirrhosis on a ventilator.

Summary of evidence

Because patients in the ICU are under the care of intensive care specialists and not hepatologists, specific recommendations regarding threshold for ventilation, pressor support, and endotracheal intubation will not be made in this guideline.

There are no data on the use of prophylactic antibiotics to prevent ventilator-associated pneumonia in patients with cirrhosis. In patients with out-of-hospital cardiac arrest, a 2-day course of antibiotic therapy with amoxicillin–clavulanate resulted in a lower incidence of early onset ventilator-associated pneumonia (VAP) as compared with the group on a placebo. However, no significant between-group differences were observed for the key clinical variables, such as duration of ventilation and 28-day mortality (59). In a meta-analysis of the studies on systemic antibiotic administration, there was decreased incidence of early onset VAP (risk ratio [RR] 0.32; 95% confidence interval [CI] 0.19–0.54) and shorter ICU length of stay (standardized mean difference −0.32; 95% CI −0.56 to −0.08) in the prophylactic antibiotic group, without any effect on mortality (RR 1.03; 95% CI 0.7–1.53) or duration of mechanical ventilation (standardized mean difference −0.16; 95% CI −0.41 to 0.08) (60). It is likely that most patients with cirrhosis in the ICU on ventilators will be on antibiotics for other reasons. However, it is not anticipated that the routine use of antibiotics will be associated with a lower risk of VAP.

In a multicenter pragmatic trial, patients on PPI had a lower risk of gastrointestinal bleeding than patients administered H_2 receptor blockers, but the difference was small. Clinically, important upper gastrointestinal bleeding occurred in 1.3% of the PPI group and 1.8% of the H_2 receptor blocker group (RR 0.73 [95% CI 0.57–0.92]; absolute risk difference, −0.51 percentage points [95% CI −0.90 to −0.12 percentage points]; $P = 0.009$). Of importance, especially as it relates to patients with cirrhosis, rates of *Clostridium difficile* infection and ICU and hospital lengths of stay were not significantly impacted by the type of gastric acid reducing medication used. Therefore, among ICU patients requiring mechanical ventilation, a strategy of stress ulcer prophylaxis with PPI use is marginally superior to H_2 receptor blockers (61). PPI use may be associated with a higher risk of diarrhea and H_2 blockers with a higher risk of delirium (62,63).

Circulation

Key concept statements

1. Higher mean arterial blood pressure (MAP) may decrease the risk of ACLF.
2. Norepinephrine is the vasopressor of choice in patients with ACLF.

Summary of evidence

Circulatory failure is one of the organ failures that defines ACLF in both the EASL-CLIF and NACSELD definitions; EASL-CLIF defines circulatory failure as the use of dopamine, dobutamine, norepinephrine, epinephrine, or terlipressin (36), and NACSELD defines circulatory failure as an MAP of <60 mm Hg or a fall of ≥40 mm Hg in systolic blood pressure from baseline after adequate fluid resuscitation (6,64). When patients with ACLF develop circulatory failure and require pressor support, norepinephrine should be given because of efficacy and favorable safety profile (31,65). In countries without access to terlipressin, norepinephrine has also been used to treat HRS-AKI by raising the MAP 10 mm Hg (66). As a result, this pressor may help to preserve renal function while treating sepsis-induced hypotension. In a meta-analysis, terlipressin when added to norepinephrine did not increase survival over norepinephrine alone in patient with septic shock (67).

As cirrhosis and portal hypertension worsens, the MAP tends to decrease, and consistent data have shown that a high MAP is protective from ACLF (6,68). Some patients with cirrhosis develop cirrhotic cardiomyopathy, whose criteria have recently been updated. Specifically, systolic dysfunction is defined as left ventricular ejection fraction of ≤50% or an absolute global longitudinal strain of <18% or >22%. The diagnosis of advanced diastolic dysfunction requires at least 3 of the following 4 criteria: (i) septal early diastolic mitral annular (e') velocity <7 cm/s, (ii) mitral inflow early diastolic velocity/e' ratio ≥15, (iii) left atrial volume index >34 mL/m^2, and (iv) tricuspid regurgitation velocity >2.8 m/s in the absence of pulmonary hypertension (69). However, neither the risk of ACLF nor its outcomes have specifically been evaluated in patients with cirrhotic cardiomyopathy.

When ACLF occurs, a hyperdynamic state is associated with a higher risk of death (70). Hemodynamic studies comparing patients with compensated cirrhosis, decompensated cirrhosis, and ACLF as defined by APASL showed that the hemodynamic changes of ACLF were similar to those of decompensated cirrhosis despite similar Child-Turcotte-Pugh (CTP) scores between the 2 latter groups (71). This indicates that measures other than CTP and liver disease severity such as hemodynamics could be associated with ACLF prognosis.

Coagulation

Recommendations

1. In patients with cirrhosis and ACLF, we suggest against INR as a means to measure coagulation risk (very low quality, conditional recommendation).
2. In patients with cirrhosis as compared to noncirrhotic populations, we suggest there is an increased risk of venous thromboembolism (VTE) (low quality, conditional recommendation).
3. In patients with ACLF and altered coagulation parameters, we suggest against transfusion in the absence of bleeding or a planned procedure (low quality, conditional recommendation).
4. In patients with cirrhosis who require invasive procedures, we recommend use of thromboelastography (TEG) or rotational TEG (ROTEM), compared with INR, to more accurately assess transfusion needs (moderate quality, conditional recommendation).

Key concept statements

1. Hypocoagulation found on TEG/ROTEM in ACLF is an independent marker of poor prognosis and is usually found in patients with systemic inflammatory response syndrome (SIRS).
2. In the absence of contraindications, such as recent bleeding and significant thrombocytopenia, hospitalized cirrhotic patients should receive pharmacologic VTE prophylaxis.
3. In patients with well-controlled decompensated cirrhosis, low-molecular-weight heparin (LMWH) may decrease the risk of new decompensation, but inadequate data exist at this time to anticoagulate patients in the absence of thrombosis.

Summary of evidence

Laboratory coagulation abnormalities are common in patients with cirrhosis and described in 2 of the 3 widely used definitions of ACLF; APASL requires an INR of ≥1.5 as part of the ACLF definition, and EASL-CLIF defines coagulation failure separately as either an INR ≥ 2.5 or platelets ≤20×10^9/L. However, neither of these parameters measure coagulation. In fact, recent data have clearly shown that INR, although strongly linked with liver function in the absence of vitamin K deficiency, does not measure coagulation in patients with cirrhosis (72). TEG and ROTEM are viscoelastic tests that measure resistance to stirring whole blood in a cuvette and therefore are more physiologic than standard testing. Normal TEG or ROTEM measurements in patients with compensated cirrhosis, decompensated cirrhosis, or ACLF can avoid the need for blood product transfusion in patients undergoing procedures, even when the INR is elevated (72,73). In patients with variceal and nonvariceal bleeding, TEG-guided coagulation assessment results in a marked decrease in transfusions with no change in the risk of rebleeding (74,75). However, when TEG or ROTEM values are abnormal, clear cutoffs for type and number of transfusions needed have not been developed. When these tests are not available, fibrinogen and platelet levels should be evaluated instead (76,77). No data have ever supported the use of prophylactic transfusions in the absence of bleeding or the need for invasive procedures (76). However, when mucosal bleeding does occur or invasive procedures are required in the presence of an abnormal TEG study, cryoprecipitate or prothrombin complex concentrate are the preferred low-volume alternatives to raise the fibrinogen level (74,76,78). Fresh-frozen plasma transfusion is not recommended because its high volume increases portal hypertension and delivers not only procoagulants but also anticoagulants.

