Review

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Transition to decompensation and acute-on-chronic liver failure: Role of predisposing factors and precipitating events

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Summary

The transition from compensated to decompensated cirrhosis results from a complex interplay of predisposing and precipitating factors and represents an inflection point in the probability of a patient surviving. With the progression of cirrhosis, patients accumulate multiple disorders (*e.g.* altered liver architecture, portal hypertension, local and systemic inflammation, bacterial translocation, gut dysbiosis, kidney vasoconstriction) that predispose them to decompensation. On the background of these factors, precipitating events (*e.g.* bacterial infection, alcoholic hepatitis, variceal haemorrhage, drug-induced liver injury, flare of liver disease) lead to acute decompensation (ascites, hepatic encephalopathy, variceal bleeding, jaundice) and/or organ failures, which characterise acute-on-chronic liver failure. In this review paper, we will discuss the current hypotheses and latest evidences regarding predisposing and precipitating factors associated with the transition to decompensated liver disease.

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Decompensation: a critical step in the natural history of cirrhosis

Compensated cirrhosis is an asymptomatic condition characterised histologically based on the extent and morphology of fibrous scar tissue in the liver. Decompensated cirrhosis is a symptomatic disease state, arising from cirrhosis, characterised clinically by the development of ascites, encephalopathy and/or gastrointestinal bleeding due to portal hypertension. Decompensated cirrhosis is a more advanced disease state which develops after a variable duration of compensated cirrhosis and represents a turning point in terms of a patient's quality of life, probability of hospitalisation, and mortality risk. The onset of decompensation may be insidious, resulting from slowly declining hepatic synthetic function and rising portal pressure. However, a significant proportion of hospital admissions occur in patients with acute onset of symptoms developing over a matter of hours or days. This acute decompensation (AD) may occur in patients with no previous evidence of impaired hepatic reserve and is associated with pathophysiological events which lead to the rapid deterioration in liver function. These precipitating events, which include infections, exacerbations of the underlying liver disease, alcoholic hepatitis, drug-induced liver injury, will be discussed later. The relative frequency of precipitating event types varies geographically. In Europe, the most frequent precipitating event of AD is bacterial infection, followed by active alcohol consumption (alcoholic hepatitis) and gastrointestinal haemorrhage.[1] In China, HBV flares remain the main precipitating event, while active alcohol consumption (~50%) has overtaken hepatitis B and hepatitis E as the main precipitating factor of decompensation in India.[2,3]

The transition from compensated to decompensated cirrhosis is accompanied by a profound change in mortality risk in the short, medium, and long term (see Table 1).[4] The short-term prognosis associated with AD is poor, particularly when accompanied by failure of other organs, categorised as acute-on-chronic-liver-failure (ACLF), with 28-day mortality rates ranging from 15%–80%, depending on the severity and number of organ failures.[1] Quality of life measures in patients with compensated cirrhosis are not dissimilar to age- and gender-matched controls but decompensation is associated with a profound deterioration in quality of life.[5] Furthermore, the need for hospital visits, admissions and healthcare costs increase substantially in patients following an episode of AD.[6]

The transition from the compensated to the decompensated state is a complex phenomenon resulting from the interaction between predisposing factors, which characterise the patient and their liver disease, and the occurrence of precipitating events (Fig. 1). Improving our understanding of the mechanisms responsible for this transition will be essential in the search for new preventive strategies. In this review paper, we will discuss the current hypotheses and latest evidence regarding predisposing and precipitating factors associated with the transition to decompensated liver disease.

