REVIEW ARTICLE

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Acute-on-Chronic Liver Failure

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Acutely decompensated cirrhosis and acute-on-chronic liver failure are two important conditions observed in patients with known chronic liver disease who have acute decompensation. Acutely decompensated cirrhosis, which is a widely accepted condition, refers to the development of ascites, encephalopathy, gastrointestinal hemorrhage, or any combination of these disorders in patients with cirrhosis.[1,2] Acute-on-chronic liver failure, a term suggested by Jalan and Williams,[3] emerged from studies showing the development of a syndrome associated with a high risk of short-term death (i.e., death <28 days after hospital admission) in patients with acutely decompensated cirrhosis. Three major features characterize this syndrome: it occurs in the context of intense systemic inflammation, frequently develops in close temporal relationship with proinflammatory precipitating events (e.g., infections or alcoholic hepatitis), and is associated with single- or multiple-organ failure. Although a substantial body of literature recognizes acute-on-chronic liver failure as a clinical entity (e.g., currently, eight registered, randomized therapeutic trials are recruiting patients with acute-on-chronic liver failure), some people doubt the existence of the syndrome. Moreover, proposed definitions of acute-on-chronic liver failure differ from one another. In this review, we examine evidence to support the concept of acute-on-chronic liver failure, and we highlight areas that are controversial.

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Defining Acute-on-Chronic Liver Failure

Although definitions of acute-on-chronic liver failure differ (see Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org), most address the role of both hepatic and extrahepatic precipitating events and include extrahepatic organ failures. The European definition, proposed by the European Association for the Study of the Liver–Chronic Liver Failure (EASL-CLIF) Consortium, includes extrahepatic organ failures, applies only to patients with acutely decompensated cirrhosis, with or without prior decompensation, and does not exclude extrahepatic precipitating events.[1] The definition is based on prospective investigation involving 1343 consecutive patients hospitalized for acutely decompensated cirrhosis.[1] Organ failures are identified with the use of a modified Sequential Organ Failure Assessment score (the EASL-CLIF Consortium organ-failure scoring system[4]) (Fig. 1A), which considers the function of the liver, kidney, and brain, as well as coagulation, circulation, and respiration, allowing stratification of patients in subgroups with different risks of death. Coagulation is included in the score because coagulation may not simply reflect the grade of liver failure in patients with severe systemic inflammation or sepsis.

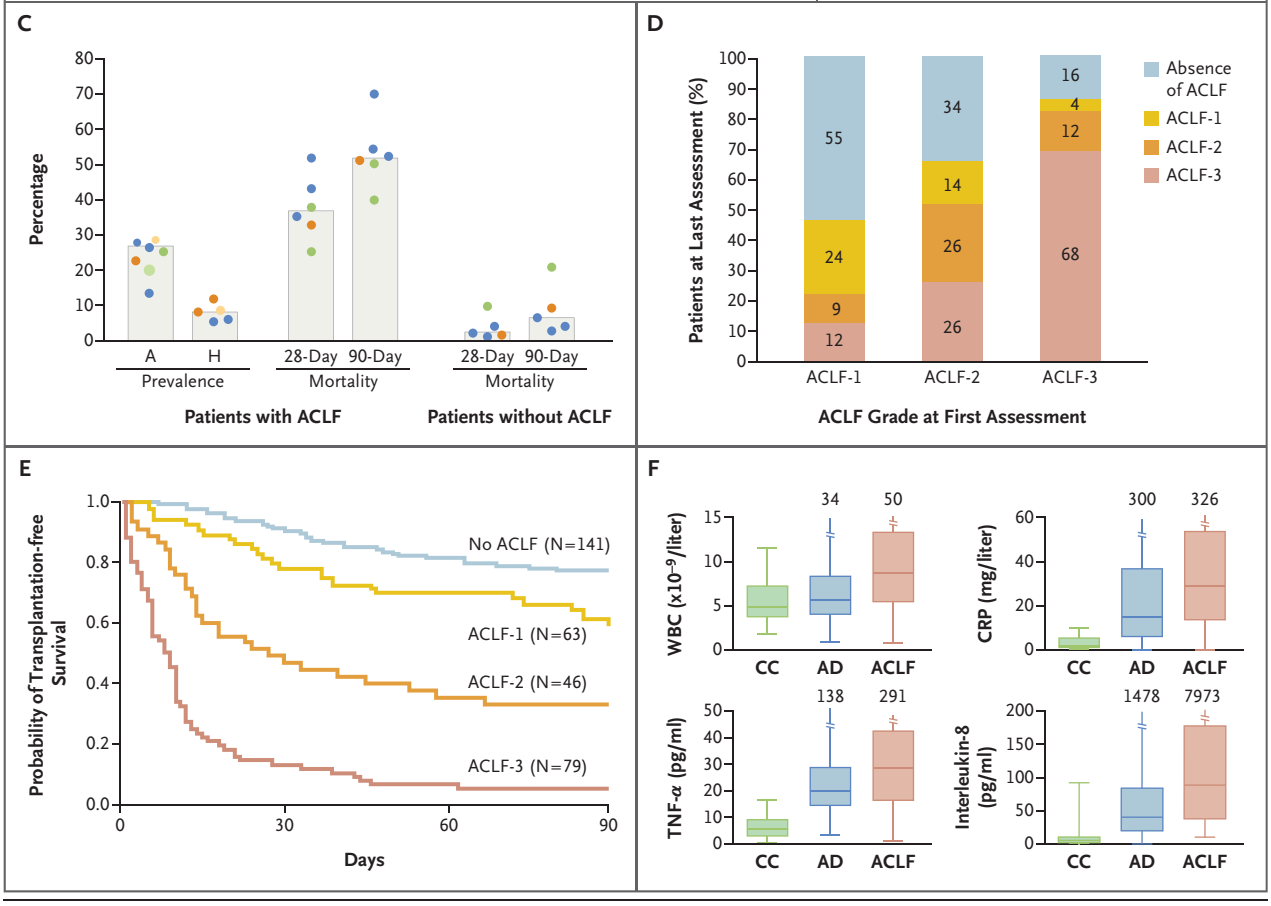
The European definition includes patients with a high risk of death less than 28 days after hospital admission (patients with kidney failure alone; those with