In the presence of ACLF, a hypocoagulable TEG is strongly associated with systemic inflammation (79,80). Therefore, it is essential to rule out infection in all patients with ACLF, but the level of suspicion for infection in patients with ACLF and hypocoagulability should be even higher.

In patients with cirrhosis without ACLF, a rebalancing in coagulation occurs; however, in specific circumstances, hypercoagulability can be found (81,82). This is particularly true in areas of low and turbulent flow, such as the portal venous system. One study showed not only a decreased rate of portal vein thrombosis but also a lower rate of decompensation in patients randomized to LMWH compared with placebo. One cannot justify therapeutic LMWH chronically in patients with cirrhosis without a thrombus being present; however, full-dose anticoagulation should be used in patients with acute thromboembolic events, especially symptomatic acute portal vein thrombosis in the absence of contraindications (76,83,84).

When considering VTE prophylaxis, meta-analysis has shown hospitalized cirrhotic patients to be at higher risk than noncirrhotic patients for VTE (85). In general, pharmacologic VTE prophylaxis has not been shown to increase the risk of bleeding; however, patients with recent bleeding (variceal hemorrhage before banding ulcers have healed and nonvariceal hemorrhage before healing has been achieved) and significant thrombocytopenia (platelets < 50×10^9/L) are not optimal candidates for pharmacologic VTE prophylaxis. In other patients, pharmacologic prophylaxis with LMWH is preferred, but systematic studies comparing prophylactic agents and strategies are lacking (83).

PRECIPITATING FACTORS

Infections

Recommendations

1. In hospitalized decompensated cirrhotic patients, we recommend assessment for infection because infection is associated with the development of ACLF and increased mortality (moderate quality, strong evidence).
2. In patients with cirrhosis and suspected infection, we suggest early treatment with antibiotics to improve survival (very low quality, conditional evidence).

Key concept statements

1. Antibiotics should be de-escalated once cultures and sensitivities are available.
2. First-line antibiotic therapy should be determined by the etiology and severity of the infection, how it was acquired (community-acquired, healthcare-associated, or nosocomial), and local resistance patterns.
3. Multidrug-resistant (MDR) bacterial infections are on the rise and must be considered when prescribing antibiotics.
4. Alterations in gut microbial composition and function are associated with infection susceptibility and ACLF.

Summary of evidence

Infection occurs in up to 40% of patients with ACLF at initial presentation and is a leading cause of ACLF in Western countries (14,64,86,87). The pathogenesis of infections in cirrhosis stems from multiple factors including altered systemic and gastrointestinal immunity, impaired intestinal barrier, changes in microbiota, and frequent instrumentation, hospitalization, and exposure to microbiota-altering therapies (88,89). In contrast with healthy subjects, patients with cirrhosis have a systemic inflammatory milieu that is exacerbated by gut microbial dysbiosis. This dysbiosis is associated with lower relative abundance of commensals, such as *Lachnospiraceae*, *Ruminococcaceae*, and higher pathobionts, such as *Enterococcaceae*, *Escherichia*, and *Streptococcus* (20). This is potentiated further with PPI and antibiotic use and multiple readmissions (17). Hospitalized patients have the greatest extent of dysbiosis, and an altered microbial composition on admission is associated independently with ACLF development, organ failure, and death (16,90).

Patients with cirrhosis who acquire an infection may not have typical symptoms of infection. Fever is relatively uncommon in patients with cirrhosis who present with an infection, and because patients with cirrhosis most often have low white blood cell (WBC) counts at baseline, a "normal" WBC count may represent a doubling or even tripling of a patient's baseline WBC count (36). Therefore, all nonelectively admitted patients with cirrhosis should be evaluated for infection with prompt initiation of antibiotics when infection is suspected to prevent ACLF development. Each hour delay in antibiotic administration in infected patients can worsen prognosis with greater mortality (91). AKI, altered mental status, and organ failure are often indicators of infection in patients with cirrhosis. Because serum C-reactive protein, procalcitonin, and bacterial DNA levels are often elevated in patients with cirrhosis, they are not diagnostic of infection, although persistently high levels correlate with mortality (92–95). Similarly, a higher neutrophil-lymphocyte ratio at admission portends an increased risk of mortality (96).

The documented presence of infection in a patient with ACLF is a strong negative prognostic factor (64,86,97). In a study of

2,675 patients with cirrhosis who were nonelectively hospitalized, 40% of whom were admitted with or developed an acute infection, the presence of infection was associated with significantly lower odds of 30-day survival (odds ratio 0.67; 95% CI 0.48–0.93) (64).

Bacterial infections are the most commonly identified infections in hospitalized patients with cirrhosis (86,87,89). The most frequent infections at admission in one large multinational prospective study were SBP (23%), urinary tract infections (19%), skin/soft-tissue infections (10%), respiratory infections (9%), and *C. difficile* (5%). Although no pathogen was identified in nearly one-quarter of patients, Gram-positive bacteria were more frequently identified (33%) than Gram-negative bacteria (27%) as the source of infection.

First-line antibiotic therapy should be determined by the etiology and severity of the infection, when/how it was acquired (community-acquired, healthcare-associated, or nosocomial), and local resistance patterns. Community-acquired infections are diagnosed <48 hours from admission in the absence of healthcare exposure in the past 90 days. Healthcare-associated infections are diagnosed <48 hours from admission in patients who have been exposed to healthcare within the past 90 days (i.e., dialysis, an invasive procedure, and reside in long-term care/rehabilitation). Nosocomial infections are diagnosed >48 hours after admission. Healthcare-associated and especially nosocomial infections are more likely to be MDR. The initial antibiotic regimen administered has a marked impact on prognosis. Therefore, it is critical to determine when and how the infection was acquired to appropriately choose the initial antibiotics (98). Use of novel polymerase chain reaction technology can shorten the time to diagnosis of pathogens and resistance patterns, thereby shortening the time to diagnosis and antibiotic de-escalation (99).

MDR pathogens have been increasing in prevalence and are reported in 22%–38% of infections in hospitalized patients with cirrhosis (100,101). The types of MDR pathogens vary by geographic region, with vancomycin-resistant enterococci being the most common in North America and extended-spectrum beta-lactamase-producing *Enterobacteriaceae* the most common in Europe (100,101). In a large multicenter European cohort, an antibiotic regime that included MDR coverage (piperacillin-tazobactam or carbapenem ± glycopeptide/linezolid/daptomycin) was more effective at managing nosocomial infections compared with "classical" empiric regimens containing a third-generation cephalosporin, amoxicillin-clavulanic acid, or quinolones. Importantly, inadequacy of a classical first-line vs a regimen covering MDR was strongly associated with 28-day mortality in patients with ACLF (50% vs 26%; $P = 0.002$) (100).

Nosocomial infections

Key concepts

1. In hospitalized patients with decompensated cirrhosis, the presence of a nosocomial infection is associated with increased risk of ACLF development and mortality.