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Table 1. Estimation of prognosis based on the stage and the type of decompensation in cirrhosis.[1,131–133]

Stage	Specificities	Time point	Mortality rates
Compensated cirrhosis	Without varices*	1-year	1%
	With varices*	1-year	3.4%
Acute decompensated cirrhosis	Variceal bleeding	1-year	20%
	Ascites	1-year	30%
	Ascites + variceal bleeding	1-year	50%
	Hepatic encephalopathy	1-year	64%
	Bacterial infection	1-year	63%
	ACLF-1 (renal failure# or 1 organ failure + renal or cerebral dysfunction&)	90-day	40%
	ACLF-2 (2 organ failures)	90-day	52%
	ACLF-3 (3 organ failures or more)	90-day	80%

ACLF, acute-on-chronic liver failure.
*If patients remained in this clinical status.
#Renal failure was defined by creatinine levels ≥2 mg/dl.
&Renal dysfunction was defined by creatinine levels of 1.5–1.9 mg/dl and cerebral dysfunction by grade I or II hepatic encephalopathy.

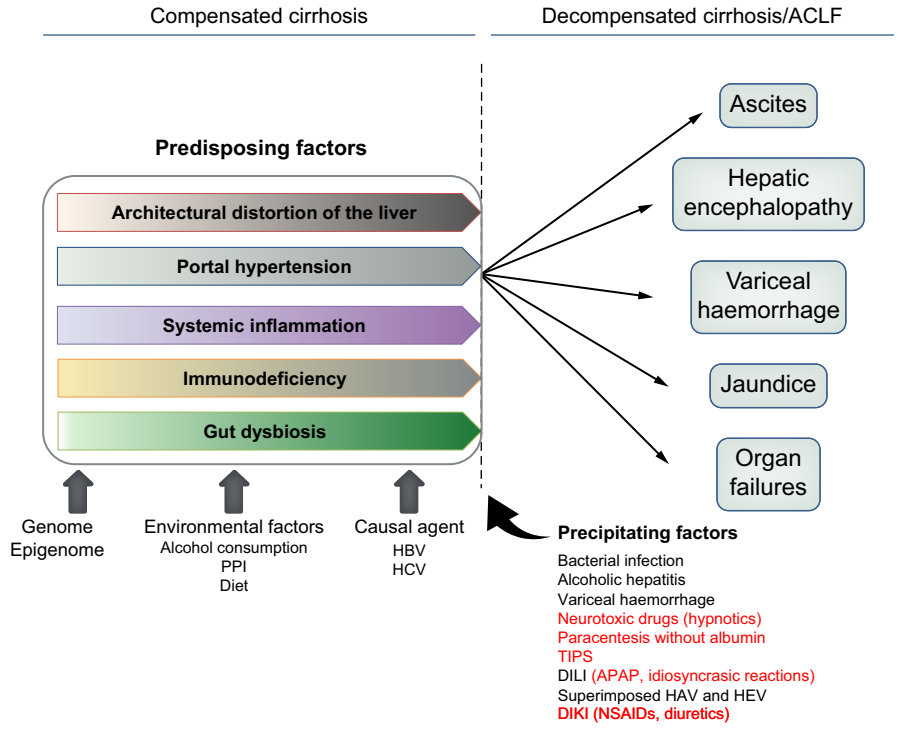

Fig. 1. Current hypothesis about transition to decompensation and acute-on-chronic liver failure. APAP, acetaminophen; DIKI, drug-induced kidney injury; DILI, drug-induced liver injury; PPI, proton pump inhibitor; TIPS, transjugular intrahepatic portosystemic shunt.

Predisposing factors

Evidence for clinically recognised factors

Liver architecture and injuries

It has been suggested that the degree of architectural distortion of the liver – in particular the thickness of fibrous septa and the size of regeneration nodules, which correlate with portal hypertension – is a predictor of liver-related events.[7] In addition, it has been shown that collagen proportionate area, used to quantify fibrosis in cirrhosis, is a predictor of clinical decompensation.[8]

The aetiology of cirrhosis also seems to influence its natural history, but studies remain scarce. One prospective study suggested that non-alcoholic fatty liver disease-related cirrhosis is associated with fewer episodes of decompensation than HCV-related cirrhosis in the pre-direct-acting antiviral (DAA) era.[9] Secondly, there is accumulating evidence that continuous liver injuries triggered by aetiological factors induce decompensation. This is mainly demonstrated by the fact that the control of aetiological factors by treatments or lifestyle interventions in patients with cirrhosis prevents future decompensation. For example, achieving a sustained virological response to DAAs significantly reduces episodes of

