Acute-on-chronic liver failure

William Bernal, Rajiv Jalan, Alberto Quaglia, Kenneth Simpson, Julia Wendon, Andrew Burroughs

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Liver Intensive Therapy Unit (W Bernal FRCP, Prof J Wendon FRCP), **and Histopathology Section, Institute of Liver Studies** (A Quaglia FRCPath), **King's College Hospital, London, UK; Liver Failure Group** (Prof R Jalan FRCP), **Institute for Liver and Digestive Health** (Prof R Jalan FRCP, Prof A Burroughs FRCP), **Division of Medicine, University College London, London, UK; Sheila Sherlock Liver Centre, Royal Free Hospital, London, UK** (Prof R Jalan, Prof A Burroughs); **and Department of Hepatology, University of Edinburgh, Edinburgh, UK** (K Simpson FRCP)

Correspondence to:
Dr William Bernal, Liver Intensive Therapy Unit, Institute of Liver Studies, King's College London, London SE5 9RS, UK
william.bernal@kcl.ac.uk

Acute-on-chronic liver failure combines an acute deterioration in liver function in an individual with pre-existing chronic liver disease and hepatic and extrahepatic organ failures, and is associated with substantial short-term mortality. Common precipitants include bacterial and viral infections, alcoholic hepatitis, and surgery, but in more than 40% of patients, no precipitating event is identified. Systemic inflammation and susceptibility to infection are characteristic pathophysiological features. A new diagnostic score, the Chronic Liver Failure Consortium (CLIF-C) organ failure score, has been developed for classification and prognostic assessment of patients with acute-on-chronic liver failure. Disease can be reversed in many patients, and thus clinical management focuses upon the identification and treatment of the precipitant while providing multiorgan-supportive care that addresses the complex pattern of physiological disturbance in critically ill patients with liver disease. Liver transplantation is a highly effective intervention in some specific cases, but recipient identification, organ availability, timing of transplantation, and high resource use are barriers to more widespread application. Recognition of acute-on-chronic liver failure as a clinically and pathophysiologically distinct syndrome with defined diagnostic and prognostic criteria will help to encourage the development of new management pathways and interventions to address the unacceptably high mortality.

Introduction

Cirrhosis, irrespective of cause, is often asymptomatic until an episode of acute decompensation. Development of liver-specific complications from portal hypertension or hepatic insufficiency, including ascites, variceal bleeding, infection, and hepatic encephalopathy, occur in as many as 15% of patients with cirrhosis each year—frequency and severity increase as hepatic functional reserve and structural distortion progressively worsen.[1–4] When acute decompensation occurs, many patients respond to standard interventions and return to a compensated state. However, as many as a third develop further hepatic or extrahepatic organ failure, or both, and in a proportion of patients disease progresses to multiorgan failure, with need for critical care support.

Hepatic and extrahepatic organ failure can occur in the context of a gradual progression of cirrhosis during months, which is commonly referred to as decompensated cirrhosis. It can also come on suddenly—ie, short-term deterioration over days to several weeks after defined or undefined precipitating illness—so-called acute-on-chronic liver failure.[5] Despite aggressive support and use of substantial resources, short-term mortality in patients with acute-on-chronic liver failure is high (often exceeding 50%).[4,6] Many of the 170 000 deaths from cirrhosis in Europe each year occur in intensive care units (ICUs), and UK estimates of ICU costs per survivor exceed £50 000.[7] In the USA, the yearly cost of ICU care for patients with cirrhosis is estimated at US$3 billion.[8] In view of the high mortality and cost of care in patients with cirrhosis, reluctance to admit them to critical care settings seems common.[9,10] However, improvements in care have led to progressive improvements in outcomes of patients admitted to hospital with acute decompensation and acute-on-chronic liver failure, and universal prognostic pessimism is not justified[7,11–14] (figures 1, 2). In this clinical Seminar, we discuss the definitions, diagnostic, and prognostic criteria of acute-on-chronic liver failure, advances in the understanding of pathogenetic mechanisms, and approaches to clinical management.

Search strategy and selection criteria

We searched PubMed and MEDLINE with the term "acute on chronic liver failure" to identify studies and publications in addition to those familiar to the authors or cited by guidelines. We used no date or language restrictions, and our final search was on Feb 23, 2015. We reviewed the references of reports identified by our search to identify further studies that might be relevant to this Seminar. References were selected on the basis of their ability to provide insight into acute-on-chronic liver failure and its clinical management and guide the reader to relevant sources for further reading.

Definition

Although clinicians have recognised acute decompensation and acute-on-chronic liver failure as separate clinical entities for many years, no universally accepted diagnostic criteria were available.[15,16] Distinct clinical and pathophysiological differences have emerged in studies, and two definitions have been proposed, by the Asia-Pacific Association for the Study of Liver Disease and the European and American associations for the study of liver disease (panel).[17,18] The differences were resolved as part of a consensus meeting organised under the auspices of the World Congress of Gastroenterology, at which the decision was made that, to be a distinct clinical entity, acute-on-chronic liver failure should be distinct from both acute liver failure and decompensated cirrhosis, with clear clinical, laboratory, and pathophysiological features, and should have a validated clinical scoring system for assessment of severity.[5] Investigators in two large, prospective, observational studies of patients—one in Europe (Chronic Liver Failure [CLIF] Consortium Acute on Chronic [CANONIC])[4] and one in Canada and the USA (North American Consortium

for the Study of End-Stage Liver Disease [NACSELD])[19]—have attempted to define groups of patients with cirrhosis at high risk of short-term mortality, which form the basis of a working definition.