Summary of evidence

Nosocomial infections have been reported in approximately 16% of patients with ACLF, many of which could have been prevented (101,102). Given the later appearance and altered microbiology of these infections, their prognosis is often worse than that of infections diagnosed on admission or within 48 hours. Among nosocomial infections, urinary tract infection was the most common (reported in one-third of hospitalized patients with cirrhosis), followed by respiratory infections and SBP. In the NACSELD experience, nosocomial infections were more likely caused by vancomycin-resistant *Enterococcus*, *C. difficile*, or fungal species than other infections (103). The risk of nosocomial infection development was higher in patients with a model for end-stage liver disease (MELD) score >20, evidence of SIRS on admission, and those already on therapy for HE. Because urinary tract infections are a common nosocomial infection, and Foley catheter placement is the greatest risk of urinary tract infection development, Foley catheters should never be used to monitor urine output nor in patients for the simple reason of limited mobility. Nosocomial infections increase the risk of ACLF development; however, increased monitoring has never been shown to decrease the risk or improve outcomes.

Fungal infections

Recommendations

1. In hospitalized patients with ACLF because of a bacterial infection who have not responded to antibiotic therapy, we suggest suspicion of an MDR organism or fungal infection to improve detection (very low quality, conditional recommendation).

Key concept statements

1. Because of underlying immune changes, altered gut microbiota, multiple interventions, and admissions, patients with cirrhosis are at significant risk of nosocomial and fungal infections.
2. In hospitalized patients with cirrhosis, development of a fungal infection is associated with increased risk of ACLF and increased mortality.

Summary of evidence

Fungal pathogens are a particularly important source of infection in patients with ACLF, most of which are nosocomial (104). The reported rate of fungal infections in hospitalized patients with cirrhosis ranges from 2% to 15%. The likelihood of fungal infections increases with greater number of organ failures, ACLF diagnosis, ICU transfer, diabetes, AKI, longer stay, and previous bacterial infection (87,105,106). It is likely that antibiotic use promotes fungal dysbiosis because the type of antecedent bacterial infection does not affect the subsequent fungal infection (104,107). As shown in microbial studies, fungal infections most often occur with *Candida* species with the highest case fatality rate for peritonitis and fungemia (104,105). Fungal infections are often not diagnosed and result in a high mortality and ACLF burden and higher likelihood of removal from LT waiting lists. Although galactomannan index and 1,3-β D Glucan are an adjunct for fungal infections and have high sensitivity, they have limited specificity, have only been studied in small series, and therefore better modalities for rapid fungal infection diagnosis are required to prevent ACLF (106).

Medications and prophylaxis

Recommendations

1. In patients with cirrhosis with a history of SBP, we suggest use of antibiotics for secondary SBP prophylaxis to prevent recurrent SBP (low quality, conditional recommendation).
2. In patients with cirrhosis in need of primary SBP prophylaxis, we suggest daily prophylactic antibiotics, although no one specific regimen is superior to another, to prevent SBP (low quality, conditional recommendation).

3. In patients with cirrhosis, we suggest avoiding PPI unless there is a clear indication, such as symptomatic gastroesophageal reflux or healing of erosive esophagitis or an ulcer, because PPI use increases the risk of infection (very low quality, conditional recommendation).

Key concept statements

1. Nonselective beta-blockers (NSBB) may decrease bacterial translocation, but patients with ACLF have difficulty tolerating clinically relevant doses.
2. Rifaximin may prevent complications of cirrhosis other than HE.
3. Concentrating or avoiding IV medications that require large sodium loads can improve volume status in patients with ACLF.

Summary of evidence

SBP prophylaxis. It is clear that secondary SBP prophylaxis decreases the risk of recurrent SBP and therefore improves outcomes (108). Daily treatment is needed to decrease the rate of MDR infections. Although most data document the utility of daily norfloxacin, in areas where this is not available, daily ciprofloxacin or trimethoprim-sulfamethoxazole may be used. No study has ever documented superiority of one regimen over another. Cohort studies with subgroup analysis of different types of SBP prophylaxis and randomized trials in the Middle East have shown that rifaximin may be at least as effective as other antibiotics used for SBP prophylaxis and possibly superior, but bacterial resistance patterns may be different in those countries (109,110). Once a resistant infection occurs in a patient on SBP prophylaxis, there is no guidance on how to proceed with SBP prophylaxis. Although the risk-benefit ratio of secondary SBP prophylaxis is clear, recent data have shown that patients admitted to the hospital on primary prophylaxis have a worse outcome than admitted patients taking secondary SBP prophylaxis (56). Of note, primary prophylaxis was studied and recommended in an era when transplant occurred at a lower MELD in patients with progressive liver disease from hepatitis C virus, and now that patients wait longer for transplant, we may need to re-evaluate the indications and drugs used for primary SBP prophylaxis.

PPI therapy. PPIs have been shown to increase the rate of infections in patients with cirrhosis (111–113). Because infections are the number one cause of ACLF in North America and Europe, it is imperative to decrease the rate of infections in our patients with cirrhosis. Because PPIs impair the oxidative burst of neutrophils, they further impair immune function in patients with cirrhosis. PPIs have a major but reversible impact on the gut microbiome, which is also associated with complications in patients with cirrhosis (17,114). As a result, it is important to only treat patients with PPIs who have an indication that cannot be adequately treated with other types of acid blockade and discontinue or change them once healing has been achieved. For example, PPIs are needed to heal gastrointestinal ulcers and erosive esophagitis and treat gastroesophageal reflux not responsive to H2 blockers (115).

NSBB. In a nonrandomized study, patients with ACLF had a lower mortality if they were admitted on an NSBB than if they were not (116). In one randomized controlled trial (RCT), carvedilol improved 28-day but not 90-day transplant-free survival in admitted patients with ACLF compared with placebo (117). NSBB are clearly indicated for both primary and secondary variceal hemorrhage prophylaxis (118), and although they may decrease bacterial translocation, it is difficult in clinical practice for patients with ACLF to tolerate clinically meaningful doses of NSBB.

Statins. Statins have been shown to decrease the rate of hepatic fibrosis, hepatic decompensation, and mortality in patients with cirrhosis; every year of statin exposure cumulatively and independently decreased mortality in patients with CTP-A and -B cirrhosis (119–121). Although little is known about statins in ACLF in humans, in a recent rat model study of lipopolysaccharide-induced ACLF, pretreatment with simvastatin reduced portal pressures, inflammation, and oxidation and led to improved survival (122). However, one must be concerned about dose-related hepatotoxicity of statins in patients with ACLF, given the recent randomized study of patients with CTP-B and -C cirrhosis that showed an increase in alanine aminotransferase (ALT) in patients randomized to 40 mg per day of simvastatin that was not seen in patients randomized to 20 mg per day or placebo (123).

Rifaximin. Rifaximin decreases the rate of overt HE recurrence. Rifaximin has also been studied for SBP prophylaxis compared with placebo and oral quinolone therapy (110). In a meta-analysis, rifaximin was superior to no antibiotics, but equivalent to an oral quinolone for SBP prophylaxis, although most studies included were small, not randomized, or did not allow rifaximin for treatment of HE (110).

Sodium content of IV medications. When choosing antibiotics in patients with a history of ascites, one should also consider the sodium content. At a minimum, always ask pharmacy to concentrate all IV medications, whenever possible or administered in 5% dextrose instead, whenever feasible.

NONINFECTIOUS PRECIPITATING FACTORS

Alcohol-associated hepatitis

Recommendations

1. In patients with severe alcohol-associated hepatitis (Maddrey discriminant function [MDF] ≥ 32; MELD score > 20) in the absence of contraindications, we recommend the use of prednisolone or prednisone (40 mg/d) orally to improve 28-day mortality (moderate quality, strong recommendation).
2. In patients with severe alcohol-associated hepatitis (MDF ≥ 32; MELD score > 20), we suggest against the use of pentoxifylline to improve 28-day mortality (very low quality, conditional recommendation).

