An Introduction To
Acute-On-Chronic Liver Failure

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Acute-on-Chronic Liver Failure (ACLF) is a devastating complication of cirrhosis, usually brought on by a precipitating event that stresses the liver, which, in turn, triggers rapid progression to multi-organ failure with high short-term mortality.

Each year in the U.S. some 41,000 people are rushed to hospital with ACLF. The greater the number of organ failures involved, the higher the mortality rate for these critically-ill patients – up to 80% within a month of hospitalization.

While medical management can be a bridge to transplantation, many ACLF patients do not qualify for or live long enough to receive a donor organ.

This paper examines ACLF, its causes, its devastating effects on patients, loved ones and society as a whole, and steps being taken to address this serious health concern.

WHAT IS ACLF?

Any understanding of ACLF must start with an understanding of chronic liver failure. The liver, the body's largest abdominal organ, carries out hundreds of critical functions, including detoxifying harmful substances, cleaning the blood, and making vital proteins, among others. The liver can regenerate most of its own cells when they become damaged. However, if injury to the liver is too severe or long lasting, regeneration is incomplete, and the liver creates scar tissue (fibrosis).

The buildup of fibrotic tissue is usually a slow and gradual process. In the early stages of fibrosis, the liver continues to function. However, as scar tissue continues to develop and replaces more healthy tissue, the liver will become cirrhotic.

Cirrhosis of the liver is a pathological diagnosis characterized by diffuse fibrosis (large amounts of dense scar tissue laid down in the liver by specialized cells), alteration of the hepatic architecture, and disruption of the intrahepatic arterial and venous flow (blood flow in the liver). With progressive cirrhosis, patients develop portal hypertension, i.e., elevated pressure in the veins draining from the stomach, intestine, spleen, and pancreas that merge into the portal vein, compared to pressure

in the blood vessels draining blood from the liver (hepatic veins) and taking it back to the heart. The life threatening complications of cirrhosis occur once portal hypertension develops and include variceal bleeding (bleeding from varicose-type veins that develop in the esophagus and stomach), ascites (fluid in the abdomen), hepatic encephalopathy (confusion that occurs due to excessive ammonia levels) and renal failure (hepatorenal syndrome).

Cirrhosis, a necessary precursor to ACLF, is historically most commonly found in patients with chronic viral hepatitis like hepatitis B or C, those with excessive alcohol use and those with fatty liver disease. The demographics are shifting, however, with the development of curative antiviral drugs and the obesity epidemic. Once a minority cause of cirrhosis, non-alcoholic fatty liver disease (NALF) is growing rapidly, and is expected to become a leading cause, along with alcohol abuse, of cirrhosis and, therefore, ACLF within a few years. As NAFL-related cirrhosis increases, it is expected to compensate for the declining viral hepatitis population, expanding the size of the cirrhosis population from present numbers. In fact, the incidence of cirrhosis has doubled over the last decade.

WHEN CIRRHOSIS ADVANCES TO ACLF

Cirrhosis is considered either compensated or decompensated. Compensated patients do not exhibit symptoms of their cirrhosis (they do not have clinically significant portal hypertension), whereas decompensated patients do have clinically significant portal hypertension which occurs when patients develop varices. Decompensation is sparked

Each year in the US, 41,000 people are hospitalized for ACLF

Mortality rates for hospitalized ACLF patients run as high as 80%

by an incident of acute stress on the background of cirrhosis. This may be an alcoholic binge, a new viral infection or a flare of an old one, or a bacterial infection — however, frequently no precipitating event can be identified.

The symptoms of decompensation, which often drive hospitalization of these patients, include jaundice (yellowing of the skin and eyes caused by an accumulation of bilirubin, which is made during the breakdown of red blood cells), presence of ascites, variceal hemorrhage (bleeding), and/or hepatic encephalopathy.

These processes may alter the barrier function of the gastrointestinal tract, making patients more susceptible to infection and other factors that can exacerbate their inflammatory state.

Within the background of cirrhosis, ACLF is brought on by an incident of acute stress, causing acute decompensation along with one or more organ failures. ACLF patients are known be in an elevated inflammatory state, which plays a crucial role in the development of the condition.

ROLE OF INFLAMMATION IN ACLF

Depending on the etiology, inflammation is at the heart of the evolution of cirrhosis. It is typically initiated by alcohol, a viral infection, or fat deposits. This inflammation promotes the fibrosis that alters the liver architecture to the point of causing cirrhosis, ultimately resulting in portal hypertension.