A

Organ System	1 Point	2 Points	3 Points
Liver	Bilirubin <6 mg/dl	Bilirubin 6.0–11.9 mg/dl	Bilirubin ≥12 mg/dl
Kidney	Creatinine <1.5 mg/dl Creatinine 1.5–1.9 mg/dl	Creatinine 2.0–3.4 mg/dl	Creatinine ≥3.5 mg/dl or RRT
Brain (West Haven criteria)	Grade 0	Grade 1–2	Grade 3–4
Coagulation	INR <2.0	INR 2.0–2.4	INR ≥2.5
Circulation	MAP ≥70 mm Hg	MAP <70 mm Hg	Vasopressor requirement
Respiration	Pao_2/Fio_2 >300 Spo_2/Fio_2 >357	Pao_2/Fio_2 201–300 Spo_2/Fio_2 215–357	Pao_2/Fio_2 ≤200 Spo_2/Fio_2 ≤214

B

Patient Group	Prevalence	28-Day Mortality	Assigned Grade
	% of patients		
Absence of OF	68.3	4.4	Absence of ACLF
Single, nonkidney OF without KD or BD	9.9	6.3	
Single KF	6.7	18.6	ACLF-1
Single, nonkidney OF with KD or BD	4.2	27.8	ACLF-1
Two OFs	7.5	32.0	ACLF-2
Three OFs	1.9	68.0	ACLF-3
Four to six OFs	1.4	88.9	ACLF-3



single, nonkidney organ failure if it is associated with kidney or brain dysfunction; and those with two or more organ failures)[1] (Fig. 1B). According to the number of organ failures at diagnosis, patients with acutely decompensated cirrhosis were stratified into four prognostic grades (no acute-on-chronic liver failure and acute-on-chronic liver failure grades 1, 2, and 3)[1] (Fig. 1B).

In a study involving 1322 prospectively enrolled patients, the Chinese Group on the Study of Severe Hepatitis B developed a definition for hepatitis B virus–related acute-on-chronic liver failure[7]; this definition is very similar to the European definition of acute-on-chronic liver failure.

Like the European definition, the definition of acute-on-chronic liver failure of the North

Figure 1 (facing page). Clinical Features of Acute-on-Chronic Liver Failure (ACLF).