Key concept statements

1. AAH leads to ACLF as a result of a combination of a severe SIRS and sepsis.

Summary of evidence

AAH is a major cause of ACLF worldwide. Most patients with ACLF in the CLIF consortium study either had alcohol use, AAH, or infection as the precipitating event (36). Similar precipitating events were noted in a study from Asia (124). Thus, active alcohol use, AAH, and bacterial infections are most frequently associated with the development of ACLF (125). At this time, it is unclear whether alcohol-related ACLF is a specific form of alcohol-associated liver disease or represents a later stage of severe AAH. Nevertheless, it is important that AAH be optimally treated to reverse ACLF. In addition, the alcohol use disorder needs to be treated.

Patients with AAH have jaundice with associated malaise, tender hepatomegaly, and features of hepatic decompensation such as ascites, HE, variceal bleeding, and bacterial infection. Typically, a history of heavy alcohol use is present for greater than 5 years, but heavy alcohol use for a duration of as little as 6 months may cause AAH (126). Heavy alcohol use is defined as more than 3 standard drinks per day for women (approximately 40 g of alcohol) and 4 standard drinks per day for men (approximately 50–60 g of alcohol). Liver biopsy is required to make a diagnosis of definite AAH, although patients may be entered into clinical protocols with a diagnosis of probable AAH (history of heavy alcohol use, typical clinical and laboratory presentation described above, and absence of confounding factors that may explain the clinical picture). Patients may have stopped drinking at the time of hospitalization, but the diagnosis may yet be made if alcohol use has continued to a period of less than 60 days before the onset of jaundice. Serum bilirubin is usually elevated (>3 mg/dL [>50 μmol/L]), as is the aspartate transaminase (>50 IU/mL), with aspartate transaminase to ALT ratio of >1.5 (126). Severe AAH has usually been defined by an MDF score of ≥32 that predicts mortality of up to 30% at 30 days. More recently, scores such as the MELD score, age, serum bilirubin, INR, and sCr (ABIC) score, and the Glasgow alcoholic hepatitis score have been found to be superior to the MDF score. For the purposes of treatment trials, severe AAH has been defined by MDF ≥ 32 or MELD score >20 (127).

Several agents have been used to treat severe AAH, but the most commonly used in the United States have been prednisone and pentoxifylline. In a multicenter French and Belgian study, the combination of prednisone and pentoxifylline has not been found to be superior to prednisone alone (128). In the intention-to-treat analysis, 6-month survival was not different between the pentoxifylline-prednisolone and placebo-prednisolone groups (69.9% [95% CI 62.1%–77.7%] vs 69.2% [95% CI 61.4%–76.9%], $P = 0.91$). In multivariable analysis, only the Lille model and the MELD score were independently associated with 6-month survival. In the STOPAH study, which was a multicenter, randomized, double-blind trial with a 2-by-2 factorial design conducted in 65 hospitals across the United Kingdom, pentoxifylline did not improve survival in patients with AAH (129). Prednisolone was associated with a reduction in 28-day mortality that did not reach significance and with no improvement in outcomes at 90 days or 1 year. Patients with an MELD score > 25 did not show a significant reduction in mortality at day 28 with prednisolone treatment even after excluding patients with sepsis or gastrointestinal bleeding. By day 90, there was no difference in mortality between treated and untreated patients identified by any score (130).

In a network meta-analysis of 22 RCTs including 2,621 patients and comparing 5 different interventions, only corticosteroids decreased risk of short-term mortality (131). Another meta-analysis of 11 studies including 2,111 patients showed that corticosteroid use reduced the risk of death within 28 days of treatment as compared with pentoxifylline, but not beyond that period (132). In determining factors associated with mortality at 2 months and 6 months, a combination of MELD score at baseline and response to treatment as determined by the Lille score at 7 days was superior to other combinations of scores (MDF + Lille; ABIC + Lille; and Glasgow alcoholic hepatitis score + Lille) (133). However, survival beyond 6 months was again only associated with abstinence from alcohol (134). In highly selected patients with severe AAH not responding to optimal medical therapy and supportive measures, LT may be considered (135,136).

In summary, severe AAH is probably the most common precipitating event for ACLF. Infection is common in these patients. Prednisone is the only pharmacological therapy associated with improved survival, but only at 28 days. In addition to prednisone, treatment of infection, nutritional supplementation, and support of failing organs are required. Abstinence from alcohol is essential for survival beyond 6 months. LT may be considered in highly selected patients (137,138).

Drug-induced liver injury

Key concept statements

1. Both prescribed and nonprescribed medications can cause drug-induced liver injury (DILI). The most common prescribed medications that cause DILI are the antimicrobials. Self-medication with complementary and alternative medicine (CAM) is common, spreading often through social media.
2. Actual prevalence of ACLF related to DILI is unknown because DILI is often underreported, and most patients have an uneventful recovery (139).
3. When DILI causes liver injury, it usually causes acute liver failure. Formal studies in patients with pre-existing liver cirrhosis are lacking. Estimated incidence in Asian countries is approximately 10%, and that in the United States is approximately 7%. DILI in the setting of advanced liver disease carries the higher risk of poor outcome.
4. Onset of ACLF occurs on average 1 month after taking the offending medication, but can be delayed for up to 3 months.
5. Mortality in DILI-related ACLF is >50%, with the ACLF grade as the only significant predictor of mortality.
6. Patient education about limiting use of pharmacological agents and avoiding use of CAM is key to the prevention of DILI-associated ACLF.
7. Patients with underlying liver disease should be monitored when prescribed new medication(s) with hepatotoxic potential.

Summary of evidence

Literature related to DILI-induced ACLF is scarce. In the database from the Drug-Induced Liver Injury Network from the United States, among the 1,089 patients with DILI-related liver injury, 107 patients either died or required an LT, of which only 68 patients were found to have DILI as the primary cause of their end point. This occurred in 5 patients who had underlying cirrhosis and were designated to have DILI-related ACLF. However, it is not clear whether among the 982 patients who survived, any had ACLF and survived (140). The only other publication relating to CAM-induced ACLF is from India, which describes the condition occurring mostly in younger men. Eighty-four of the 1,666 patients with cirrhosis had decompensation related to CAM use; of these, 30 developed ACLF (141). On multivariate analysis, the only independent predictor of overall mortality was the ACLF grade, with 100% of patients with ≥grade 2 ACLF having died at a mean of 120 days.

Viral hepatitis

Key concept statements

1. Patients with underlying liver disease can develop ACLF if they contract any of the known viral hepatitides.
2. Hepatitis B flares are a common cause of ACLF in Asian countries and may present like acute liver failure.
3. A hepatitis B flare often occurs in patients either spontaneously or on abrupt stopping of their antiviral medications.
4. Other viral infections that cause ACLF are hepatitis A and E infections superimposed on chronic liver disease or hepatitis D superimposed on hepatitis B viral (HBV) infection.
5. Bacterial infections are a common trigger of ACLF in patients with viral hepatitis, which should be monitored for and treated promptly.
6. Vaccinate patients with chronic liver disease against hepatitis A and hepatitis B if they are not already immune.