In ACLF, the inflammatory response is not limited to the liver; rather, it involves the entire body. Systemic inflammation is a hallmark feature of patients with acute decompensation (AD) of cirrhosis and plays a crucial role in the development of ACLF. The white cell count and plasma C-reactive protein levels, both indicators of inflammation, are higher in patients with ACLF than in those with AD and no organ failures, that is, those without ACLF.[1] Bacteria are an important trigger for this systemic inflammatory response in ACLF.

Bacteria express molecular structures known as pathogen-associated molecular patterns (PAMPs) that are specifically recognized by germ line-encoded receptors called pattern-recognition receptors (PRRs) located at the surface or within innate immune cells.[2] [3].

The engagement of PRRs results in the activation of signaling cascades that activate transcription factors (e.g., nuclear factor (NF)-jB, AP-1, interferon (IFN)-regulator factor (IRF) 3, among others).[4] [5] These induce hundreds of genes including those encoding major inflammatory cytokines.[6]

This inflammatory response is beneficial in that it plays a major role in host resistance to infection, i.e. the reduction of bacterial burden. However, the inflammatory response to bacterial components may be excessive and associated with collateral tissue damage (immunopathology) resulting in organ failure (OF).

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[1] Moreau R, Jalan R, Gines P, et al; CANONIC Study Investigators of the EASL–CLIF Consortium. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology* 2013;144(7):1426–1437, 1437.e1–1437.e9

[2] Kawai T, Akira S. Toll-like receptors and their crosstalk with other innate receptors in infection and immunity. *Immunity* 2011;34:637–650.

[3] Foster SL, Hargreaves DC, Medzhitov R. Gene-specific control of inflammation by TLR-induced chromatin modifications. *Nature* 2007;447:972–978.

[4] Gustot T, Durand F, Lebrec D, Vincent JL, Moreau R. Severe sepsis in cirrhosis. *Hepatology* 2009;50:2022–2033.

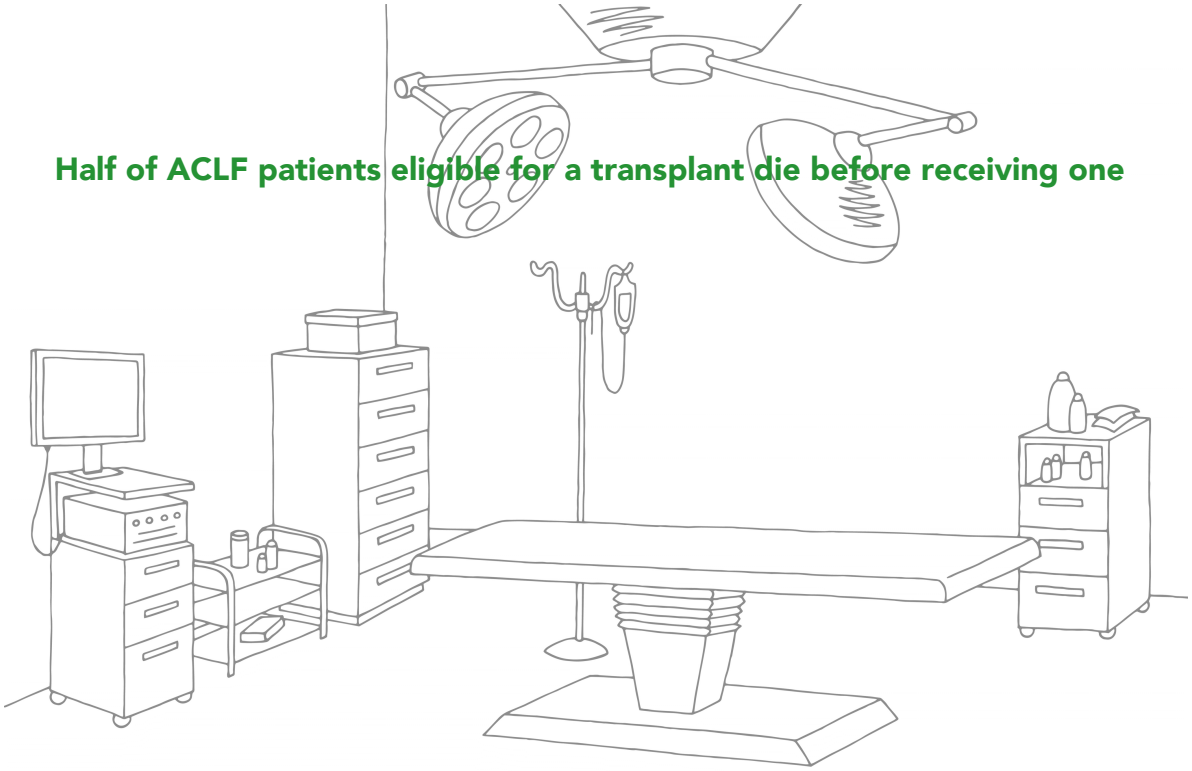
[5] Kawai T, Akira S. Toll-like receptors and their crosstalk with other innate receptors in infection and immunity. Immunity 2011;34:637–650.