Panel A shows the European Association for the Study of the Liver–Chronic Liver Failure Consortium organ-failure score.[4] Each organ system function receives a score ranging from 1 point (close to normal) to 3 points (abnormal). The dark-gray cells indicate the definition of each organ failure, and the light-gray cells the definition of each organ dysfunction. Patients treated with mechanical ventilation received a respiratory score of 3 points. To convert the values for bilirubin to micromoles per liter, multiply by 17.1. To convert the values for creatinine to micromoles per liter, multiply by 88.4. F_{IO_2} denotes fraction of inspired oxygen, INR international normalized ratio, MAP mean arterial pressure, Pa_{O_2} partial pressure of arterial oxygen, RRT renal-replacement therapy, and Sp_{O_2} oxygen saturation as measured by pulse oximetry. Panel B shows the prevalence of ACLF and associated 28-day transplantation-free mortality according to diagnostic criteria and grade at admission among 1287 European patients hospitalized with acutely decompensated cirrhosis.[1] BD denotes brain dysfunction, KD kidney dysfunction, KF kidney failure, and OF organ failure. Panel C shows the prevalence of ACLF at admission and during hospitalization and 28- and 90-day mortality among patients hospitalized for acutely decompensated cirrhosis with or without ACLF. Each circle represents the value for either prevalence or mortality in one of the eight large-scale investigations using the consortium's diagnostic criteria: the CANONIC study[1] (1343 patients) and PREDICT study (completed; enrolled 1375 patients [ClinicalTrials.gov number, NCT03056612]) in Europe (orange circles); the Li et al. study[5] (890 patients), KACLiF study[6] (1235 patients), and COSSH study[7] (1031 patients) in Asia (blue circles); the studies by Mahmud et al.[8] (80,383 patients) and Hernaez et al.[9] (72,316 patients) in the United States (green circles); and the ACLARA study (recruiting patients [1077 already enrolled]) in Latin America (yellow circles). The top of each column represents the median value for the measure. A denotes the percentage of patients who had ACLF at admission, and H the percentage of patients who were free of ACLF at admission but in whom ACLF developed during hospitalization. Panel D shows the course of ACLF during hospitalization according to the initial ACLF grade.[10] At the first assessment, 202 patients had ACLF-1, 136 had ACLF-2, and 50 had ACLF-3. The course of ACLF was extremely dynamic — resolving, improving, or worsening, frequently within a few days, in a substantial number of patients or changing after a steady course. Panel E shows the probability of transplantation-free survival according to ACLF status, assessed 3 to 7 days after the initial diagnosis.[10] The group of 141 patients in whom ACLF resolved within 3 to 7 days had the highest probability of survival, even though approximately half these patients initially had ACLF grade 2 or 3. Differences were significant across groups. Panel F shows the severity of systemic inflammation according to the white-cell count (WBC)[1] and plasma levels of C-reactive protein (CRP),[1] tumor necrosis factor α (TNF-α),[11] and interleukin-8[11] in patients with compensated cirrhosis (CC) and no history of acute decompensation (39 patients) or acute decompensation (AD) with or without ACLF (85 and 237 patients, respectively). Differences were significant across groups. The numbers above the box plots are the highest values, and the boxes show the interquartile range, as well as median values (horizontal lines); the I bars denote the highest and lowest values of the distribution.

American Consortium for the Study of End-Stage Liver Disease applies only to patients with acutely decompensated cirrhosis, does not exclude extrahepatic precipitating events, and considers organ failures (defined by shock, grade 3 or 4 hepatic encephalopathy, or need for dialysis or mechanical ventilation) as components of the syndrome.[12] The definition is based on an investigation involving 507 patients with cirrhosis and ongoing infection.[12] Acute-on-chronic liver failure was defined by the presence of two or more extrahepatic organ failures. This definition has been validated in a large North American cohort of infected and noninfected patients with cirrhosis.[13]

Unlike the other definitions, the definition of the Asian Pacific Association for the Study of the Liver does not include extrahepatic organ failures.[2,14,15] Rather, the definition is based on the opinions of experts who considered acute-on-chronic liver failure to be an acute hepatic insult (e.g., hepatitis B virus reactivation or acute alcoholic hepatitis), manifested as jaundice and coagulopathy and complicated within 4 weeks by clinical ascites, encephalopathy, or both. The definition applies only to patients with no prior decompensation and those with noncirrhotic chronic liver disease. Accordingly, patients with prior decompensation and those with acutely decompensated cirrhosis are not included in the definition. Extrahepatic insults, such as sepsis or gastrointestinal hemorrhage, are viewed not as conditions that precipitate acute-on-chronic liver failure but as complications of this syndrome.[16] Extrahepatic organ failures are considered to be manifestations of either progressive acute-on-chronic liver failure or complicating infections but not components of the syndrome.

CLINICAL FEATURES

In a European study that used the European criteria and involved patients hospitalized with acutely decompensated cirrhosis, acute-on-chronic liver failure was present in 22.6% of the patients at admission and developed during hospitalization in another 8.3%.[1] Newly developed acute-on-chronic liver failure occurred within days after admission (maximum interval, 2 weeks), indicating that acute-on-chronic liver failure in patients with cirrhosis occurs simultaneously with, or very early after, acute decompensation.[1] Acute-on-chronic liver failure was particularly prevalent among patients with alcoholic cirrhosis; 60% of patients had hepatic precipitating conditions (alcoholic hepatitis), ex-

trahepatic precipitating conditions (most often infections), or both. The fact that the remaining 40% of patients did not have a clinically identifiable precipitating event[1] is consistent with the notion that acute-on-chronic liver failure can occur for reasons yet to be identified. The 28-day and 90-day transplantation-free mortality rates were 32.8% and 51.2%, respectively, among patients with acute-on-chronic liver failure and 1.8% and 9.8%, respectively, among those without acute-on-chronic liver failure[1] (Fig. 1C).