Summary of evidence

HBV infection is the most common etiology of liver cirrhosis in Asian endemic countries. Hepatitis B–associated ACLF therefore is much more common in Asia than in Western countries, contributing to 15% of cases of ACLF in Asian Pacific countries (142,143). In most cases, the HBV flares are spontaneous, although reactivation because of inappropriate withdrawal of nucleot(s)ide analogs, nucleot(s)ide analog resistance, and during chemotherapy are also common (144). Hepatitis B flares seem to be particularly common in patients with underlying chronic liver disease, especially in those with decompensated cirrhosis. These patients may have reduced capacity for hepatocyte regeneration. Of course, other viral hepatitis occurring either *de novo* or superimposed on other chronic viral hepatitis infection can also precipitate ACLF (145,146). Clinicians need to be aware of the association between hepatitis D viral and HBV infections.

The development of ACLF in patients with HBV infection seems to be driven by intense inflammation that is both sterile and infection-related (147). It has been shown that damage-associated molecular patterns released from necrotic hepatocytes and breakdown of extracellular matrix can initiate an intense sterile inflammatory response. Because alcohol consumption may be prevalent among patients with hepatitis B infection, such patients can have submassive necrosis.

Surgical procedures

Key concept statements

1. Surgery of any type in patients with cirrhosis is associated with significant risks of organ failure and ACLF development when compared with patients without cirrhosis.
2. In patients with cirrhosis contemplating surgery, both the Mayo Clinic score and the VOCAL PENN score are available on-line for calculating the risks of mortality with surgery (148,149).
3. Acute hepatic decompensation and the presence of infection are significant risk factors for the development of ACLF after surgery.
4. The development of ACLF after surgery is associated with significantly reduced survival compared with patients without ACLF.
5. Patients with cirrhosis who require surgery should be carefully selected because perioperative management of such patients also impacts survival.

Summary of evidence

The performance of surgery in patients with cirrhosis is associated with significant risks of postsurgical decompensation, and this may progress to ACLF in a percentage of patients. Therefore, surgery is usually not recommended unless the benefits outweigh the risks. The Mayo Clinic calculator for postsurgical risks of mortality has been in use for more than a decade and has been validated in other study populations (148,150,151) and can be found here (https://www.mayoclinic.org/medical-professionals/transplant-medicine/calculators/post-operative-mortality-risk-in-patients-with-cirrhosis/itt-20434721). More recently, the VOCAL PENN score also takes into account the type of surgery being performed (149) (http://www.vocalpennscore.com) and improves on the prediction of 30-day mortality. However, these studies have always considered mortality as an end point, rather than AD or the development of ACLF as end points. In a recently published single-center study that assessed the outcomes of cirrhotic patients who underwent surgery, of the 330 patients, 81 (24.5%) developed ACLF by EASL-CLIF criteria within 28 days of surgery (152). The patients who developed ACLF were older and had higher baseline CTP and MELD scores. Abdominal nonliver surgery was associated with ACLF development most frequently (35%). Most patients developed grade 1 ACLF, with the most common organ failure being renal failure defined as an sCr of $>$2.0 mg/dL. Other organ failures occurring at lower frequency were circulatory (25.9%), respiratory (25.9%), brain (13.6%), and liver failure (13.6%). Increasingly, more patients developed ACLF during longer term follow-up, with eventually 40% of patients developing ACLF at the end of 1 year. AD and infection at the time of surgery are the 2 most important factors for the development of ACLF after surgery. Once ACLF develops, 37% of patients eventually improved, 49% remained stable, whereas 14% deteriorated. The factors that predict mortality after the development of ACLF include liver surgery, alkaline phosphatase with a cutoff of 164 IU/L, and an MELD score with a cutoff of 10.

Other factors that have been studied to predict mortality in patients with cirrhosis undergoing elective surgery include American Society of Anesthesiology class, high-risk surgery such as cardiovascular and open abdominal surgery vs all other types of surgery which are considered lower risk, and the level of the hepatic venous pressure gradient (HVPG) (153). An HVPG of $>$16 mm Hg was associated with an increased risk of mortality at 1 year (hazard ratio of $>$ 2.5), and for an HVPG of $\geq$20 mm Hg, the hazard ratio for death at 1 year was 5.67.

Nonsurgical interventions

Key concept statements

1. Nonsurgical interventions can also precipitate ACLF, but the exact incidence is unknown.
2. It seems that patients with more severe liver dysfunction are at higher risk of the development of ACLF with endoscopic retrograde cholangiopancreatography (ERCP).
3. For every nonsurgical intervention proposed for cirrhotic patients, it is imperative to weigh the risks, benefits, and potential for ACLF development.
4. Patients need to be closely monitored in the postprocedure period for the development of ACLF.

Summary of evidence

The CANONIC study from the EASL-CLIF consortium has identified therapeutic paracentesis and the insertion of a transjugular intrahepatic portosystemic stent shunt (TIPS) as the nonsurgical interventions that may precipitate ACLF in admitted cirrhotic patients (36). However, no details about the ACLF episodes related to these interventions are provided. In a clinical vignette describing the use of TIPS in the management of complications of portal hypertension, the development of ACLF was mentioned as a possible complication of TIPS insertion because these patients can develop new HE and worsening of liver function (154). Once again, no details are provided as to the incidence and predictive factors for the development of ACLF post-TIPS insertion. It has been postulated that continued bacterial translocation post-TIPS insertion may be the trigger that drives an ongoing inflammatory response that is responsible for the development of ACLF. Indeed, markers of systemic inflammation and bacterial translocation predicted mortality in post-TIPS patients (155,156).

However, there is a detailed report on ERCP inducing ACLF in patients with decompensated cirrhosis (157). ERCP was mostly performed for acute cholangitis, choledocholithiasis, biliary stricture, and stent replacement. Of the 441 ERCP procedures performed, 158 were performed in patients with established cirrhosis, with decompensation being present at the time of ERCP in 71 cases (45%). ACLF developed in 11.4% (18/158) cases within 1 month of ERCP. This was significantly higher than the ACLF rate of 3.2% in the no intervention group. The majority belonged to ACLF grade 1 (55%), with 35 (22.2%) patients belonging to ACLF grade 2 and grade 3. ACLF was more common in the patients who developed adverse events in the post-ERCP period (7/27 or 25.9% vs 11/131 or 8.3% in those without post-ERCP adverse event, $P = 0.01$). The only independent predictor for the development of ACLF after ERCP was an MELD score of ≥15.

This study also evaluated the ACLF rates in other non-ERCP interventions among cirrhotic patients. ACLF developed in 17.5% of patients who underwent various other interventions, with RRT being the most common precipitant, followed by therapeutic paracentesis, non-ERCP endoscopies, and TIPS insertion.

TREATMENTS

GENERAL

Critical care management

Key concept statements

1. Management of the ACLF patient is best accomplished by a multidisciplinary team approach including expertise in critical care and transplant hepatology.
2. The goal of treatment is reversal of the precipitating cause, treatment of sepsis, support of the failing organ(s), and LT in selected patients.

Summary of evidence

Patients with cirrhosis require admission to the ICU for support of failing organs. Such a situation occurs in patients with severe AAH, and infections or acute hepatitis, usually drug or viral, superimposed on chronic liver disease (158). Infections may progress to septic shock where almost 65% of patients will die. Dire although this might sound, this mortality is a significant improvement from the near fatal outcome 20 years ago (159). In patients without cirrhosis, septic shock is identified by the need for vasopressor support to maintain an MAP of ≥65 mm Hg and serum lactate level ≥2 mmol/L (>18 mg/dL) in the absence of hypovolemia (160). Nationwide, more than 50% of patients meeting criteria for ACLF have in-hospital mortality. Intensive care management of the ACLF patient involves early goal-directed therapy, intravascular volume resuscitation, broad-spectrum antibiotic administration within 1 hour of presentation, monitoring of tissue oxygenation, support of failing organs including consideration of artificial liver support, and LT in selected patients. An overview of managing ACLF in critical care is shown in Figure 5.