[6] Sarin SK, Kumar A, Almeida JA, Chawla YK, Fan ST, Grag H, et al. Acute-on- chronic liver failure: consensus recommendations of the Asian Pacific Association for the study of the liver (APASL). *Hepatol Int* 2009;3:269–282.

Systemic inflammation and the development of OFs are attributed to bacterial infection in approximately 30% of patients with ACLF.[7] These patients have sepsis-induced ACLF. Bacterial components and pro-inflammatory cytokines are known to induce nitric oxide (NO) synthase in arteriolar walls of the systemic circulation and on cardiac tissue resulting in increased production of the vaso-relaxant NO, impairment in cardiac inotropic function, arterial hypotension and decreased oxygen delivery to tissues.[8] Bacterial components and pro-inflammatory cytokines target the endothelium of microvasculature in vital organs favoring the formation of microthrombi (and tissue hypoxia) as well as adhesion and transendothelial migration of various circulating cells. Influx of phagocytes in tissues may induce tissue damage (cell dysfunction, apoptosis or necrosis) via release of oxygen reactive species.[9] All these features contribute to OFs.

Another important trigger of systemic inflammation is alcohol. Severe alcoholic hepatitis (inflammation of the liver) (SAH) represents approximately 25% of the cases of ACLF.[10] Severity is related to the development of OFs. Systemic inflammation

Half of ACLF patients eligible for a transplant die before receiving one



Each ACLF episode runs $116,000 to $180,000 just for ICU costs

[7] Moreau R, Jalan R, Gines P, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology* 2013;144:1426–37, 1437.e1–9.

[8] MacMicking JD, Nathan C, Hom G, Chartrain N, Fletcher DS, Trumbauer M, et al. Altered responses to bacterial infection and endotoxic shock in mice lacking inducible nitric oxide synthase. *Cell* 1995;81:641–650.

[9] Russell JA. Management of sepsis. N Engl J Med 2006;355:1699–1713.

[10] Moreau R, Jalan R, Gines P, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology* 2013;144:1426–37, 1437.e1–9.

develops in patients with SAH and correlates with the outcome suggesting a role of inflammation in the development of OFs.[11]

Excessive alcohol consumption is associated with intestinal dysbiosis (microbial imbalance) and increased intestinal permeability, which favor translocation of viable bacteria.[12] This may explain why spontaneous bacterial peritonitis is the most common infection at admission of patients with SAH. However, systemic inflammation is also observed in patients with SAH without clinically detectable bacterial infection.

In about 40%–50% cases, patients with ACLF have systemic inflammation for which there are no clinically identifiable triggers.

ACLF TOO OFTEN LEADS TO DEATH

ACLF is graded into three categories (grades 1–3) based on the number of OFs, with higher grades associated with increased mortality. Liver and renal failures are the most common OFs, followed by coagulation, brain, circulatory and respiratory failure. ACLF-1 (one OF) is associated with a 28-day mortality rate of 22%, ACLF-2 (2 OFs) of 32% and ACLF-3 (3 or more OFs) of 79%. By comparison, the mortality rate in decompensated cirrhotic patients without ACLF is 4.9%.

CURRENT MANAGEMENT OF ACLF

Most ACLF treatment focuses on factors that may be precipitating the failure, and on symptomatic relief. Typically, patients are admitted to the intensive care unit, and if an infection is suspected, they are treated immediately with broad-spectrum antibiotic therapy. Studies have shown that rapid initiation of antibiotic treatment in ACLF patients with sepsis (within one hour of hypotension and signs/symptoms of infection) can significantly improve outcomes when compared to administering antibiotics within six hours.[13]

Additionally, patients with hepatitis B virus-related ACLF have significantly lower 3-month mortality if treated with nucleot(s)ide analogues compared to those who do not (45% vs. 73%). Furthermore, patients with variceal bleeding who are treated with antibiotics may have improved outcomes.

