

Acute-on-chronic liver failure: A new disease or an old one hiding in plain sight?

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Conflict of Interest:

R.J. has served as a speaker, a consultant and an advisory board member for Sequana Medical, Yaqrit, Mallinckrodt, Organovo, Prometic, Takeda, has received research funding from Yaqrit, Takeda, owns stocks and shares in Yaqrit, Ammun, Cyberlive and owns the patent Yaq-001; DIALIVE; Ornithine Phenylacetate; TLR4 antagonist.

Introduction

Clinical states of cirrhosis were traditionally represented in a comprehensive multistate model including compensated cirrhosis, decompensated cirrhosis, and late decompensated cirrhosis. Acute-on-chronic liver failure (ACLF - which is the first of several bewildering acronyms used in this field*) adds substantially to this multistate model by identifying a subgroup of cirrhotic patients who progress rapidly following acute decompensation (AD) to develop organ failure(s) (OF[s]), and who experience high short-term mortality (Figure 1).

Since its initial description [1], nearly 1000 papers have been published describing the clinical characteristics, prognostic models and pathophysiology of ACLF. A number of studies describing novel approaches to treatment are also being developed. Over 10 definitions for the ACLF syndrome exist. Yet, so far, there has been only one prospective study - with the specific aim of defining the ACLF syndrome - which was performed by the European Association for the Study of the Liver (EASL)-Chronic Liver Failure (CLIF) Consortium, namely the **CLIF Acute-oN-ChrONic Liver Failure In Cirrhosis (CANONIC) Core Study** [2]. According to the results of this study, ACLF is defined as a specific syndrome in cirrhotics characterized by AD, OF(s) and high short-term mortality. AD itself is defined as the development of ascites, hepatic encephalopathy, gastrointestinal hemorrhage and/or bacterial infections. ACLF may develop in patients without or with a prior history of AD(s). OFs involve the liver, kidney, brain, coagulation, respiratory system and/or the circulation, and are defined either by (i) the original CLIF- Sequential Organ Failure Assessment (SOFA) score that has been adapted for liver patients (CLIF-SOFA) or (ii) by its simplified version, the CLIF-Consortium (C) OF score [3]. The CLIF C ACLF score combines the CLIF-OF score with the patient's age and white blood cell (WBC) count, to generate a composite score of 0–100 to allow prognostication of individual patients. This has been shown to be superior to the conventional prognostic scores used for patients with cirrhosis such as the Child-Turcotte-Pugh score, the MELD score and the MELD-Sodium score (3).

High short-term mortality means a 28-day mortality rate $\geq 15\%$. Specific and cardinal pathophysiologic features of ACLF are systemic and hepatic inflammation [2,4]. It is not clear if systemic inflammation, manifested by elevated white cell count and C-reactive protein levels, represents an alteration of host response to injury or an inability to resolve inflammation.

A detailed review of ACLF is beyond the scope of this article that will focus on its historical aspects. This review will also discuss the impact the discovery of ACLF is having on healthcare, the economy, commerce, public policy and international collaborations.

Historical Perspective

The ACLF concept as we know it today was first described by Jalan and Williams [1]. The inspiration for considering this a new syndrome was the clinical observation that relatively young patients with cirrhosis were presenting to the hospital for the first time in multiorgan failure, ending up in the intensive care unit (ICU) and then dying. The background to this was the previous clinical observation made by Jalan et al., in Edinburgh, [5] that insertion of a transjugular intrahepatic portosystemic shunt (TIPS) in 4 patients with uncontrolled variceal bleeding and sepsis led to the development of a syndrome that resembled Acute Liver Failure (ALF) with the typical ALF manifestation of severe intracranial hypertension (Figure 2). Cerebral edema, as seen in ALF is rare in cirrhosis even with AD. One of the huge advantages that we had at The Middlesex and University College London Hospitals (which were where the clinical arm of the Institute of Hepatology was based at University College London) was relatively easy access to the fantastic intensive care facilities, which embraced these very complex patients. The lack of a liver transplant service paradoxically was an advantage as it meant that competition for ICU beds was limited, since patients with ALF ended up in liver transplant centers, such as the Royal Free and Kings College Hospitals. The second factor that consolidated these early ideas was recognition of the importance of systemic inflammation in driving multiorgan dysfunction, namely severe portal hypertension, hepatic encephalopathy, and renal dysfunction [6-8]. Finally, we were able to secure funding from The Foundation for Liver Research and Industry to treat patients in clinical trials, by targeting inflammation using albumin dialysis and anti-tumor necrosis factor- α (TNF α) therapy, providing us with access to relatively large numbers of patients [6-7]. Together, these early studies created the framework for ascertaining the elements that define ACLF. The early data suggested that the occurrence of OFs changed the natural history of cirrhotic patients with AD. From the pathophysiological perspective, inflammation, and especially the Systemic Inflammatory Response Syndrome (SIRS), was recognized as a distinctive feature. The chronology of activity to establish studies in ACLF is shown in Table 1.