More rapid completion of a 3-hour sepsis-care bundle and rapid administration of antibiotics is associated with lower risk-adjusted in-hospital mortality in patients with sepsis (91). An MAP goal of ≥60 mm Hg in patients with cirrhosis, rather than 65 mm Hg, is recommended without specific targets for ventricular filling pressure, volume, lactate, or central venous oxygen saturation (ScvO2) (31). Placement of an arterial line and central venous access in patients with circulatory shock is highly recommended. Echocardiography is the preferred modality for monitoring fluid status during fluid resuscitation. Because patients have elevated intra-abdominal pressure because of ascites, monitoring of central venous pressure may be inaccurate. Monitoring of abdominal pressure using a bladder catheter is not recommended routinely. Careful large-volume paracentesis is recommended in patients with tense ascites (161). To assess volume status, dynamic measurements in response to fluid boluses are recommended. When the inferior vena cava is compressed by tense ascites, collapsibility is difficult to assess. Therefore, monitoring volume status by respiratory variations of the inferior vena cava may be inaccurate. A bladder catheter should be placed for monitoring urine output as a marker of volume status because sCr levels may be low in patients with sarcopenia despite renal insufficiency (31). A pulmonary arterial catheter to monitor pulmonary arterial pressure is recommended only in patients with pulmonary arterial hypertension.

Serum lactate may be elevated in patients with cirrhosis because of impaired hepatic clearance or because of tissue hypoxia. In patients who are hemodynamically unstable, until proven otherwise, an elevation in serum lactate suggests tissue hypoxia. If serum lactate rises on serial measurements, tissue hypoxia is much more likely.

It is critical that effective broad-spectrum antibiotics be administered within 1 hour of ICU admission in patients with cirrhosis because every hour delay in administration of antibiotics is associated with almost doubling in mortality (162). The choice of antibiotics depends on local susceptibility patterns. Empiric therapy with meropenem and vancomycin is recommended in patients with cirrhosis and septic shock. When vancomycin-resistant *Enterococcus* infection is suspected, linezolid or daptomycin should be used (163). When the MAP is ≤60 mm Hg despite volume resuscitation, norepinephrine is used as vasopressor therapy. Side effects of norepinephrine include arrhythmias, bradycardia, and tissue ischemia. Cardiac preload and inotropic function are improved by norepinephrine. If MAP does not increase despite norepinephrine, hydrocortisone is administered in a dose of 50 mg every 6 hours. Although steroids are associated with improved resolution in shock, there is no long-term survival benefit (164).

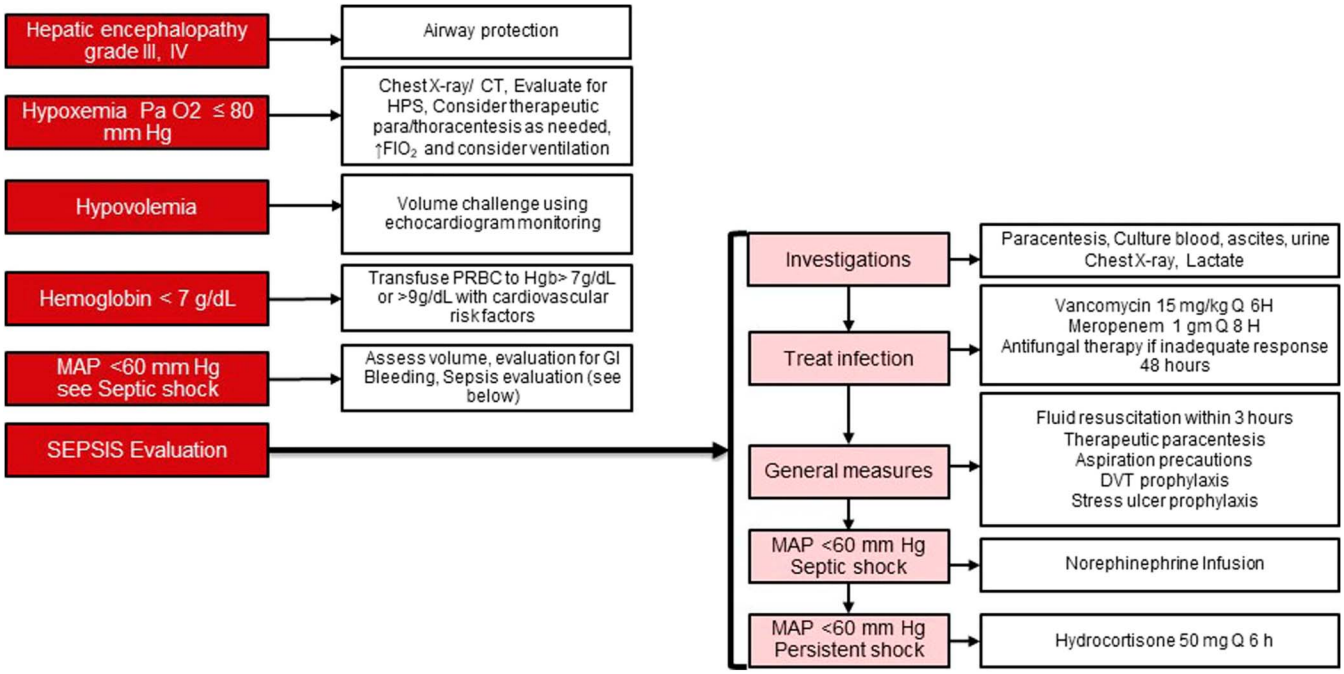

Figure 5. Suggested algorithm for the critical care management of acute-on-chronic liver failure in cirrhosis. CT, computed tomography; DVT, deep venous thrombosis; GI, gastrointestinal; HPS, hepatopulmonary syndrome; MAP, mean arterial blood pressure; PRBC, packed red blood cells.

Nutrition

Recommendations

1. In patients with cirrhosis who are hospitalized, we suggest against the routine use of parenteral nutrition, enteral nutrition, or oral supplements to improve mortality.

Key concept statement

1. Caution is advised when using enteral nutritional support in those at high risk of aspiration, such as those with HE.

Summary of evidence

There are no clinical trials specifically evaluating the use of nutritional support in patients with ACLF. In the absence of data, adherence to published guidelines on nutritional support in critically ill patients with cirrhosis is recommended (165,166). Maintaining a daily caloric intake of 35- to 40-cal/kg body weight/day that includes a daily protein intake of 1.2- to 2.0-g/kg body weight/day is recommended (167). Enteral feeding should be used if the patient is unable to meet nutritional needs by mouth alone. Parenteral feeding should be considered in patients who cannot meet their nutritional needs using the gastrointestinal tract or in those with an unprotected airway, such as in patients with grade 3–4 HE. In an RCT of patients with severe AAH receiving enteral nutritional support, 4% developed aspiration pneumonia that was believed to be related to enteral feeds (168).

SPECIFIC TREATMENTS

Use of albumin

Recommendation

1. In hospitalized patients with cirrhosis, we recommend against daily infusion of albumin to maintain the serum albumin >3 g/dL to improve mortality, prevention of renal dysfunction, or infection (moderate quality, strong recommendation).