The definition includes patients with both compensated and decompensated cirrhosis and is inclusive of the fact that disease can occur in patients with chronic but non-cirrhotic liver disease, making possible, for example, inclusion of patients with chronic hepatitis B virus infection in whom acute-on-chronic liver failure can be triggered by reactivation of viral replication or de-novo and superimposed infection with other hepatotrophic viruses (typically hepatitis A or E viruses). Non-cirrhotic acute-on-chronic liver failure has been called type A disease, and can be distinguished from acute liver failure only by histopathological evidence of substantial hepatic fibrosis. Type B disease is proposed to occur in patients with compensated cirrhosis with hepatic deterioration after a major insult such as infection, surgery, or acute alcoholic hepatitis. Type C disease occurs with similar precipitants but in patients with a previous or contemporaneous episode of cirrhotic decompensation (figure 3). This proposed classification recognises that acute-on-chronic liver failure is probably a syndrome with several causes rather than a single disease, and is defined by the development of both hepatic and extrahepatic organ failure.

Severity

The CANONIC study was designed to develop diagnostic criteria for acute-on-chronic liver failure that would identify patients with a 28 day mortality of more than 15%. In this multicentre study,[4] 1343 patients with cirrhosis were assessed, who were admitted to hospital with acute decompensation complicated by rapid onset of ascites, hepatic encephalopathy, gastrointestinal bleeding, or bacterial infection. A predefined modification of the Sequential Organ Failure Assessment (SOFA) score,[20] which is used in other critical illness, provided the CLIF-SOFA score (later simplified to the CLIF Consortium [CLIF-C] organ failure score; appendix), which can be used to define the presence of specific organ systems failure (table). Patients with organ failure were classified as having acute-on-chronic liver failure, with three grades of severity. Patients with acute decompensation had 28 day mortality of less than 5%. Mortality associated with acute-on-chronic liver failure increased with increasing organ failure: patients in whom one organ had failed had 28 day mortality of about 20%, which increased to greater than 70% in those in whom three organs had failed (figure 4).

The most common cause of acute-on-chronic liver failure was alcoholic liver disease, the main identified precipitating illness was infection, and the extrahepatic organs that failed most often were the kidneys. Prognostic importance of single organ failure varied by the specific system involved. Subsequent external validation studies of the scoring system have shown significant association with survival, although the main organ failure can vary with differences in cause.[14,22–26]

Different definitions of organ failures were used in the NACSELD study,[19] in which 507 patients with cirrhosis who were admitted to hospital with infection were assessed; findings were similar to those of CANONIC. Patients with severe liver disease were more likely to develop acute-on-chronic liver failure than were those with less severe disease, and survival worsened as the number of failing extrahepatic organ systems rose.

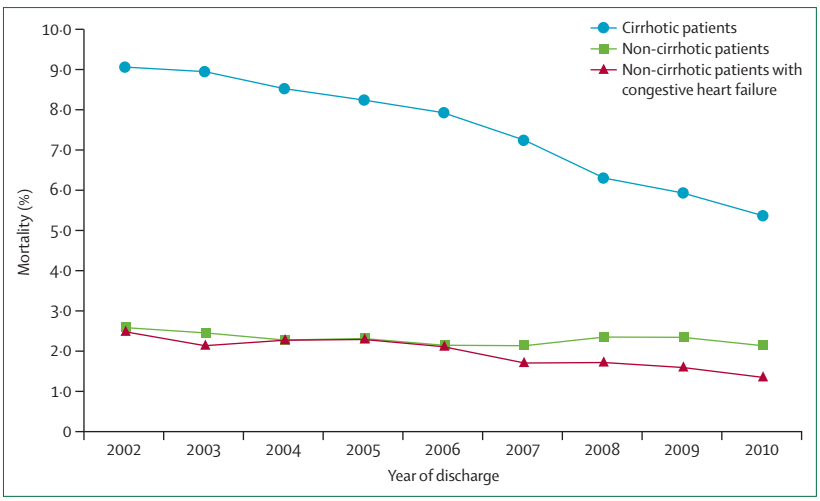

***Figure 1*: Mortality of patients admitted to hospital with cirrhosis in the USA, 2002–10**
n=781 515 for patients with cirrhosis, who were matched 1:1 with non-cirrhotic and congestive-heart-failure patients on age, sex, and year of discharge. Mortality fell by 41% in patients with cirrhosis. Data: Schmidt et al.[11]

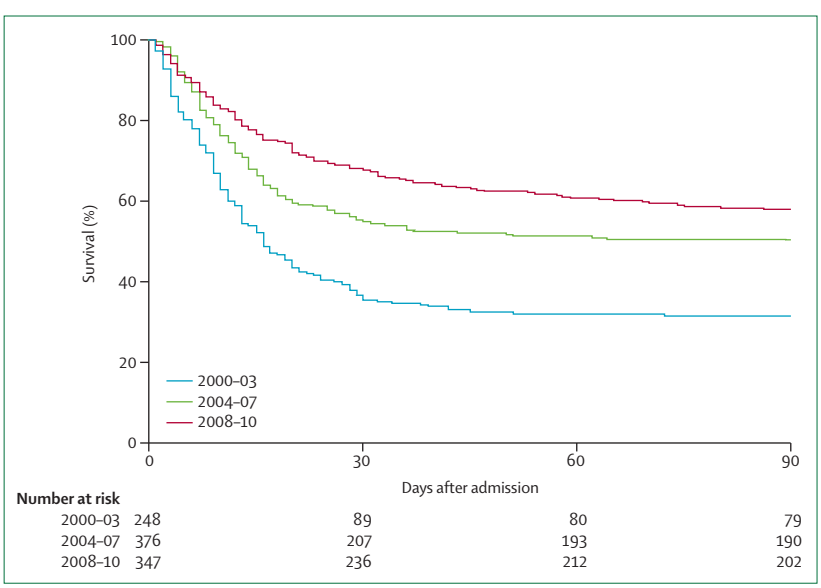

***Figure 2*: Kaplan-Meier graphs of survival of patients with cirrhosis admitted to the Liver Intensive Therapy Unit, King's College Hospital, London, UK, 2000–10**
n=971, p<0·001 for the log rank comparison of different periods. Source: MacPhail et al.[14]