The first meeting to develop the idea further was entitled 'Towards defining ACLF'. This was held at the American Association for the Study of Liver Disease (AASLD) meeting in 2003 (Figure 3.). Its proponents were the late Andy Blei (Northwestern University, Chicago IL), Vicente Arroyo (University of Barcelona, Barcelona), Patrick Kamath (Mayo Clinic, Rochester MN) and Guadalupe Garcia-Tsao (Veterans' Affairs Connecticut Healthcare System, West Haven CT and Yale University, New Haven CT) in addition to Rajiv Jalan and Roger Williams (University College Hospital, University of London). A number of key investigators in the field of cirrhosis were invited to discuss the idea of existence of this syndrome, and a proposal to perform a prospective study was developed. A supplement was produced from this meeting funded by a small grant from Teraklin Ltd, the company owning the molecular adsorbent recirculating system (MARS) device. The initial idea was to develop an International Chronic Liver Failure Study Group (ICLFSG). This meeting was followed in 2004 by a meeting at University College London, entitled 'Prospects for Liver Support', the proceedings of which were published [9]. At this time, support for the concept of ACLF had started to take shape with both enthusiasm and also healthy skepticism. A smattering of talks at various meetings around the world entitled 'Acute-on-Chronic Liver Failure', started to be entertained.

The idea of the ICLFSG was discussed further over the following year, culminating in a debate as to whether the American and European Consortia should be run separately given the logistical difficulties. As a result of a letter sent by Vicente Arroyo to the Secretary General of EASL, seeking their blessing, in 2007, the European Association for the Study of the Liver-Chronic Liver Failure (EASL-CLIF) Consortium was formed. This partnership with EASL was crucial in providing the governance framework on which the future success of the Consortium relied. The Consortium received an unrestricted grant from Grifols, a Spanish multinational pharmaceutical and chemical manufacturer, to perform the first prospective study to develop diagnostic and prognostic criteria for ACLF - which was started in 2009 and published in 2013 supporting the hypothesis [2]. This landmark study has been cited over 1000 times and was led by Professors Richard Moreau (Paris, France), Rajiv Jalan (London, UK), Pere Gines (Barcelona, Spain), Paolo Angeli (Padova, Italy), Dr Marco Pavesi (Barcelona, Spain) and Professor Vicente Arroyo (Barcelona, Spain) (Figure 3).

This activity in Europe was paralleled by developments in Asia, led by Professor Shiv Sarin (Institute of Liver and Biliary Sciences, New Delhi, India, Figure 3) under the auspices of The Asian Pacific Association for the Study of the Liver (APASL). APASL took a different

approach and defined ACLF in 2009 based upon a consensus rather than the results of a prospective study [10]. In the US, the North American Consortium for the Study of End Stage Liver Disease (NACSELD) was formed by Drs Jasmohan Bajaj (Virginia Commonwealth University, VA), Patrick Kamath (Mayo Clinic, Rochester MN), Florence Wong (Toronto General Hospital, Toronto Canada) and Gaudalupe Garcia-Tsao (Veterans' Affairs Connecticut Healthcare System, West Haven CT and Yale University, New Haven CT) [11] (Figure 3). The key components of the definitions of ACLF by four major organizations are shown in Table 2. Very active groups working on ACLF have since been developed in China led by Professor Hai Li (Renji Hospital, Shanghai) and Professor Lanjuan Li (Hangzhou). As mentioned above, over this period, about 1000 peer-reviewed papers, reviews and chapters have been published and this new syndrome has started to have an influence world-wide in several areas, as discussed below.