When ACLF is associated with a precipitating factor (i.e., bacterial infections, GI bleeding, alcoholism, drug toxicity), early identification and treatment of the precipitating factor are essential. However, this may not prevent the development or worsening of the syndrome. In addition, as stated earlier, in up to 50% of patients a precipitating factor may not be identified. Moreover, available data suggest that although the precipitating factor may be the trigger of ACLF, it may not be an essential predictor of prognosis.

Despite all current aggressive medical management, mortality at 30 and 90 days in ACLF remains high. Unfortunately, many ACLF patients do not qualify for transplantation (advanced age, active alcoholism, concomitant diseases and the presence of associated failing organs, etc.), and even if they do — given that transplant candidates far outnumber donors — many do not live long enough to receive a liver. In fact, half of all ACLF patients that qualify for

[11] Michelena J, Altamirano J, Abraldes JG, et al. Systemic inflammatory response and serum lipopolysaccharide levels predict multiple organ failure and death in alcoholic hepatitis. *Hepatology* 2015;62:762–72.

[12] Arroyo V, Moreau R, Kamath PS, et al. Acute-on-chronic liver failure in cirrhosis. *Nat Rev Dis Primers* 2016;2:16041.

[13] Yaseen M. Arabi, "Antimicrobial Therapeutic Determinants of Outcomes From Septic Shock Among Patients With Cirrhosis," *Hepatology,* ; Jody C. Olson, "Intensive Care of the Patient with Cirrhosis," *Hepatology,* Vol. 54, No. 5, 2011

transplantation, die before a suitable donor organ is available.

That's the bad news. The good news is that for patients receiving a new liver, one-year survival is very high. In a study[14] of patients with ACLF grade 2 and 3, survival at 90 days without liver transplant was under 20%, versus 80% in patients who received a transplant.

Other treatments, such as extracorporeal liver support, have been studied but have not demonstrated a mortality benefit and so have not been established as standard of care.[15]

THE ECONOMIC BURDEN OF ACLF

Acute and chronic liver diseases account for substantial use of healthcare resources, and strain families that have loved ones suffering from this disease — who many times not only undergo an emotional toll, but are forced to make sacrifices to become the care givers. While ACLF accounts for a small percentage of those with liver disease, their inpatient hospital care is so intense and they place a higher burden on

CHARACTERISTICS OF ACLF PATIENTS BY GRADE*

Grade	Definition	28-Day Transplant-free Mortality Rate
Acute Decompensation without ACLF	No organ failure	4.7%
	Single-organ failure (liver, coagulation, circulation, lungs) in patients with serum creatinine levels <1.5 mg/dL and no hepatic encephalopathy	
	Single cerebral failure in patients with serum creatinine levels <1.5 mg/dL	
ACLF Grade 1	Single kidney failure	22.1%
	Single-organ failure (liver, coagulation, circulation, lungs) in patients with serum creatinine levels ranging from 1.5–1.9 mg/dL and/or grades 1–2 hepatic encephalopathy	
	Single cerebral failure in patients with serum creatinine levels ranging from 1.5–1.9 mg/dL	
ACLF Grade 2	Two organ failures	32.0%
ACLF Grade 3	Three organ failures or more	78.6%

*This table is based on the CANONIC study conducted in 2011, which prospectively enrolled 1343 patients with cirrhosis hospitalized in 29 Liver Units from 8 European countries. The definition of the Presence or Absence of ACLF and of ACLF Grades Based on Results Obtained at Enrollment in the CANONIC Study. ACLF was present in 23% of patients at hospital admission or developed in 11% of patients who did not have ACLF at admission; a total of 303 patients had ACLF. Enrolled patients were hospitalized for at least 1one day and had an acute development of large ascites, hepatic encephalopathy, gastrointestinal hemorrhage, bacterial infections, or any combination of these. For the diagnosis of organ failures, investigators used a modified SOFA scale, called the CLIF-SOFA scale, which had been designed specifically by the Writing Committee of the CANONIC study before the onset of this study.

[14] Richard Moreau et al, "Acute-on-Chronic Liver Failure Is a Distinct Syndrome That Develops in Patients With Acute Decompensation of Cirrhosis," *Gastroenterology,* 2013;144:1426-1437.