See Online for appendix

Panel: Definitions of acute-on-chronic liver failure

World Congress of Gastroenterology (consensus definition)[5]
"A syndrome in patients with chronic liver disease with or without previously diagnosed cirrhosis which is characterized by acute hepatic decompensation resulting in liver failure (jaundice and prolongation of the INR [International Normalized Ratio]) and one or more extrahepatic organ failures that is associated with increased mortality within a period of 28 days and up to 3 months from onset"

Asia-Pacific Association for the Study of Liver Disease[17]
"Acute hepatic insult manifesting as jaundice and coagulopathy, complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease"

European and American associations for the study of liver disease[18]
"Acute deterioration of pre-existing, chronic liver disease, usually related to a precipitating event and associated with increased mortality at 3 months due to multi-system organ failure"

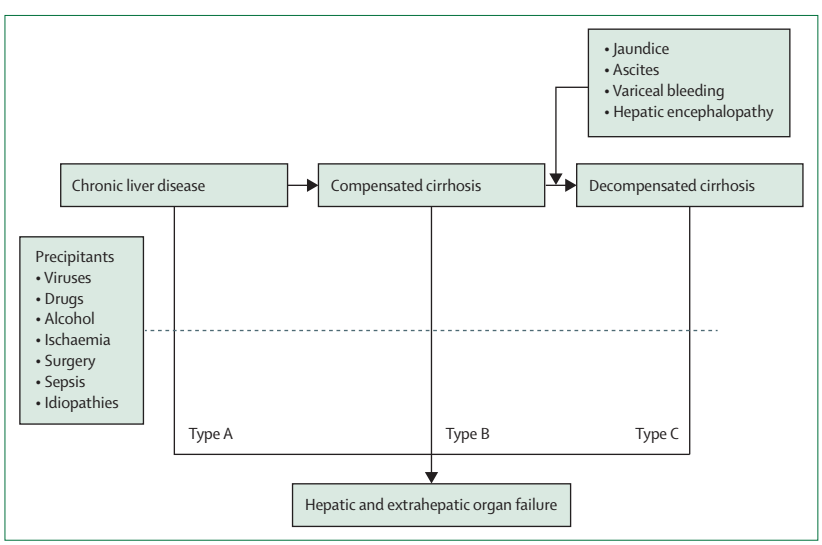

***Figure 3*: Assessment and proposed classification of acute-on-chronic liver failure within natural history of cirrhosis**
Proposed unified classification for acute-on-chronic liver failure, which can develop after a precipitating insult in patients with non-cirrhotic chronic liver disease (type A) or compensated (type B) or decompensated (type C) cirrhotic liver disease. Source: Jalan and colleagues, 2014.[5]

Clinical course and outcome prediction

About 10% of patients admitted with acute decompensation will develop acute-on-chronic liver failure while in hospital.[4,21,28] In the CANONIC study,[28] roughly 50% of patients who presented with acute-on-chronic liver failure improved; around 20% deteriorated, and in these patients mortality was greater than 50%. Improvement was most common (55%) in those who had only one failing extrahepatic organ, and became less likely with increasing organ failure. The course of illness during patients' first days in hospital were significantly linked to eventual outcome, suggesting that recognition and aggressive early management could be key to improvement of survival.

In a prognostic model designed to predict survival, CLIF-C organ failure score, age, and white cell count were independent predictors of mortality.[21] These factors were incorporated into a new score, the CLIF-C Acute-on-Chronic Liver Failure (ACLF) score, which was compared with the clinical scoring systems used to assess severity of chronic liver disease: the Model for End-Stage Liver Disease (MELD) and the Child-Pugh score.[29,30] The CLIF-C ACLF score measures both hepatic and extrahepatic organ dysfunction and it discriminates significantly better between survivors and non-survivors than did MELD and the Child-Pugh systems, which underestimated the risk of death in acute-on-chronic liver failure. MELD and the Child-Pugh score form the basis of organ allocation in liver transplantation systems, and thus patients with acute-on-chronic liver failure who are being considered for liver transplantation might be at a disadvantage. In intensive care units, such scores might be used in decision making for admission, but their predictive value is inadequate for them to form the sole criterion to assess futility of continued care.[14] Serial application seems better at predication of outcome than a single observation on admission.[14]

Clinical characteristics and pathophysiology

Predisposition

Acute-on-chronic liver failure is complex and its clinical features and pathophysiology can be thought of in terms of the predisposition, injury, response, and organ (PIRO) framework that was developed for the classification of patients with severe sepsis.[31,32]

In the CANONIC study, cirrhotic patients presenting with acute decompensation who developed acute-on-chronic liver failure (type C) were significantly younger and more likely to have alcoholic cirrhosis than were those who did not develop acute-on-chronic liver failure, and acute-on-chronic liver failure was significantly less likely to progress in those with hepatitis C virus infection.[4] In patients with alcoholic cirrhosis, risk of acute-on-chronic liver failure and subsequent mortality was similar in those with a clinical diagnosis of acute alcoholic hepatitis and those with acute decompensation due to another cause, suggesting that once acute-on-chronic liver failure develops, its severity determines outcome more strongly than does the underlying cause.[4]