Impacts of recognition of ACLF as a new syndrome

Impacts on Healthcare

The acceptance of ACLF as a new syndrome has stimulated widespread research across the world, with the setting up of new Consortia as described above. The investment of resources into these Consortia have led to the following benefits:-

- *Reduction in mortality of ACLF patients:* In-hospital mortality of ACLF patients has reduced significantly from 65% to about 45% [12], albeit still unacceptably high.
- *Liver Transplantation:* In most parts of the world, organ allocation for liver transplantation is based on using the MELD score or its variant(s). New prognostic models and scoring systems for patients with ACLF have been developed that perform better than the MELD score [3] and suggest that patients with ACLF are served poorly by the current organ allocation system. The results of these developments are helping to bring about discussions regarding changes to the organ allocation policies [13-14].
- *Development of new guidelines of care:* Recognising the devastating outcome of ACLF, a Consensus meeting, endorsed by the American Society of Transplantation (AST), the American Society of Transplant Surgeons (ASTS), and EASL, was organised. The document arising therefrom details therapeutic strategies to manage patients with ACLF [15].
- *Regulatory Authority Policies:* The Food and Drug Administration (FDA) has recently recognised the importance of ACLF and awarded orphan drug designation to two

drugs for the treatment of ACLF TAK-242 (Akaza) and Trimetazidine (Martin Pharmaceuticals).

Impacts on the Economy

The use of the CLIF classification and scores allows early risk stratification of patients into those without and with ACLF and the identification of patients who are likely to die. This allows earlier engagement with the Intensive Care Unit (ICU) and liver transplantation teams, resulting in an increase in the total number of ICU admissions yet a reduction in mortality [12], (see Table 3 for an assessment of the cost of ACLF to the US economy, in comparison with other serious illnesses. On the other hand, new thresholds for futility of ongoing ICU care for patients with ACLF have been identified, to permit the release of precious ICU beds with the hope that patients and relatives will not be unduly distressed [16-18].

Impacts on Commerce

Targeting ACLF is a growing priority in the various Pharma and Biotech companies that are involved in developing suitable drugs and devices. The ACLF research area is currently employing at least 150 researchers across the world, while the drug companies that are involved in ACLF research are investing over \$500M into drug development. Examples of investment into ACLF are pharmaceuticals developed by Mallinckrodt, and Takeda's investment in Ambys. Cell therapy approaches are being developed by Promethera, while drug and device development is being undertaken by small and medium-sized enterprises, (SMEs) such as Versantis, Yaqrit, Akaza, Thoreris and Martin Pharma.

Impacts on Public policy and Practitioners

ACLF is making a huge impression on public policy in relation to allocation of organs, the effort for which is being spearheaded by the European Liver and Intestine Transplant Association (ELITA) and the CLIF Consortium, who aim to find appropriate justification to allocate priority for patients with ACLF. The realisation that ACLF is indeed a reversible condition is transforming early referral pathways in clinical networks, thereby yielding more rapid access to ICU care and facilitating recruitment of these patients into clinical trials.

Impacts on International development

ACLF is fostering international collaborations, which are improving the global relationships for liver diseases. Given the vast variations in the prevalence of liver diseases that are

factors in ACLF world-wide and the differences in both the aetiology of liver disease - predominantly alcohol in Europe, non-alcoholic steatohepatitis (NASH) in the US and chronic viral hepatitis in the Far East - and triggers of AD (Table 2) – infection, alcoholic hepatitis, and reactivation of hepatitis B etc. – close collaborations in terms of exchanges of students, data, and clinical care pathways are underway. This will favor better international relations and overall improvement in the care of patients.

Conclusions and Future perspectives

It is clear that the discovery of ACLF as a distinct syndrome that occurs in patients with cirrhosis has re-classified cirrhosis, provided novel insights into disease pathogenesis, and generated new therapeutic targets. The academic funding organisations have taken notice of the importance of this syndrome and have started to invest in research groups studying ACLF. Many pharmaceutical companies have started to take an interest in finding solutions for this patient population, whose outlook has improved somewhat but not sufficiently yet, over the past 30 years. ACLF continues to cost the taxpayer huge sums of money (Table 3). Increasing awareness of the ACLF syndrome, however, is leading to rapid referral of these patients to specialist centers. New research is leading to the discovery of new biomarkers and therapeutic targets. Liver transplantation is being used increasingly for these patients, as rescue therapy. Taken together, it is to be expected that mortality rates of ACLF will start to plummet as physician awareness, education and research advance, and patients are engaged in clinical trials and new therapies blossom.