[15] Francois Durand, "Management of Acute-on-Chronic Liver Failure," *Semin Liver Dis* 2016;36:141–152.

the healthcare system in human resources and dollars.

For instance, the average length of hospital stay for a patient suffering with cirrhosis is seven days, versus 16 days for an ACLF patient[16]. Due to the higher risk of mortality, the level of care given needs to be more specialized and resource intensive. In economic terms, in-hospital costs are 3.5 times higher for an ACLF patient versus a decompensated cirrhosis patient without ACLF.[17]

Since ACLF often is a result of acute complications such as sepsis, spontaneous bacterial peritonitis, or gastrointestinal bleeding or from superimposed events such as acute viral hepatitis, drug-induced liver injury, alcohol consumption, or ischemic hepatitis, the high likelihood of death requires more intensive treatment.

The mean ICU charges per admission can range from $116,000 to $180,000 per episode[18] - or more than $4 billion annually to the U.S. healthcare system.[19]

Obviously this cost burden doesn't take into account other related costs of caring for these patients or the effects this has on society as a whole. Since the average age of ACLF patients is only 56 years,[20] there are the hidden costs of lost worker productivity/wages, and in many cases, the loss of a breadwinner in the family.

[16] Patrick S. Kamath, M.D., Acute on Chronic Liver Failure, *Clincial Liver Disease*, VOL 9, No. 4, April 2017
[17] Alina M. Allen, et al, Time Trends in the Health Care Burden and Mortality of Acute on Chronic Liver Failure in the United States, *Hepatology*, VOL. 64, NO. 6, 2016
[18] Jody Olson el al, Intensive Care of the Patient with Cirrhosis, *Hepatology,* 2011;1;54;1864—1872
[19] Rowen K. Zetterman, Understanding Acute-on-Chronic Liver Failure, *Medscape,* Jan 19, 2016; $116,000 X 40,000.
[20] Alina M. Allen, et al, Time Trends in the Health Care Burden and Mortality of Acute on Chronic Liver Failure in the United States, *Hepatology*, VOL. 64, NO. 6, 2016

FUTURE PROGRESS IN TREATING ACLF

It's been over two decades since publication of the first article proposing the hypothesis that acute-on-chronic liver failure was likely to be a distinct clinical condition,[21] and yet, despite all the advancements in so many other areas of medical science during that same period, when it comes to ACLF, much research and discovery is yet to be done. Hopefully efforts occurring in this field now and of those in the future will lead to novel biomarkers and therapeutic strategies that will help patients suffering from this devastating disease.

Martin Pharmaceuticals, a clinical stage pharmaceutical company, is passionate about bringing life-changing advances to patients with rare diseases or challenging medical conditions. We are proud to be actively taking steps to find answers for ACLF patients. Our drug, LIVANTRA®, shows great promise[22] in saving and improving the lives of these victims.

Normal livers get most of their energy by metabolizing fat. As cirrhosis progresses, this mechanism becomes defective and energy production shifts to using glucose instead. The defective fat metabolism, however, inhibits this process and so the liver begins to suffer from energy failure and toxic molecules, called reactive oxygen species, are created. If left unchecked, these reactive oxygen molecules can damage DNA and intracellular membranes in an already-injured/cirrhotic liver, initiating cell death pathways that lead to apoptotic hepatocyte death (programmed death in liver cells).

At the molecular level, LIVANTRA inhibits β-oxidation of free fatty acids (FFA) by

[21] Azeem Alam et al, Acute-on-chronic liver failure: recent update, *J. Biomed Res,* 2017; 31(4): 283–300
[22] See MartinPharma.com for results from a human study of our drug in ACLF patients.

selectively inhibiting the long-chain 3-ketoacyl coenzyme A thiolase, which is the final enzyme in the FFA β-oxidation pathway. By turning off this key mechanism, liver cells are able to get and use more glucose for energy, creating molecular building blocks that allow the liver to again carry out its essential functions.

LIVANTRA shifts the generation of energy in the liver from fatty acid oxidation to a process called glycolysis. This prevents formation of toxic molecules and prevents cell death. This glycolysis strategy, employed by all actively growing cells in the body, can be temporarily induced by LIVANTRA to restore proper energy balance and allow the liver to recover from the acute insult of ACLF.

LIVANTRA is an investigational drug and is not approved by FDA. For more information on LIVANTRA, please go to our website: MartinPharma.com.

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