Injury (precipitating event)

A precipitating event is not necessary for a diagnosis of acute-on-chronic liver failure. In more than 40% of patients who develop the disorder, no precipitating event is noted.[4,33] The mechanism of acute deterioration in this population is unknown and necessitates further study. These patients have clinical signs of a similar

inflammatory response to those with an identified precipitating event. Perhaps laboratory investigations do not identify infective precipitants or covert acute alcoholic hepatitis, or possibly a spontaneous self-resolving infection or episode of intestinal bacterial translocation has occurred.[31,34,35]

The most frequently identified precipitating event is infection. Patients with cirrhosis have greatly increased risks of severe bacterial infection and are twice as likely to die from sepsis as are non-cirrhotic people.[36–41] 40–50% of hospital admissions for patients with cirrhosis are because of sepsis; the most common infections are spontaneous bacterial peritonitis, pneumonia, and urinary tract infections.[38,40] 30% of patients die within a month of admission and another 30% are dead at 1 year.[37] By contrast with the substantially improved outcomes in patients with cirrhosis and primary variceal bleeding, survival in those with severe sepsis seems to have improved little in the past 20 years.[11,37] Predisposition for sepsis in cirrhosis is multifactorial. Genetic predisposition, particularly for spontaneous bacterial peritonitis, is associated with specific polymorphic variants of *NOD2* and *TLR2*.[42] A highly complex pattern of compromised cellular and humoral immune defences and immunodeficiency coexist, which worsens with increasing severity of liver disease.[41,43–48]

The role and importance of portal hypertensive variceal bleeding as a precipitant seems to be changing. Mortality rates associated with variceal bleeding have fallen substantially in the past 20 years, and are now often less than 20%, and a strong evidence base for therapy has been developed.[13,14,49,50] Early deaths and acute-on-chronic liver failure after variceal bleeding now usually occur only in patients with advanced cirrhosis (Child-Pugh grade C); mortality in early-stage disease (grade A) is now less than 5%.[50–52] These improvements are a result partly of improved initial care and early endoscopy and partly of management of basic principles of airway, breathing, and circulation to prevent procedure-related aspiration and pneumonia (detailed discussion is outside the scope of this Seminar).[50,51,53] Infection is closely associated with bleeding due to portal hypertension: potential mechanisms include increases in portal pressure, impairment of liver function, and haemostatic derangement.[54,55] Appropriate antibiotic prophylaxis reduces the likelihood of early rebleeding and improves survival, and should be given routinely to patients presenting with acute variceal haemorrhage.[51,53,56,57]

Other precipitants can independently or in concert trigger acute-on-chronic liver failure. In patients with alcoholic cirrhosis, an alcohol binge and development of acute alcoholic hepatitis can bring on the disease, although this mechanism remains contentious. Other precipitants include hepatotoxic drugs, hepatic injury from ischaemia after hypotension or congestion from cardiac failure, or acute infection with hepatitis A and E viruses (especially in the Middle East and Asia).[58]

	Score=1	Score=2	Score=3
Liver (bilirubin)	<103 μmol/L	104–206 μmol/L	>206 μmol/L
Kidney (creatinine)	<175 μmol/L	176–310 μmol/L	>310 μmol/L or renal replacement
Brain grade (West-Haven)	0	1–2	3–4
Coagulation (international normalised ratio)	<2·0	2·0–2·4	≥2·5
Circulation (mean arterial pressure)	≥70 mm/Hg	<70 mm/Hg	Vasopressors
Respiratory:			
$Pa0_2/Fi0_2$	>300	201–300	≤200
$Sp0_2/Fi0_2$	>357	215–357	≤214

Values at study enrolment. A score of 3 is the definition of organ failure for each system, except for the kidney, for which a score of 2 or more is the definition. $Pa0_2$=partial pressure of oxygen. $Fi0_2$=fraction of inspired oxygen. $Sp0_2$=peripheral capillary oxygen saturation. Source: Jalan and colleagues, 2015.[21]

Table: **The Chronic Liver Failure Consortium organ failure score**

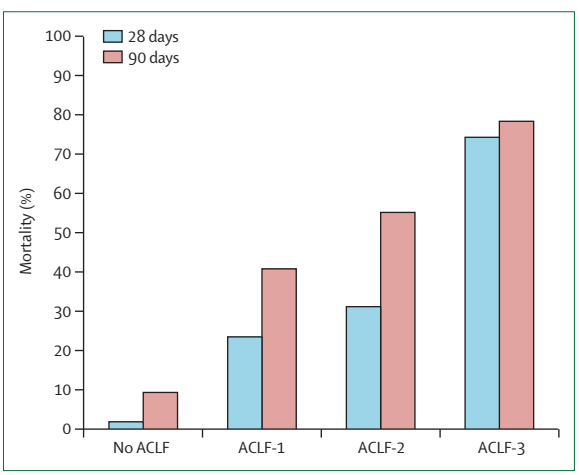

Figure 4: **Mortality in patients admitted to hospital with cirrhosis, by ACLF grade**

n=1343. ACLF-1 means renal or cerebral failure only, or renal dysfunction with other organ failure; ACLF-2 means double organ failure; and ACLF-3 means that three or more organs have failed. Grading applied to all types of liver failure (ie, A–C). ACLF=acute on-chronic liver failure.