The prevalence of acute-on-chronic liver failure and the associated mortality rate are also high in large-scale studies performed outside Europe but using European criteria[5-9,17] (Fig. 1C). The disorder has been found to have a variable course — resolving, improving, or worsening within a few days or following a steady course[10] (Fig. 1D). Consequently, the prognosis for patients with each grade of acute-on-chronic liver failure was less accurate when estimated at the time of diagnosis than when estimated 3 to 7 days later[10] (Fig. 1E).

In a North American study using the North American definition of acute-on-chronic liver failure among patients nonelectively hospitalized for acutely decompensated cirrhosis, the prevalence of acute-on-chronic liver failure was 10%, and the 30-day mortality rate was 41% (vs. 7% mortality in the absence of the syndrome).[13] Thus, the prevalence differs depending on the definition used.[9]

A flare of hepatitis B virus infection is a common precipitating factor for acute-on-chronic liver failure in Asia. In a study using the Asian Pacific criteria for acute-on-chronic liver failure, 76% of patients with cirrhosis and hepatitis B virus–related acute-on-chronic liver failure had complications, including bacterial or fungal infection in 32% of patients, the hepatorenal syndrome in 15%, and gastrointestinal hemorrhage in 9%.[16] The 28-day and 90-day transplantation-free mortality rates were 27.8% and 40.0%, respectively.

A Veterans Health Administration study involving a large series of patients with compensated cirrhosis investigated newly developed acute-on-chronic liver failure and compared the Asian Pacific and European definitions.[8] The incidence rate of acute-on-chronic liver failure was 5.7 cases per 1000 person-years (95% confidence interval [CI], 5.4 to 6.0) with the Asian Pacific criteria and 20.1 per 1000 person-years (95% CI, 19.5 to 20.6) with the European criteria. The 28-day and 90-day mortality rates for acute-on-chronic liver failure were 41.9% and 56.1%, respectively, with the Asian Pacific criteria and 37.6% and 50.4%, respectively, with the European definition.[8]

PATHOPHYSIOLOGY

The pathophysiology of acute-on-chronic liver failure is still largely unknown. Systemic inflammation may play a role. Patients with acute-on-chronic liver failure have intense systemic inflammation and oxidative stress, unlike patients who have acute decompensation but no organ failure[11,18,19] (Fig. 1F). Studies of acute-on-chronic liver failure have shown that systemic inflammation correlates directly with the severity of the syndrome; the greater the intensity of systemic inflammation, the larger the number of organ failures at enrollment and the higher the short-term mortality.[11] Bacterial infections[11,19] and acute alcoholic hepatitis[20] are two precipitants of systemic inflammation that are frequently associated with acute-on-chronic liver failure[1] (Fig. 2A). The mechanisms by which gastrointestinal hemorrhage may precipitate acute-on-chronic liver failure are less clear. However, severe hemorrhage may cause ischemic hepatitis,[22] resulting in cell necrosis and release of inflammatory stimuli. Moreover, gastrointestinal hemorrhage confers a predisposition to the development of bacterial infections.[27] In the 40% of patients with cirrhosis who have systemic inflammation and acute-on-chronic liver failure without any identifiable precipitating condition,[1] translocation of bacterial by-products from the intestinal lumen to the systemic circulation may occur.[23] The mechanisms by which systemic inflammation may cause the failure of one or more organs in patients with cirrhosis are summarized in Figure 2A and 2B.[21,26]

PRINCIPLES OF TREATMENT

The Model for End-Stage Liver Disease with the addition of the serum sodium level (MELD-Na) score, in addition to scores based on the number of failing organs, provides accurate prognostica-

tion for individual patients with acute-on-chronic liver failure.[2,4,7,13] The main principle of treatment is to diagnose and treat the precipitating event and then provide supportive therapy. Organ support in an intensive care unit, with care overseen by physicians who are experts in liver management, may be of benefit for patients with life-threatening, single- or multiple-organ failure who do not have a response to standard therapy. Table S2 provides information on management. Many therapeutic recommendations are based on clinical practice or on studies involving critically ill patients without cirrhosis.[28] In the future, different therapies may be validated, depending on the precipitating event (hepatic or extrahepatic).

TREATING THE PRECIPITATING EVENT

Bacterial or Fungal Infection

The prevalence of infections, either precipitating or complicating the syndrome, is about 50% among patients with acute-on-chronic liver failure and 70% among patients with three or more organ failures.[19] The causative microbes are most often bacteria, but fungi can be involved.[19] Treatment of infections should be started as soon as possible. The choice of antimicrobial therapy relies on the organism isolated (if any), suspected site of infection, site of acquisition, and local antimicrobial-susceptibility patterns.