The author of Ecclesiastes bemoans the monotony of life, and alleges that ‘... there is nothing new under the sun’. Notwithstanding, the appreciation that ACLF is a syndrome distinct from simple AD was essentially a new observation, even though it is highly likely that it indeed represented an old disease hiding in plain sight.

*Abbreviations

ACLF: Acute-on-Chronic Liver Failure

AST: American Society of Transplantation

ASTS: American Society of Transplant Surgeons

CLIF: European Foundation for the study of Chronic Liver Failure

CLIF-OF: European Foundation for the study of Chronic Liver Failure Organ Failure score

ELITA: European Liver and Intestine Transplant Association

FDA: Food and Drug Administration

ICLFSG: International Chronic Liver Failure Study Group

ICU: Intensive Care Unit

INR: International Normalized Ratio

MELD: Model for End-Stage Liver Disease

NASH: Nonalcoholic Steatohepatitis

SIRS: Systemic inflammatory response syndrome

SME: Small and Medium-sized Enterprises

SOFA: Sequential Organ Failure Assessment

WBC: White Blood Cell count

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Tables

Table 1: Chronology of development of the idea and organizational activity in ACLF worldwide

1. 1997 Jalan R et al. Elevation of intracranial pressure following transjugular intrahepatic portosystemic stent-shunt for variceal haemorrhage. *J Hepatol* 27: 928-933
2. 2002 Jalan R and Williams R. Acute-on-chronic liver failure: Pathophysiological basis of therapeutic options. *Blood Purif* 20: 252-261
3. 2003 "Towards defining ACLF" meeting at AASLD - Blei, Arroyo, Kamath, Garcia-Tsao, Jalan and Williams - plans for International Chronic Liver Failure Study Group shelved.
4. 2004 "Prospects for liver support" [University College London]
 - concept of ACLF gaining acceptance
 - Jalan R, Sen S, Williams R. Prospects for extracorporeal liver support, *Gut* 53: 890-898
5. 2007 European Association for the Study of the Liver (EASL) -Chronic Liver Failure (CLIF) Consortium
 - first prospective study specifically to define ACLF started in 2009
6. 2009 Asia Pacific Association for the Study of the Liver (APASL)
 - 1st consensus definition of ACLF
7. 2012 Publication of the 1st comprehensive review detailing pathophysiology. Jalan et al. *J Hepatol*. 57(6):1336-48
8. 2013 Publication of the CANONIC study. Moreau et al. *Gastroenterology*. 144(7):1426-37
9. 2014 Publication of the CLIF-C ACLF score. Jalan et al. *J Hepatol*. 61(5):1038-47
10. 2014 North American Consortium for the Study of End Stage Liver Disease (NACSELD) established.

Table 2: Variations in definitions of ACLF worldwide

Consortium	APASL	EASL-CLIF	NACSELD	WGO
Diagnostic Parameters	Acute jaundice & coagulopathy, followed by ascites ± HE <4 wks in undiagnosed/diagnosed chronic liver disease, incl cirrhosis	Specified criteria using CLIF-OF score(s) for organ failure, 28-day mortality >15% from acute decompensation of cirrhosis, without/with prior decompensation. often due to infection	Specified criteria for 2 or more organ failures in patients with infection, at or during admission.	Acute hepatic decompensation resulting in jaundice and elevated INR and 1 or more organ failures, with increased mortality in 28-90 days. With or without previously diagnosed cirrhosis
Exclusion Criteria	Bacterial infection or previous acute decompensation	Patients admitted electively for procedures or therapy, or those with HCC outside Milan criteria, or on Immunosuppressive therapy, with HIV or with severe chronic extrahepatic disease	Outpatients with infection, any patient with HIV infection/ prior organ transplants/ disseminated malignancies.	None stated

Abbreviations:

APASL – Asian Pacific Association for the Study of the Liver; EASL-CLIF – European Association for the Study of the Liver-Chronic Liver Failure Consortium; NACSELD – North American Study of End-Stage Liver Disease; WGO – World Gastroenterology Organization ; HE – hepatic encephalopathy; CLIF-SOFA - European Association for the Study of the Liver-Chronic Liver Failure score; HCC – Hepatocellular carcinoma; HIV – Human immunodeficiency virus; INR – International Normalised Ratio