Response

The systemic inflammatory response is a hallmark of acute-on-chronic liver failure. In the CANONIC study, increased white cell count at admission to hospital was an independent predictor of mortality and a key way to differentiate the disorder from acute decompensation. This increase in white cell count seemed to be independent of the presence of confirmed bacterial infection or a diagnosis of alcoholic hepatitis—ie, it represented a non-specific response to inflammation. Mortality progressively increased with increasing white cell count at admission (appendix).[4]

Immune responses of patients with cirrhosis that progresses to organ failure are abnormal. An initial pro-inflammatory cytokine response can occur, in parallel with or followed by a prolonged and inappropriate period of so-called immune paralysis, predisposing to secondary nosocomial infection.[45,59–61]

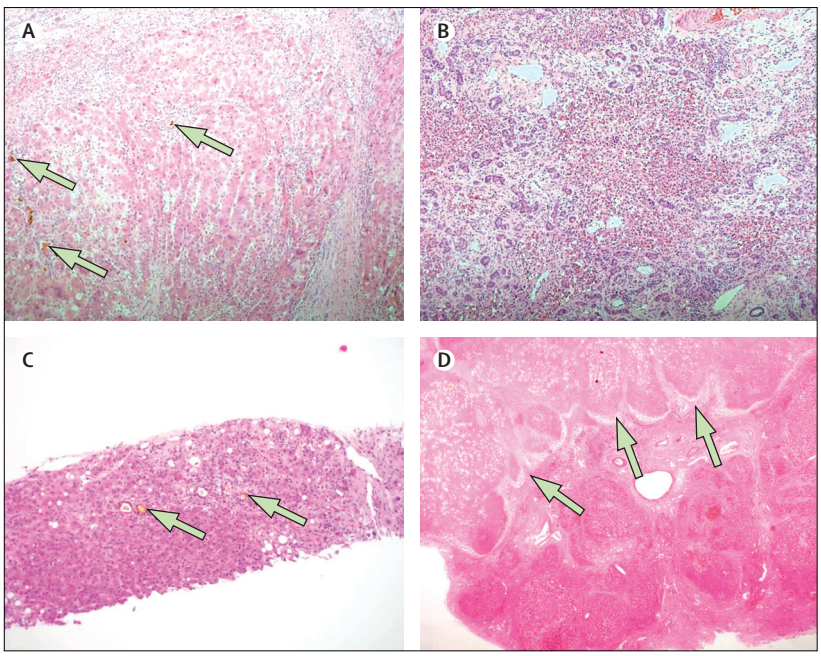

***Figure 5*: Histopathological appearance in the explant liver of a 43-year-old woman with acute-on-chronic liver failure (A, B); in the core needle biopsy of a 52-year-old man with acute-on-chronic alcoholic liver disease (C); and in the explant liver of a 24-year-old man who underwent transplantation because of autoimmune hepatitis and acute-on-chronic liver failure (D)**

Areas of bridging fibrosis, parenchymal nodule formation, and cholangiolar cholestasis (shown by the arrows, A) alternate with area of recent parenchymal collapse (B). Severe bridging fibrosis with parenchymal nodule transformation is shown in (C); arrows show presence of cholangiolar cholestasis. In (D), advanced-stage chronic liver disease with bridging fibrosis and parenchymal nodule formation can be noted in the lower half of the picture. Arrows shown confluent areas of ischaemic-type parenchymal necrosis. All slides are stained with haematoxylin & eosin, 100x magnification for (A–C), 20x for (D).

Immune paralysis is common in acute-on-chronic liver failure, correlates with severity of organ failure and risk of sepsis, and is associated with notably increased mortality.[44,45,59,62,63]

Organ failure

Although basic mechanisms of development and progression of acute-on-chronic liver failure are unclear, liver parenchymal cell injury and death are probably important at an early stage. Mechanisms and extent of cell injury or death might vary depending on underlying cause and precipitating event.

Histopathology

With the exception of changes noted in acute alcoholic hepatitis, the hepatic histopathological aspects of acute-on-chronic liver failure are poorly defined, and few studies have been done.[64] The limited results available suggest heterogeneity in appearance—unsurprising in view of the complexity and varied nature of underlying illnesses and precipitants (figure 5). Specific findings seem to relate closely to systemic manifestations of the disorder and to survival. In a prospective study, [65] transjugular liver biopsies taken from 54 patients with alcoholic liver disease within 72 h of development of acute-on-chronic liver failure were compared with 48 biopsies from patients with chronic hepatic decompensation undergoing elective transplant assessment. Ductular cholestasis, cholangiolitis, Mallory-Denk bodies, hepatocellular ballooning, and steatosis were significantly more frequent in the acute-on-chronic group than in the transplant group, and ductular cholestasis was significantly related to the presence of systemic inflammatory response syndrome and independently related to mortality. Review of liver biopsies from 50 patients with a clinical diagnosis of acute-on-chronic liver failure of various causes showed a similarly complex histological pattern; fibrosis, ductular proliferation, and apoptosis were independently associated with poor outcome.[66]

In a study of patients in China with hepatitis B virus cirrhosis,[33] histopathological review of 174 livers removed at transplantation showed areas of sub-massive hepatic necrosis in 40% of patients, correlating with clinical measures of liver injury and acute-on-chronic liver failure severity. Necrosis occurred most often in patients with viral reactivation or bacterial sepsis.[33] Coagulative necrosis of regenerative nodules in patients with chronic liver disease resulting from ischaemia has been described in paediatric patients with biliary atresia and congenital hepatic fibrosis or adult patients with alcoholic liver disease, variceal bleeding, and hypotension.[67,68] The overall pattern of histological features shows the underlying chronic liver disease and superimposed effects of not only precipitants including sepsis and ischaemia, but also disordered hepatic regeneration and recovery.