Acute Variceal Hemorrhage

Standard medical treatment includes the combination of a safe vasoconstrictor (terlipressin, somatostatin, or analogues such as octreotide or vapreotide, administered from the time of admission and maintained for 2 to 5 days) and endoscopic therapy (preferably endoscopic variceal ligation, performed at diagnostic endoscopy <12 hours after admission), together with short-term antibiotic prophylaxis with ceftriaxone.[27] The only vasoconstrictor currently available in the United States is octreotide.[27]

Alcoholic Hepatitis

Prednisolone therapy is indicated for patients with severe alcoholic hepatitis.[20] The Lille score is used for early identification of patients who will not have a response to treatment.[20] The score is calculated on the basis of age, bilirubin and albumin values, prothrombin time, baseline status with respect to renal failure, and the change in bilirubin levels between day 0 and day 7 of prednisolone therapy. The score ranges from 0 to 1. A score of 0.45 or higher at the seventh day of treatment indicates no improvement in the response to prednisolone and a low probability of short-term survival, as compared with patients who have a response; treatment should be discontinued. A score below 0.45 indicates a positive response to treatment, which should be continued for up to 28 days. The response to prednisolone is negatively correlated with the number of organ failures at baseline.[29]

Hepatitis B Virus Reactivation

Nucleoside or nucleotide analogues should be started immediately in all patients with hepatitis B virus infection at presentation, pending confirmation of the infection on the basis of the viral DNA level. Potent antiviral drugs, such as tenofovir, tenofovir alafenamide, or entecavir, should be used.[2]

SUPPORTIVE THERAPY

Cardiovascular Support

Acute kidney injury is the most common organ failure in patients with acute-on-chronic liver failure in Western countries.[1] For patients with acute kidney injury, management includes withdrawal of diuretics and volume expansion (with intravenous albumin), as well as urine tests to determine whether the renal injury is acute tubular necrosis or type 1 hepatorenal syndrome[24] (Fig. 2A). If there is no response to volume expansion, treatment with a vasoconstrictor (terlipressin or norepinephrine) should be started, particularly if urine tests point to type 1 hepatorenal syndrome.[24] The likelihood of a renal response to vasoconstrictor therapy is inversely related to the number of organ failures at baseline.[25] For the management of persistent shock, norepinephrine is the first-line vasopressor agent.[28]

Treatment of Encephalopathy

If the airway cannot be protected, intubation is required. Lactulose is used for the initial therapy, but its use should not be permitted to lead to profuse diarrhea. The administration of enemas to clear the bowel is a useful adjunct to oral lactulose. Albumin dialysis may be used when