Key point

The transition from compensated to decompensated cirrhosis represents a turning point in terms of quality of life, probability of hospitalisation, and mortality risk.

decompensation in patients with compensated HCV-related cirrhosis.[10] This has also been suggested for patients with HBV treated with nucleos(t)ide analogues[11] and patients with primary biliary cholangitis treated with ursodesoxycholic acid.[12] Moreover, in a retrospective study, behavioural and/or pharmacological treatment for alcohol use disorder was associated with a significant decrease in decompensation.[13]

Clinically significant portal hypertension

The development of portal hypertension is central to decompensation of cirrhosis. It has been observed that the incidence of clinical decompensation begins to increase when the hepatic venous pressure gradient (HVPG) exceeds 10 mmHg, the threshold defining clinically significant portal hypertension (CSPH).[14] Variceal haemorrhage generally occurs when HVPG exceeds 12 mmHg.[15] Moreover, a recent large randomised controlled trial suggested that long-term administration of β-blockers prevents decompensation, not only by reducing the occurrence of variceal haemorrhage but also the development of ascites.[16]

Kidney alterations: renal vasoconstriction, deranged autoregulation

In advanced cirrhosis, renal sodium and fluid retention occur before the development of ascites.[17–19] These changes are pathophysiologically linked to the compensatory homeostatic activation of the renin-angiotensin-aldosterone system, the sympathetic nervous system and, in later stages, the non-osmotic hypersecretion of arginine vasopressin. Neurohormonal activation aims to counterbalance the reduction in effective arterial blood volume secondary to portal hypertension-related vasodilation and, as cirrhosis progresses, to decreased cardiac output and systemic inflammatory response.[20] In the kidney, enhanced neurohormonal activity affects renal function, with sodium and solute-free water retention and, eventually, vasoconstriction, leading to ascites, oedema, and renal failure.[21–23] In this context, the increased activity of the sympathetic nervous system has been associated with the progressive impairment of renal autoregulation. While in healthy individuals renal autoregulation maintains constant renal blood flow independently of fluctuations in systemic arterial pressure,[24] patients with cirrhosis are characterised by a progressive shift downward and rightward on the renal autoregulation curve.[25] As a consequence, they have fragile kidney function and are prone to developing kidney failure.[26] In fact, for the same value of renal perfusion pressure, the corresponding renal blood flow is progressively reduced from compensated to decompensated patients, being the lowest in patients with more severe liver disease and hepatorenal syndrome.[20,25]

Extrahepatic comorbidities

Patients with a combination of compensated cirrhosis and type 2 diabetes (T2D) have an increased risk of episodes of decompensation.[27] The mechanisms responsible for this susceptibility are currently incompletely understood. T2D is a well-known risk factor for bacterial infection and some studies have suggested that diabetes confers an additional risk of infection in patients with compensated cirrhosis.[28] In contrast, in decompensated cirrhosis, diabetes does not increase the risk of infection.[29]

Patients with decompensated cirrhosis are particularly vulnerable to developing sarcopenia due to impaired oral intake and increased gluconeogenesis from skeletal muscle protein. Frailty and sarcopenia are currently considered to be independent predictors of mortality in decompensated cirrhosis, but it remains unknown whether they are predisposing factors in the transition to decompensated cirrhosis.[30]