Inflammation

Hepatic inflammation is closely related to liver cell injury and necrosis and contributes both to systemic inflammatory status and to the development and severity of portal hypertension.[69–72] In cirrhosis, the presence of portal hypertension results in splanchnic vasodilation and altered flow into the portal circulation; hepatic inflammation results in further increased vascular resistance in the intrahepatic circulation and increased arterio-venous shunting.[70,72–74] These changes could exacerbate systemic translocation of gut-derived microorganisms into the circulation and contribute to the induction of the systemic inflammatory response and evolution of extrahepatic organ dysfunction in acute-on-chronic liver failure.[75] Hepatic inflammatory state could be a target for future therapies in some patients.[76] Anti-inflammatory drugs have been tested in patients with acute alcoholic hepatitis: anti-tumour-necrosis-factor antibody therapy (infliximab) acutely reduced the severity of portal hypertension and improved hepatic perfusion. Corticosteroids are also beneficial, and poor response to corticosteroids suggests that patients are unlikely to survive with medical therapy alone.[77,78]

Supportive care

Patients with acute-on-chronic liver failure and substantial organ dysfunction or failure are best cared for in a critical care environment. Most clinical care does not differ substantially from that deployed in other critically ill patients. Rapid identification and treatment of the precipitant and the delivery of supportive care that addresses all aspects of evolving or established multiple organs systems failure are basic principles of management. Microcirculatory dysfunction and tissue hypoxia or dysoxia are probably central to this process.[79] Clinical management includes rapid restoration of metabolic and haemodynamic stability and provision of nutritional support, in tandem with organ-specific supportive care. In many patients, such an approach will result in resolution of organ failure and hepatic recompensation.

Infection

Infection is the key precipitant and presents major challenges. When bacterial infection is suspected, prompt administration of appropriate antibiotics improves survival. In a study of more than 600 patients with cirrhosis in septic shock, mortality progressively increased for each hour of delay before antibiotic therapy after onset of hypotension (appendix) and was higher when the first antibiotics given were inappropriate (adjusted odds ratio 9·5, 95% CI 4·5–20·7).[80] In hospital patients with cirrhosis, rates of fungal colonisation are high, but invasive infection is uncommon. Prophylactic antifungal therapy in patients with acute-on-chronic liver failure is generally not advised unless other predisposing factors, such as immunosuppression, are present. Invasive aspergilloisis infection is increasingly recognised as a cause of morbidity and mortality in patients with acute alcoholic cirrhosis given corticosteroids, in whom candidaemia and cytomegalovirus infection can also occur.[81]

Cardiovascular failure

Cardiovascular failure in acute-on-chronic liver failure is associated with very high mortality (often >50%).[19] In cirrhosis, cardiac output is high and systemic vasodilation is common, effects which are thought to relate to low-level intestinal bacterial translocation and increased circulating concentrations of vasoactive and pro-inflammatory mediators.[34] Patients can have increased total blood volume, but distribution is dysfunctional, and they usually have effective central hypovolaemia. Small decreases in arterial tone after infective or inflammatory insults can rapidly precipitate hypotension.[8] Low-grade cardiac diastolic dysfunction (a feature of cirrhotic cardiomyopathy) is present in as many as half of patients with cirrhosis, but its relation to circulatory and renal failure in acute-on-chronic liver failure is not well characterised.[82–84] Although the main causes of hypotension are hypovolaemia and vasodilatation, reduction in cardiac output from baseline that is unresponsive to fluid therapy can occur in patients with acute-on-chronic liver failure, and predicts high risk of death.[8,73,85] Management of such patients is complex and necessitates interventions based on echocardiographic findings and invasive haemodynamic monitoring.

Choice of fluid for intravenous volume repletion remains controversial. Albumin is a multifunctional circulating protein that is reduced in quantity and altered in function in acute-on-chronic liver failure but its role as intravenous fluid therapy is unclear.[63,86,87] In patients at risk of acute-on-chronic liver failure from spontaneous bacterial peritonitis, prophylactic intravenous albumin could reduce the incidence of renal failure and liver failure and improve survival, although this survival benefit has not been noted for patients with established disease and other bacterial infections.[88,89] In hypotension unresponsive to intravenous fluid challenge, noradrenaline and vasopressin receptor agonists are often used, but more data are needed to inform choice of vasoconstrictors.[8,90]

Adrenal insufficiency is reported in as many as 75% of critically ill patients with cirrhosis and severe sepsis, which correlates with functional liver reserve and disease severity and is closely associated with haemodynamic instability, development of renal failure, and increased mortality.[91,92] Use of supplemental corticosteroids for septic shock in acute-on-chronic liver failure speeds up reversal of shock and vasopressor requirement, but no survival benefit has been shown.[93,94] A large randomised clinical trial of corticosteroid supplementation in acute-on-chronic liver failure is underway.[95]

For the **randomised clinical trial** see https://www.clinicaltrialsregister.eu/ctr-search/trial/2010-024273-38/CZ

Renal failure

Renal dysfunction (kidney injury) frequently complicates acute-on-chronic liver failure, is closely linked to the presence of systemic inflammatory state, and is of major prognostic importance.[4,24,96] Hepatorenal syndrome represents a liver-specific functional renal failure with high mortality, resulting from the combination of marked sympathetic and neurohumoral systems' activation, with splanchnic vasodilatation, systemic hypotension, and intense renal vasoconstriction.[97]

However, renal failure in acute-on-chronic liver failure is not a single diagnosis: in nearly 500 patients in hospital with cirrhosis and clinically significant renal dysfunction, 3 month survival was only 15% in those developing hepatorenal syndrome, but these patients accounted for only 13% of all cases.[98] Patients with cirrhosis whose renal failure had other causes were more than twice as likely to survive. In view of the clinical importance and complexity of renal dysfunction in patients with cirrhosis, new consensus criteria for acute kidney injury have been proposed; these criteria are based on dynamic changes in serum creatinine concentrations and define stages of severity, progression, regression, and response to treatment.[99] Analysis of urinary biomarkers can help to further subclassify renal failure in patients with cirrhosis.[100]