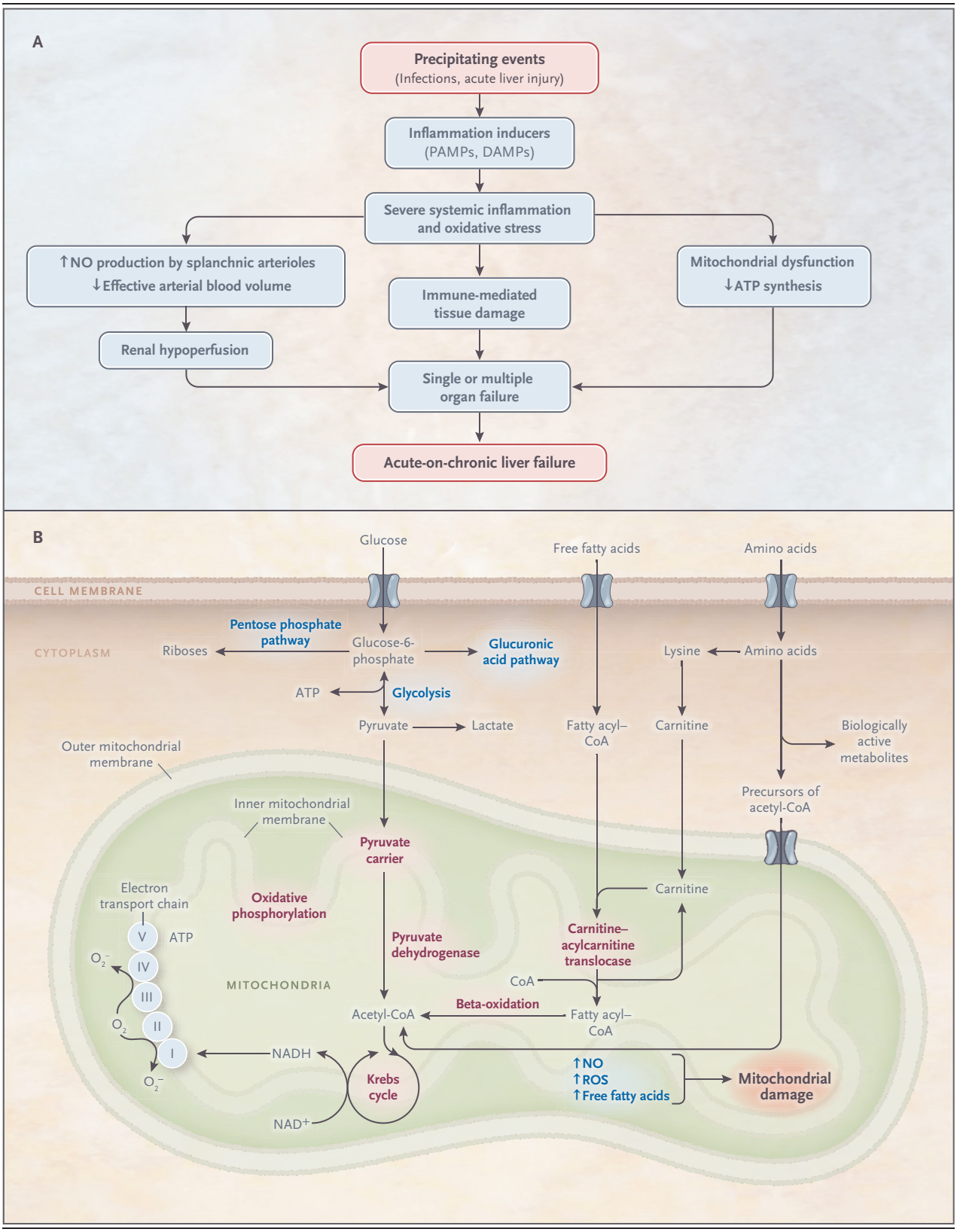


Figure 2 (facing page). Pathophysiology of ACLF in Patients with Cirrhosis.
Panel A shows the potential mechanisms of systemic inflammation in patients with cirrhosis and ACLF and the mechanisms by which systemic inflammation may cause organ failure in these patients. The mechanisms of systemic inflammation depend on the precipitating event. In patients with sepsis-related ACLF, the recognition of pathogen-associated molecular patterns (PAMPs) by pattern-recognition receptors of the innate immune system explains the induction of the systemic inflammatory response.[21] In the context of sepsis, exaggerated inflammation can cause collateral tissue damage and necrotic cell death, resulting in the release of damage-associated molecular patterns (DAMPs) that may perpetuate inflammation by acting on the same pattern-recognition receptors that are triggered by pathogens.[21] In patients with acute-on-chronic liver failure related to primary liver injury (e.g., alcoholic hepatitis), systemic inflammation can result from the release of DAMPs by necrotic hepatocytes but can also result from PAMPs related to infection, which is common in patients with alcoholic hepatitis.[20] In patients with severe gastrointestinal hemorrhage, liver ischemia may cause hepatocyte necrosis[22] and subsequent DAMP-induced inflammation. In patients with acute-on-chronic liver failure in the absence of any clinically clear precipitating event, systemic inflammation may result from translocated bacterial PAMPs from gut lumen.[23] Intense systemic inflammation can cause the failure of one or more organs through different mechanisms that are not mutually exclusive. First, in splanchnic arteriolar walls, inflammation can stimulate nitric oxide (NO) production, causing NO-mediated splanchnic vasodilatation, reduction in the effective arterial blood volume, homeostatic activation of endogenous vasoconstrictors, intense renal vasoconstriction, renal hypoperfusion, reduction in the glomerular filtration rate, and ultimately, type 1 hepatorenal syndrome (an acute kidney injury that is specific for cirrhosis and is a form of ACLF).[24,25] Second, intense inflammation can cause tissue damage, leading to the failure of one or more organs.[21] Finally, in peripheral organs, systemic inflammation may induce mitochondrial dysfunction and thereby reduce ATP production, an effect that would contribute to organ failure.[26] Panel B summarizes the main metabolic pathways involved in cellular energy production. Under normal conditions, glucose enters the cytosol and is phosphorylated to glucose-6-phosphate, the starting point for glycolysis, the pentose phosphate pathway, and glucuronic acid synthesis. During glycolysis, glucose-6-phosphate is converted to pyruvate, which is then metabolized in the mitochondria to acetyl-coenzyme A (acetyl-CoA) through the action of pyruvate dehydrogenase. Other sources of acetyl-CoA are fatty acids and amino acids. Fatty acids bind to carnitine to form fatty acyl carnitines, which cross the mitochondrial membrane through the action of carnitine–acylcarnitine translocase. The replacement of carnitine by CoA gives rise to fatty acyl–CoA, which is then metabolized through mitochondrial fatty acid beta-oxidation to produce acetyl-CoA. Amino acids can be metabolized into acetyl-CoA through specific metabolic pathways. Acetyl-CoA molecules are oxidized in the Krebs cycle, which leads to reduced NADH, which in turn activates the electron transport chain and triggers the synthesis of ATP by oxidative phosphorylation. This process is the most efficient means of ATP generation and is associated with the release of superoxide anion (O_2^-). Blue and red represent up-regulated and down-regulated metabolic processes, respectively, which may occur in the context of systemic inflammation in ACLF, as suggested by results of high-throughput metabolomics performed in patients with ACLF.[26] In peripheral organs, systemic inflammation may inhibit both the translocation of fatty acids into the mitochondria and their beta-oxidation, resulting in decreased ATP production. In addition, systemic inflammation may inhibit the electron transport chain and cause mitochondrial damage through NO activation and accumulation of free fatty acids and reactive oxygen species (ROS). Together, these mechanisms would contribute to ACLF development.