Current directions for research on predisposing factors

Gut dysbiosis

As the anatomical and functional relationship between the intestine and the liver, the gut-liver axis has been proposed to play a major role in the development of complications of cirrhosis and is discussed in detail in another chapter of this supplement. Typically, in patients with cirrhosis, the microbiome can be characterised by decreased microbial diversity, a loss of beneficial commensals, and an increase in potential pathogens.[31] Cirrhosis affects both the number of different species (alpha diversity) and the composition of species (beta diversity). The results for alpha diversity are not consistent in the literature, a factor that may be explained by differences in analytical techniques.[31–33] The alteration in microbial diversity reduces the resilience of the microbiome, making it susceptible to perturbations. The dysbiotic microbiome can find a new steady state and the dysbiosis itself may promote disease progression.[34] This raises the question of whether changes in the composition of the microbiome are the cause or the consequence of the disease, and whether they are involved in the progression of compensated to decompensated cirrhosis. There is no clear-cut answer to this question. When trying to differentiate cause from consequence, factors that contribute to dysbiosis need to be studied. Medications, aetiology, disease severity, nutritional status, and inflammation impact on the composition

of the gut microbiome in cirrhosis and seem to overlap, at least partially.[35]

Drug intake is another driver of dysbiosis in cirrhosis: proton pump inhibitor use has been associated with reduced colonization resistance in patients with cirrhosis and healthy volunteers.[36,37] Also "oralization", defined as the increased abundance of bacterial species that are typical inhabitants of the oral cavity is a common feature found in cirrhosis and also in non-cirrhotic individuals who take proton pump inhibitors.[36,38–42] The combination of gastric acid loss and alcohol aggravates dysbiosis and leads to additional liver damage.[43] Increasing severity of liver disease is associated with oralization,[31,35,38,44] and diet and nutritional status affect microbial composition in patients with cirrhosis.[32,35]

Intestinal dysbiosis has been hypothesised to impair the intestinal barrier and cause bacterial translocation (or translocation of bacterial products, called pathogen-associated molecular patterns [PAMPs]) contributing to intestinal and systemic inflammation.[45] Decompensated cirrhosis is also associated with altered expression of tight junction proteins in the duodenum.[46] From a clinical point of view, this concept is supported by studies showing an association between dysbiosis, markers of intestinal permeability, inflammation, bacterial translocation, and complications of cirrhosis.[37,47–50]

In contrast to gastrointestinal bacteria, very little is known about the role of the gastrointestinal mycobiome and nothing is known about the virome. In the near future, we must explore the link between mycobiome and virome alterations and decompensation. The impact of these alterations on AD and ACLF is currently being explored in the Horizon 2020 project MICROB-PREDICT (https://microb-predict.eu/).

Cirrhosis-associated immune dysfunction

Cirrhosis is associated with a multifaceted state of immune dysfunction, cirrhosis-associated immune dysfunction (CAID), which involves both immunodeficiency and persistent proinflammatory immune cell activation. CAID affects the innate and the adaptive arms of the immune system as well as cellular and acellular mechanisms.[51,52] The causes of CAID are also multifactorial, with well described mechanisms including: increased translocation of bacterial products due to impaired intestinal permeability, leading to activation of pattern recognition receptors and inadequate immune activation; a dysfunctional local immune surveillance system in the liver and reduced synthesis of proteins in the liver (such as antimicrobial substances, pattern recognition receptors); and impaired albumin function.[53]

Systemic inflammation is a consequence of this immune stimulation and contributes to haemodynamic disturbances and portal hypertension, accelerating the development of decompensation and organ failures. Indeed, several studies have corroborated a positive correlation between progressive CSPH, increasing (systemic) inflammation, and evolving decompensation culminating in ACLF.[54–58] As such, CSPH, together with systemic inflammation, is considered fundamental in the progression to ACLF. Recently, this was further corroborated by the PREDICT study, which subdivided AD into 3 subtypes (stable or unstable decompensated cirrhosis and pre-ACLF) defined by the absence of hospital readmission, the presence of readmission, or development of ACLF, respectively, during a follow-up of 3 months.[4] In this study, the main driver of ACLF development seemed to be a worsening of systemic inflammation, while the unstable course of patients with unstable decompensated cirrhosis without ACLF seemed to be driven by severe portal hypertension. The tight interaction of CSPH and inflammation has been suggested as a predisposing factor in ACLF development. First, portal hypertension-induced venous congestion and splanchnic neoangiogenesis induce microcirculatory dysfunction leading to increased intestinal permeability (and thus bacterial translocation).[59–61] Secondly, inflammation self-perpetuates and further enhances the dynamic component of increased intrahepatic vascular resistance, triggering or further escalating extrahepatic organ failure and thus shaping the host response to injury.[62] Thirdly, as portal hypertension progresses, impaired cardiac function (so-called cirrhotic cardiomyopathy) and hyperdynamic or hypodynamic circulation increasingly take effect, which not only compromises basal effective circulating volume but also predisposes to an incompetent cardio-haemodynamic compensatory system in response to potential additional deleterious precipitants, expediting end-organ dysfunction.[63,64] Fourthly, clinical manifestations of portal hypertension are aggravated by its progression and, therefore, impact on end-organ function (*e.g.* the brain in cases of hepatic encephalopathy, the kidney in cases of refractory ascites) or indirectly promote infectious complications (*e.g.* (aspiration) pneumonia, spontaneous bacterial peritonitis).[65,66]