Key concept statements

1. Albumin has several potential benefits beyond the oncotic effect.
2. IV albumin is recommended to prevent AKI and subsequent organ failures in patients diagnosed with SBP.
3. IV albumin is not recommended to prevent organ failures in patients with cirrhosis who have infections other than SBP.
4. Five-percent albumin is often used for rapid volume resuscitation, whereas for more sustained volume expansion, we recommend 25% albumin.

Summary of evidence

IV albumin has been used to prevent AKI and renal failure in SBP and is also recommended to prevent postparacentesis circulatory dysfunction (169,170). Because of the reduction in the quantity and impaired quality of albumin in patients with cirrhosis, which worsens with advancing disease, albumin could have potential uses in other indications as well (171). Two studies evaluating the routine outpatient use of IV albumin came to differing conclusions. The ANSWER trial, which included outpatients with relatively early stage decompensated cirrhosis in an open-label fashion, showed a clear improvement in mortality and cirrhosis-related complications, whereas the MACHT trial, which included more advanced patients on the LT list and included midodrine therapy, did not show benefit (172–174). Subsequent analysis of the ANSWER trial showed that reaching a serum albumin of 4.0 g/dL provided the best improvement for survival (174). However, a recent RCT in admitted cirrhotic patients showed that daily infusion of albumin to maintain a serum albumin of ≥30 g/L was of no benefit in terms of preventing a combination of infection, renal dysfunction, or death (175). There were more patients in the albumin arm who developed pulmonary edema and respiratory infections (175,176). There is also currently no evidence that

inpatients with infections other than SBP benefit from routine IV albumin (54,177). Despite these challenges, surveys and uncontrolled experiences have found that clinicians use albumin for conditions as varied as hyponatremia, HE, hypoalbuminemia, hypervolemia, and other infections in both inpatient and outpatient settings (178,179). Given the expense, logistic challenges of setting up infusions and potential for causing pulmonary edema, the effectiveness of IV albumin in conditions other than SBP and postparacentesis circulatory dysfunction needs more study.

When rapid volume expansion is required, 5% albumin is used. The expansion in volume is approximately equal to the volume of 5% albumin infused and occurs within about 15 minutes. When 25% albumin is used, the volume expansion is 3.5–5 times the volume infused, but takes longer to achieve. In patients with cirrhosis who have longstanding hypervolemia, 25% albumin is preferred.

INTERVENTIONS OTHER THAN TRANSPLANT OR SPECIFIC ORGAN SUPPORT

Liver-assist devices

Key concept statements

1. Artificial liver support systems, with or without a biological component, theoretically can take over some of the functions of the liver, but whether they provide any clinical benefit is still unclear.
2. Plasma exchange has been shown to improve survival in patients with acute liver failure; however, its effect in ACLF is unknown.

Summary of evidence

Various artificial and bioartificial extracorporeal liver support systems have been tried as a treatment for ACLF (180,181). Artificial extracorporeal liver support systems are simple dialysis systems that allow for the removal of water-soluble and albumin-bound toxins from the patient's plasma. Examples of artificial extracorporeal liver support systems are molecular adsorbent recirculating system (MARS) and single-pass albumin dialysis. With these systems, the patient's blood is dialyzed against an albumin-containing dialysate to remove the unwanted toxins. The Fractionated Plasma Separation and Adsorption (Prometheus) liver support system works through a slightly different principle. The patient's blood is first passed through a specialized membrane, and the blood cells and large protein molecules are separated from the plasma and molecules smaller than 250 kD. The filtered plasma is then passed through 2 adsorbents, a neutral resin and an anion-exchange resin, before it is combined with the blood cell filtrate. The blood cells and adsorbed plasma are then dialyzed by a high-flux dialyzer to remove water-soluble toxins. It should be noted that these artificial extracorporeal liver support systems can only perform the detoxifying functions of the liver. The bioartificial extracorporeal liver support systems, by contrast, can provide synthetic and detoxifying functions of the liver. These latter devices require a source of cells, traditionally human or porcine hepatocytes. Although they sound attractive, the technology is complex, and it requires a critical cell mass. There is also the concern for xenotransmission, and therefore, they have not been popular. At the current time, there are no extracorporeal liver support systems that have been approved for clinical use in the United States, but these systems may be available through clinical trials in some settings.

To date, there is no strong evidence that these artificial liver support systems are useful in the management of patients with ACLF. The studies by and large only enrolled modest numbers of patients. The RCT assessing the use of MARS for ACLF (182) reported that MARS was able to decrease sCr and serum bilirubin (a molecule removal function of the dialysis system without necessarily improving renal or liver function) and reduce HE to a greater extent than the control group. However, there was no improvement in survival. The other study assessed the use of Prometheus in the treatment of ACLF (183). Once again, there was a significant reduction in serum bilirubin with Prometheus use, most likely from the filtering function of the Prometheus system, but this did not result in improvement in survival.

Improvement in short-term survival has been demonstrated using plasma exchange in patients with hepatitis B infection and ACLF (184). The APASL definition of ACLF was used in this study. Therefore, the results cannot be directly translated to patients in the west, and further studies are needed (185).

Granulocyte colony-stimulating factor

Recommendation

1. In patients with cirrhosis and ACLF, we suggest against the use of granulocyte colony-stimulating factor (G-CSF) to improve mortality (very low evidence, conditional recommendation).

Key concept statement

1. In patients with ACLF, administration of G-CSF has been shown to reduce short-term mortality in adult cohorts in Asia but not in Western cohorts or in children, suggesting that the impact of G-CSF may vary according to precipitating ACLF factors or other unmeasured confounders.

Summary of evidence

G-CSF has been studied to reduce mortality in patients with ACLF in several randomized clinical trials (186–189). A meta-analysis of these 2 trials conducted in Asia (India and China) including a total of 50 patients with ACLF and 52 controls (one placebo-controlled, one without any treatment) found that G-CSF administration significantly reduced short-term mortality (relative risk 0.56; 95% CI 0.39–0.80) (190). Adverse events in the treatment arm included fever, herpes zoster reactivation, nausea, and rash. Although these results were favorable, these small trials included predominantly patients with ACLF secondary to HBV reactivation or AAH without evidence of sepsis, so generalizability of these results to patients with other common etiologies of ACLF and/or active (non-HBV) infection is limited. Interim analysis of data from an RCT of 176 patients with ACLF at 18 European centers did not demonstrate a benefit of G-CSF on 90-day or 360-day transplant-free survival, overall survival, CLIF-C OF score, MELD score, or the occurrence of infections (189). In an RCT of children (mean age 7 years) with ACLF, G-CSF administration did not reduce 30- or 60-day mortality compared with standard of care (186). Based on the current data, use of G-CSF in adults or children with ACLF cannot yet be recommended as part of routine management.