severe hepatic encephalopathy is refractory to lactulose.[30]

Extracorporeal Liver Support

Two large, randomized trials showed that albumin dialysis, as compared with standard medical therapy, did not improve short-term survival among patients with acute-on-chronic liver failure.[31,32] More recently, an extracorporeal liver-assist device that incorporates hepatocytes was also found to be no more effective than the standard of care.[33] Randomized trials are currently assessing plasma exchange (e.g., APACHE trial; ClinicalTrials.gov number, NCT03702920) and strategies targeting albumin exchange and endotoxin removal (DIALIVE trial, NCT03065699) in patients with acute-on-chronic liver failure.

LIVER TRANSPLANTATION

The 1-year survival rate after liver transplantation among patients with acute-on-chronic liver failure and one or two organ failures does not differ significantly from the rate among patients without acute-on-chronic liver failure.[34,35] For patients with three or more organ failures, the 1-year post-transplantation survival rate may approach 80%,[34-36] as compared with a survival rate of less than 20% among patients who do not undergo transplantation.[34,35] These data provide compelling evidence in favor of transplantation for patients with acute-on-chronic liver failure.

CONCLUSIONS

Acute-on-chronic liver failure is a syndrome that affects patients with chronic liver disease; is characterized by intense systemic inflammation, organ failure, and a poor prognosis; and frequently develops in close association with precipitating events. Whether extrahepatic organ failure is a component of the syndrome or a consequence of its progression is unclear, and the potential role of bacterial infections as precipitating conditions is debated. Acute-on-chronic liver failure is a major challenge for clinicians and a stimulus for research in cirrhosis.