Table 3. Economic Burden of Acute-on-Chronic Liver failure in the United States

	Total cost/yr	Mean Cost per Admission	Admissions per year (#)	Hospital stay	Mortality (%)
Cirrhosis	\$10 bill	\$14,894	658,884	7 d	7%
ACLF	\$1.8 bill	\$51,841	32,335	16 d	50%
Pneumonia	\$17 billion (all costs, including outpatient)	\$7,206 or \$4913	1.1 million	5.2 d	4.1%
Chronic Heart Failure	\$32 billion? (all costs, including outpatient)	\$10,775	1 million	5 d	5.3%
Sepsis	\$24.3 billion	\$19,330	808,000	8.8 d	

Modified from Allen et al. 2016 (12)

Figure Legends

Figure 1. Pathophysiological Stages of Cirrhosis and ACLF. This is the concept that was agreed by the World Gastroenterology Organization (WGO) Working Party referred to in Table 2. (reproduced with permission from Jalan et al. *Gastroenterology* 2014; 147:4-10).

Figure 2. Cerebral edema in cirrhosis patients. First report of cerebral edema and severe intracranial hypertension in septic patients with cirrhosis, following placement of transjugular intrahepatic portosystemic shunts (TIPS). The X-axis depicts the time since insertion of transjugular intrahepatic stent-shunt; the Y-axis shows the intracranial pressure in mm Hg. These data first led to the idea that a patient with cirrhosis can manifest the cardinal sign of acute liver failure giving birth to the idea that a new syndrome, acute on chronic liver failure (ACLF) may exist. (data from: Jalan et al. *J Hepatol.* 1997; 27: 928-933)

Figure 3. Key ACLF investigators worldwide

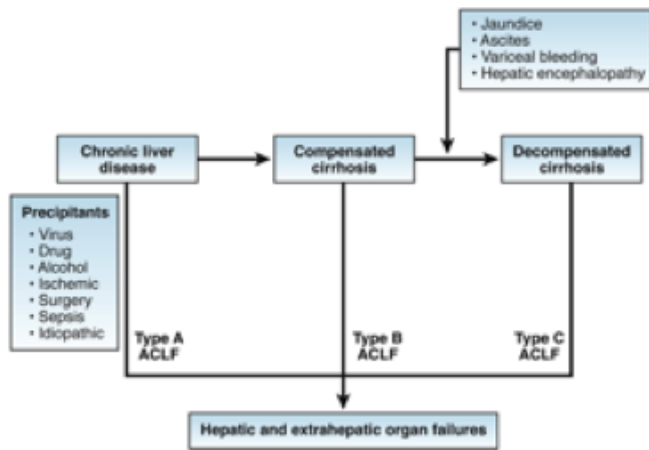


Figure 1

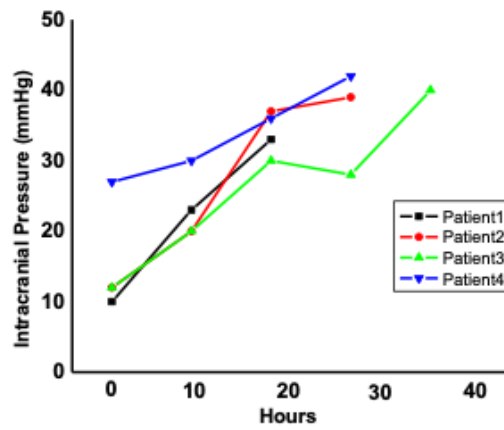


Figure 2

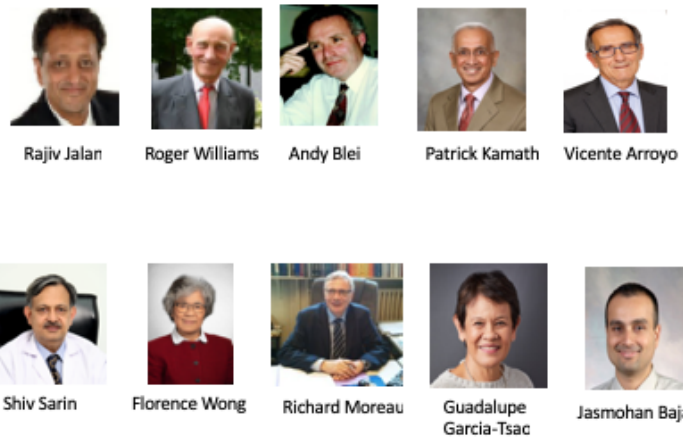


Figure 3