An algorithm for the management of acute kidney injury has codified many of the practices in current use (appendix).[99] Use of drugs with nephrotoxic effects and radiological contrast agents is avoided in patients at risk of kidney injury. However, appropriate cross-sectional imaging should be done if needed; renal function should be closely monitored.[8,97] In some settings, antibiotic prophylaxis can reduce risk of hepatorenal syndrome and improve survival.[101] In patients with acute alcoholic hepatitis, early use of pentoxifylline and N-acetylcysteine could reduce the risk of renal dysfunction, but this hypothesis was not supported in large randomised controlled trials.[77,102–104]

Bacterial infection is a frequent precipitant of renal dysfunction in cirrhosis; infection should always be looked for, and thresholds for antibiotics should be low.[97] Plasma volume expansion is done in patients with clinically suspected hypovolaemia, although the choice of fluids is based on clinical judgment (as is use of vasopressors). Intravenous albumin and terlipressin are frequently given in combination, resulting in expansion of circulating volume, increased systemic blood pressure, reversal of splanchnic vasodilation, improved renal perfusion, and possible non-colloidal albumin-specific effects.[8,97] Results of randomised controlled trials[105–109] suggest reversal of hepatorenal syndrome in as many as half of patients given this combination, and an improvement in short-term survival, although survival benefits were not shown in a large 2014 trial.[109]

Cerebral effects

Changes in consciousness as a result of hepatic encephalopathy are frequent in acute-on-chronic liver failure and range from mild sleepiness, confusion, and agitation to frank coma. These changes indicate very impaired underlying hepatic function. More than 60% of patients with alcoholic cirrhosis admitted to hospital with a first episode of hepatic encephalopathy are dead within a year.[2,110] In those with acute-on-chronic liver failure, encephalopathy is strongly and independently related to an increased risk of death, but clinically relevant cerebral oedema is very rare.[4,111,112] Current pathogenetic models of hepatic encephalopathy focus on the combined effects of genetic factors and neurotoxic effects, mainly as a result of hyperammonaemia, hyponatraemia, and systemic inflammation.[111]

Removal of neurotoxins, including ammonia, from the circulation is impaired in hepatic failure. Their cerebral effects are increased by systemic inflammatory mediators that modulate cerebral endothelial, vascular, and astrocytic function.[111] In patients with cirrhosis, infection often triggers or worsens hepatic encephalopathy; encephalopathy, the systemic inflammatory response, and extrahepatic organ failure are closely associated.[113]

Initial clinical management of hepatic encephalopathy in acute-on-chronic liver failure is focused on protection of the airway; endotracheal intubation is indicated if the patient's conscious level decreases. Treatment of precipitating factors—such as sepsis, constipation, dehydration, hyponatraemia, and other electrolyte imbalance—and discontinuation of any contributory drugs are essential.[114] Generic treatments, such as lactulose, to reduce nitrogen absorption from the intestine are often commenced, but their role and that of non-absorbable antibiotics, including rifaximin, is currently unclear or has not been assessed in patients with acute-on-chronic liver failure.[114,115] Protein restriction is not beneficial and could worsen an already compromised nutritional state.[116] Drugs that rapidly lower ammonia concentrations, such as enteral polyethylene glycol, have shown promise, and other drugs specifically targeting ammonia (eg, ornithine phenylacetate) are under investigation.[117,118] In controlled trials in acute-on-chronic liver failure, extracorporeal liver support with a molecular adsorbent recirculating system transiently decreases the severity of encephalopathy but does not improve survival.[119,120]

Coagulation defects

Coagulation status is always abnormal in patients with acute-on-chronic liver failure, but the functional consequences are uncertain. Standard coagulation assays, including prothrombin time or international normalised ratio, are poorly predictive of bleeding complications, as a result of the complex coagulation disturbance noted in patients with chronic liver disease.[121–124] Dynamic functional assays could provide a better overview of complication risk and guide to treatment. Blood coagulation can be rebalanced by the parallel reduction of procoagulant and anticoagulant factors, and, rather than hypocoagulopathy, a prothrombotic state can occur.[125] This balance is fragile and unstable and secondary factors, such as infection, can tip it towards either haemorrhage or thrombosis.

Altered coagulation status with enhanced bleeding risk can result from the effects of systemic homoeostatic disturbance from acidosis, uraemia, hypocalcaemia, hypothermia, or sepsis. Addressing of these systemic issues forms the basis of initial management of active haemorrhage and prevention of procedure-related bleeding complications. Approaches to coagulation support should be individualised but, in general, fresh frozen plasma is not recommended for empirical correction of prolongation of clotting times and is associated with adverse effects including volume overload, increased portal pressure, and transfusion reactions.[126,127] Thrombocytopenia is common in acute decompensation and acute-on-chronic liver failure but does not always represent a bleeding risk because of concomitant high circulating concentrations of von Willebrand factor and increased platelet adhesion.[128] However, hypocoagulabilty could be more common in patients with chronic liver disease and a platelet count of less than 100×10^9 per litre or hypofibrinogenaemia, and support might be needed in those with bleeding complications or who require invasive procedures.[129]