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REFERENCES

1. Moreau R, Jalan R, Ginès P, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology 2013;144(7):1426-37.
2. Sarin SK, Choudhury A, Sharma MK, et al. Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific Association for the Study of the Liver (APASL): an update. Hepatol Int 2019;13:353-90.
3. Jalan R, Williams R. Acute-on-chronic liver failure: pathophysiological basis of therapeutic options. Blood Purif 2002;20:252-61.
4. Jalan R, Saliba F, Pavesi M, et al. Development and validation of a prognostic score to predict mortality in patients with acute-on-chronic liver failure. J Hepatol 2014;61:1038-47.
5. Li H, Chen LY, Zhang NN, et al. Characteristics, diagnosis and prognosis of acute-on-chronic liver failure in cirrhosis associated to hepatitis B. Sci Rep 2016;6:25487.
6. Kim TY, Song DS, Kim HY, et al. Characteristics and discrepancies in acute-on-chronic liver failure: need for a unified definition. PLoS One 2016;11(1):e0146745.
7. Wu T, Li J, Shao L, et al. Development of diagnostic criteria and a prognostic score for hepatitis B virus-related acute-on-chronic liver failure. Gut 2018;67:2181-91.
8. Mahmud N, Kaplan DE, Taddei TH, Goldberg DS. Incidence and mortality of acute-on-chronic liver failure using two definitions in patients with compensated cirrhosis. Hepatology 2019;69:2150-63.
9. Hernaez R, Kramer JR, Liu Y, et al. Prevalence and short-term mortality of acute-on-chronic liver failure: a national cohort study from the USA. J Hepatol 2019;70:639-47.
10. Gustot T, Fernandez J, García E, et al. Clinical Course of acute-on-chronic liver failure syndrome and effects on prognosis. Hepatology 2015;62:243-52.
11. Clària J, Stauber RE, Coenraad MJ, et al. Systemic inflammation in decompensated cirrhosis: characterization and role in acute-on-chronic liver failure. Hepatology 2016;64:1249-64.
12. Bajaj JS, O'Leary JG, Reddy KR, et al. Survival in infection-related acute-on-chronic liver failure is defined by extrahepatic organ failures. Hepatology 2014;60:250-6.
13. O'Leary JG, Reddy KR, Garcia-Tsao G, et al. NACSELD acute-on-chronic liver failure (NACSELD-ACLF) score predicts 30-day survival in hospitalized patients with cirrhosis. Hepatology 2018;67:2367-74.
14. Sarin SK, Kumar A, Almeida JA, et al. Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific Association for the study of the liver (APASL). Hepatol Int 2009;3:269-82.
15. Sarin SK, Kedarisetty CK, Abbas Z, et al. Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific Association for the Study of the Liver (APASL) 2014. Hepatol Int 2014;8:453-71.
16. Chen T, Yang Z, Choudhury AK, et al. Complications constitute a major risk factor for mortality in hepatitis B virus-related acute-on-chronic liver failure patients: a multi-national study from the Asia-Pacific region. Hepatol Int 2019;13:695-705.
17. Amarapurkar D, Dharod MV, Chandnani M, et al. Acute-on-chronic liver failure: a prospective study to determine the clinical profile, outcome, and factors predicting mortality. Indian J Gastroenterol 2015;34:216-24.
18. Bernsmeier C, Pop OT, Singanayagam A, et al. Patients with acute-on-chronic liver failure have increased numbers of regulatory immune cells expressing the receptor tyrosine kinase MERTK. Gastroenterology 2015;148(3):603-615.e14.
19. Fernández J, Acevedo J, Wiest R, et al. Bacterial and fungal infections in acute-on-chronic liver failure: prevalence, characteristics and impact on prognosis. Gut 2018;67:1870-80.
20. Lucey MR, Mathurin P, Morgan TR. Alcoholic hepatitis. N Engl J Med 2009;360:2758-69.
21. Angus DC, van der Poll T. Severe sepsis and septic shock. N Engl J Med 2013;369:840-51.
22. Cárdenas A, Ginès P, Uriz J, et al. Renal failure after upper gastrointestinal bleeding in cirrhosis: incidence, clinical course, predictive factors, and short-term prognosis. Hepatology 2001;34:671-6.
23. Fernández J, Clària J, Amorós A, et al. Effects of albumin treatment on systemic and portal hemodynamics and systemic inflammation in patients with decompensated cirrhosis. Gastroenterology 2019;157:149-62.
24. Ginès P, Schrier RW. Renal failure in cirrhosis. N Engl J Med 2009;361:1279-90.
25. Piano S, Schmidt HH, Ariza X, et al. Association between grade of acute on chronic liver failure and response to terli-

pressin and albumin in patients with hepatorenal syndrome. Clin Gastroenterol Hepatol 2018;16(11):1792-1800.e3.
26. Moreau R, Clària J, Aguilar F, et al. Blood metabolomics uncovers inflammation-associated mitochondrial dysfunction as a potential mechanism underlying ACLF. J Hepatol 2020;72:688-701.
27. Garcia-Tsao G, Bosch J. Management of varices and variceal hemorrhage in cirrhosis. N Engl J Med 2010;362:823-32.
28. Nadim MK, Durand F, Kellum JA, et al. Corrigendum to "Management of the critically ill patients with cirrhosis: a multidisciplinary perspective." J Hepatol 2016; 64:717-35.
29. Sersté T, Cornillie A, Njimi H, et al. The prognostic value of acute-on-chronic liver failure during the course of severe alcoholic hepatitis. J Hepatol 2018;69:318-24.
30. Romero-Gómez M, Montagnese S, Jalan R. Hepatic encephalopathy in patients with acute decompensation of cirrhosis and acute-on-chronic liver failure. J Hepatol 2015;62:437-47.
31. Kribben A, Gerken G, Haag S, et al. Effects of fractionated plasma separation and adsorption on survival in patients with acute-on-chronic liver failure. Gastroenterology 2012;142(4):782-789.e3.
32. Bañares R, Nevens F, Larsen FS, et al. Extracorporeal albumin dialysis with the molecular adsorbent recirculating system in acute-on-chronic liver failure: the RELIEF trial. Hepatology 2013;57:1153-62.
33. Thompson J, Jones N, Al-Khafaji A, et al. Extracorporeal cellular therapy (ELAD) in severe alcoholic hepatitis: a multinational, prospective, controlled, randomized trial. Liver Transpl 2018;24:380-93.
34. Artru F, Louvet A, Ruiz I, et al. Liver transplantation in the most severely ill cirrhotic patients: a multicenter study in acute-on-chronic liver failure grade 3. J Hepatol 2017;67:708-15.
35. Sundaram V, Jalan R, Wu T, et al. Factors associated with survival of patients with severe acute-on-chronic liver failure before and after liver transplantation. Gastroenterology 2019;156(5):1381-1391.e3.
36. Thuluvath PJ, Thuluvath AJ, Hanish S, Savva Y. Liver transplantation in patients with multiple organ failures: feasibility and outcomes. J Hepatol 2018;69:1047-56.

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