Table 6. Future directions for ACLF research

Areas of need in ACLF	Specific steps needed to address the gaps
Burden of ACLF	1. Consortia that include both transplant and nontransplant centers 2. Education about ACLF beyond academic centers
Definition	1. Focus on narrowing the differences between different society definitions 2. Simplifying definitions to increase generalizability 3. Focus on separate diagnostic and prognostic markers 4. Could conventional prognostic scoring systems in patients with ACLF perform better if markers of systemic inflammation and circulatory dysfunction are included?
Pathogenesis	1. Research to identify PAMPs and DAMPs as diagnostic biomarkers of the mechanism of ACLF 2. Excessive responses to DAMP(s) might also be under control of genetic factors, and appropriate genomewide association studies are required 3. No comprehensive description of the landscape of circulating immune-suppressed cells is available in patients with ACLF 4. Cytokine/chemokine signatures for identification and grading of systemic inflammation are required 5. Changes in microbiota in differing stages of ACLF
Organ failure management and transplant	1. Prevention/early diagnosis/treatment 2. Biomarkers should be developed to identify early tissue dysfunction before failure sets in 3. Not organ failure management but prevention of organ failures is critical 4. Changes in bacteriology and increasing importance of infections as modulators of ACLF are needed 5. Organ-specific therapies are required 6. Bridging therapies with liver-assist devices and elucidating the role of LT 7. Which is the most appropriate time to decide prognosis in patients with ACLF (given the dynamic course of ACLF)? 8. Appropriate cutoffs for futility vs transplantation 9. Prospective randomized trials of additional priority for transplant listing in those with ACLF
Team approach to ACLF management	1. Greater multidisciplinary coordination between palliative care, transplant, and inpatient hepatology services 2. Improved education of trainees, professionals involved in ICU, infectious disease, LT care, and palliative care professionals

ACLF, acute-on-chronic liver failure; DAMP, damage-associated molecular pattern; ICU, intensive care unit; LT, liver transplant; PAMP, pathogen-associated molecular pattern.

Stem cell therapy

Key concept statement

1. Stem cell therapy represents a novel and promising therapeutic strategy to bridge patients with ACLF to more definitive therapy (e.g., control of acute infection, LT), but evidence to support its use in routine clinical practice is currently insufficient.

Summary of evidence

A meta-analysis of 4 RCTs and 6 nonrandomized clinical trials (conducted in China, Iran, and Switzerland) evaluating the effect of stem cell therapy on patients with ACLF demonstrated overall decrease in total bilirubin, ALT, albumin, and MELD score at 12 months of therapy but not in INR (191). A meta-analysis of only the RCTs was not reported. This meta-analysis was limited by high heterogeneity and analysis of multiple types of stem cells/stem cell sources together (mononuclear cells, mesenchymal stem cells, umbilical cord, and bone marrow). This meta-analysis did not evaluate the effect of stem cell therapy on the definitive outcome of mortality. In one small open-label controlled trial, 24 patients with ACLF secondary to HBV reactivation who were randomized to receive human mesenchymal stem cells were compared with 19 control patients who received saline placebo. There were lower rates of death in the stem cell–treated arm at 72 weeks (21% vs 47%; $P = 0.02$) (192). Although these data are provocative, many questions remain about the types of patients who would benefit from this therapy, precluding recommending use of stem cells in routine clinical practice.

Transplant vs futility for ACLF

Recommendations

1. In patients with cirrhosis and ACLF who continue to require mechanical ventilation because of adult respiratory distress syndrome or brain-related conditions despite optimal therapy, we suggest against listing for LT to improve mortality (very low evidence, conditional recommendation).
2. In patients with end-stage liver disease admitted to the hospital, we suggest early goals of care discussion and if appropriate, referral to palliative care to improve resource utilization (very low evidence, conditional recommendation).

Summary of evidence

Data on transplant patterns in patients with ACLF are derived from MELD and MELD-Na score-based organ allocation systems. The

first prospective analysis by NACSELD demonstrated that patients who had ACLF before transplant had acceptable outcomes after liver transplantation (193). In secondary analyses of large data sets, patients with cirrhosis whose ACLF status was defined retroactively have been analyzed in the context of transplant "suitability" and survival (194). A retrospective analysis of the United Network for Organ Sharing database showed that EASL-CLIF ACLF-3 patients did well after transplant, whereas those on mechanical ventilation did not. Another retrospective study of 127 US Veterans Administration centers found that MELD-Na did not correlate with ACLF severity (195). However, studies have also shown that even within the current allocation system, patients who were retroactively labeled ACLF by investigators experienced acceptable post-transplant outcomes (196). Therefore, controversy exists as to whether ACLF in and of itself deserves extra MELD points. Given the probable selection bias toward transplanting only the "best" of ACLF-3 patients (using criteria that cannot be captured by administrative data set analyses), further research is needed before recommending MELD exception points for ACLF (197). A recent survey of US-based transplant clinicians showed that there is no consensus in providing additional MELD points or extending live donor transplant to patients with ACLF (198). The United Network for Organ Sharing database analyses have demonstrated that MELD-Na underestimates 1- and 3-month mortality risk in patients hospitalized with ACLF (195). This places patients with ACLF at a significant disadvantage with respect to receiving timely LT in a traditional MELD-based liver allocation system (199). Given this high risk of mortality, we recommend early advance care planning in all patients admitted with ACLF, even when under consideration for LT.

Studies evaluating outcomes after LT in patients with ACLF have demonstrated acceptable outcomes after LT, but should be interpreted with caution, given inherent selection bias toward transplanting only those who are most likely to achieve favorable outcomes (200–202). Rates of survival after liver transplantation do not seem to differ significantly by ACLF grade with the exception of patients with ACLF-3 (194). Patients with ACLF-3 experienced a higher rate of complications after liver transplantation (e.g., infections, hepatic artery, biliary, and neurologic complications) and a longer length of stay (both in the hospital and in the ICU) (194,201). Predictors of poor outcomes after LT have included mechanical ventilation, higher donor risk index, older age, and LT $>$ 30 days after listing (200). In a multicenter study of 152 patients with ACLF-3 at the time of LT, 4 factors (age $\geq$ 53 years, pretransplant arterial lactate $\geq$ 4 mml/L, mechanical ventilation with PaO2/FiO2 $\leq$ 200 mm Hg, and pretransplant leukocyte count $\leq$ 10 g/L) were combined into the Transplantation for ACLF-3 Model score, with a cutoff of 2 points identifying a high-risk group with an 8% 1-year survival (compared with 84% for those with a Transplantation for ACLF-3 Model score $\leq$ 2) (203). However, this decision is not always straightforward, and selection of very sick patients (extrahepatic organ failure) for LT is more art than science. Among patients with identical MELD or ACLF scores, the decision regarding proceeding with LT may depend on the presence or absence of frailty; portal hypertension; previous abdominal surgery; ventilator for HE vs respiratory failure; rising vs decreasing pressor requirement; and good vs marginal donor liver offer. Depending on these factors, patients with identical ACLF and MELD scores may range from considering transplant for one patient but comfort-focused measures only for another. Several studies have demonstrated that hospice services are markedly underused among inpatients with cirrhosis, despite their high risk of death and limited life expectancy after hospitalization for acute illness (204,205). The continued paucity of donor organs, the recent major changes in the US allocation system and the lack of diagnostic biomarkers that are unique to ACLF beyond decompensated cirrhosis and outside of organ failures exacerbate this situation.

CONCLUSIONS

ACLF has emerged as a major cause of mortality in patients with cirrhosis and chronic liver disease worldwide. The varying definitions that focused on established organ failure have reduced generalizability and potential for prevention of ACLF in different settings. Prevention of major precipitating factors such as infections and alcohol is critical in improving the prognosis of individual organ failures (brain, circulatory, renal, respiratory, and coagulation), and judicious use of antibiotics and antifungal medications is required. Critical care management strategies and LT potential listing should be balanced with futility considerations in those with a poor prognosis. Table 6 lists several future important aspects of ACLF that need to be investigated to improve the translational insight and clinical management of this growing population.

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CONFLICTS OF INTEREST

Guarantor of the article: Jasmohan S. Bajaj, MD, MS, FACG.
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