Other therapies

Liver transplantation

Survival after liver transplantation is worse for recipients who are in hospital at the time of surgery than in those at home, and worse still in those who were in the intensive care unit; post-transplantation length of stay and resource use are also substantially increased.[130–134] In patients with acute-on-chronic liver failure, difficulties in urgent transplantation assessment, active substance dependence, paucity of organ donors, sepsis, and circulatory failure often preclude emergency liver transplantation. In the CANONIC study,[4] 9% of patients with acute-on-chronic liver failure underwent transplantation within 28 days of admission, and 15% within 90 days.[4] In patients in whom two or three other organs had also failed, mortality without liver transplantation was more than 80%, but only 20% in patients who received a transplant. The success of liver transplantation in some patients with corticosteroid-resistant acute alcoholic hepatitis shows that excellent outcomes can be obtained if appropriate recipients can be selected for transplantation.[135] Patients with acute-on-chronic liver failure seem to tolerate marginal liver grafts remarkably well, but increasing recipient age (particularly >60 years) is consistently associated with increased mortality.[136–138]

However, transplantation is usually an option only in patients assessed and listed for transplantation before they develop acute-on-chronic liver failure. Even then, only a proportion are eligible because of progression of illness or development of contraindications. Of 221 Canadian patients listed for liver transplantation who deteriorated and needed intensive care, 106 (48%) died while awaiting surgery.[138] Previously, organ allocation systems did not prioritise specifically on the basis of acute-on-chronic liver failure, but introduction of the Share 35 protocol in the USA gave new wait-list priority to regional candidates with MELD of 35 or greater, which reduced waitlist mortality by 30% and did not result in an increase in post-transplant mortality.[139] Use of scoring systems specific for acute-on-chronic liver failure could help to further refine this process.[21] Expedited transplantation assessment should be also be considered for survivors of acute-on-chronic liver failure after discharge from the intensive care unit because such an episode of disease substantially increases medium-term mortality.[2,4,24,27,37]

Extracorporeal liver support devices

The use of various biological and non-biological extracorporeal liver support devices has been explored in acute-on-chronic liver failure. These aim to replace the functions of the failing liver, allowing hepatic recovery or stabilising clinical state to enable transplantation.[140,141]

Non-biological systems remove from the blood the toxins that potentially cause hepatic injury and extra-hepatic organ failure—including bilirubin, ammonia, and bile acids—through membrane filtration and adsorption. Two large randomised controlled trials of non-biological devices have been done. In the Recompensation of Exacerbated Liver Insufficiency with hyperbilirubinemia and/or Encephalopathy and/or renal Failure (RELIEF) multicentre study,[119] 189 patients with acute-on-chronic liver failure were randomly assigned to standard medical therapy with or without the use of a molecular adsorbent recirculating system (a form of whole-blood albumin dialysis with charcoal and anion-exchange resin adsorbent columns in series with standard renal replacement, which removes both water-soluble and protein-bound toxins).[140] Use of the molecular adsorbent recirculating system resulted in biochemical changes and improved resolution of encephalopathy, but did not significantly improve survival in either intention-to-treat or per-protocol analysis.[119] The Prometheus device combines a plasma separation technique with adsorption and renal-replacement components and more effectively clears protein-bound and water-soluble molecules than does albumin dialysis.[142] However, in a randomised controlled trial[143] of 145 patients with acute-on-chronic liver failure, those in whom Prometheus was used in addition to standard medical therapy had significant reductions in serum bilirubin concentrations but no improvements in survival.[143]

In biological liver support systems, biochemically active hepatocyes support not only hepatic detoxification but also metabolic and synthetic functions.[140] The hepatocyte type and its structural arrangement present challenges, as does maintenance of the large mass of cells. These technical issues along with cost have delayed large-scale efficacy testing in acute-on-chronic liver failure, and randomised controlled trials have been reported only in abstract form.[140] These devices are of little use in the treatment of acute-on-chronic liver failure, but the technology is continuously evolving and large-scale trials of new biological systems are ongoing. Even if these devices do not improve overall survival, specific patient subgroups might benefit from their use (eg, stabilisation of the patient until transplantation),[141] and trials are focused on specific subgroups of acute-on-chronic liver failure.

Improving outcomes

Outcomes for patients with acute-on-chronic liver failure have substantially improved, but further improvements are dependent on advances that address key steps in disease evolution. Testing and refinement of the definitions of the disorder will help with research and intervention trials and contribute to incremental improvement in supportive care, as has already been achieved with variceal bleeding. As the design and application of extracorporeal devices improve on the basis of better understanding of acute-on-chronic liver failure, they could lead to clinically meaningful outcomes. Transplantation could be effectively used in more patients.

However, the greatest improvements in survival will probably result from development and implementation of steps to identify the patients with cirrhosis at greatest risk for organ failure at an early stage and introduction of effective interventions to prevent this development. Because of the major contribution of, and persistently high mortality associated with, bacterial infection, sepsis and host inflammatory response are important targets for both improved diagnostics and early therapeutic interventions. Assessment of treatment strategies and improvements in outcomes are dependent upon increased access to critical care for a group of patients who are often unfairly disadvantaged.[9,10]

Contributors

WB, JW, and AB conceived the Seminar and WB wrote initial drafts. With the exception of AB, all authors contributed in detail to the writing of the final version of the Seminar.

Declaration of interests

WB has received consulting fees from Ocera Therapeutics and Vital Therapies. RJ received research funding from Vital Therapies, has served on scientific advisory boards for Conatus Pharma, received lecture fees from Gambro, is doing a research collaboration with Gambro and Grifols, and is the principal investigator of a study sponsored by Sequana Medical. He invented the drug L-ornithine phenyl acetate, which University College London has licensed to Ocera Therapeutics, and is the founder of Yaqrit and Cyberliver. AQ, KS, and JW declare no competing interests.

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