In parallel to this systemic inflammation, cirrhosis is associated with several alterations in the innate and adaptive components of the immune system leading to immunodeficiency, reviewed in detail elsewhere.[53] This state is characterised by an impaired response to microbial challenge and vaccination, and an increased probability of bacterial translocation leading to a high

Key point

This transition is characterised by the occurrence of ascites, variceal bleeding and/or hepatic encephalopathy or organ failures (in the case of ACLF).

Key point

Numerous factors that predispose patients to acute decompensation have been described and/or suspected (*e.g.* degree of liver architecture disturbances, portal hypertension, renal vasoconstriction, bacterial translocation, gut dysbiosis, genetic polymorphisms).

risk of bacterial infection, a well-known precipitant of AD.[67] The majority of these abnormalities are described in already decompensated cirrhosis and they worsen in parallel with the severity of liver failure.[68,69] Some studies have suggested that some alterations, in particular for neutrophils, are already present in compensated cirrhosis.[70,71]

Course of cirrhosis: decrease of tolerance to organ damage

In contrast to what might be expected, the CANONIC study revealed that patients with previous AD developed a less severe form of ACLF, lower levels of inflammatory mediators, and lower rates of 30-day mortality than patients without previous AD.[1] A potential explanation for this apparent discrepancy was attributed to a differential decrease in *tolerance* which reflects the intrinsic capacity of host organs to endure the effects of a deleterious inflammatory response. Previous episodes of AD might, therefore, prime and stretch the mechanisms of tolerance, giving patients an advantage compared to those with no history of decompensation who seem unprepared for the inflammatory tsunami that culminates in ACLF.

Shi *et al.* confirmed this specific finding from CANONIC by documenting that previous decompensation had no impact on the immediate short-term mortality of patients with ACLF.[72] Additionally, they demonstrated that patients with ACLF and a previous AD were distinct from those without as they were older and had less hepatic injury but suffered relatively more non-hepatic precipitating insults and displayed increased delayed mortality.

Recently, Trebicka *et al.* anatomised the role of previous AD by demonstrating that compensated and recompensated patients have different pathways of inflammasome activation and systemic inflammation.[73] As such, they highlight the fact that patients who primarily exhibit a high degree of immune incompetence and develop AD nonetheless might suffer an increased risk of ACLF development. This premise is supported by a higher rate of detectable interleukin-1β, indicative of exaggerated inflammation, among recompensated patients. Moreover, these findings were paralleled by animal studies where the increased intrahepatic *Il1b* gene expression signature pinpoints hepatic inflammation as the primary origin of this elevated inflammatory condition after recompensation. Therefore, previous AD can shape response patterns and impact outcomes in a given patient.

Albumin alterations

Altered albumin structure and function is well described in cirrhosis. Oxidation of albumin, especially irreversibly oxidised albumin, increases with disease progression in cirrhosis, is predictive for survival in cirrhosis, and may play a role in systemic inflammation.[74,75] Higher levels of ischaemia-modified albumin are associated with bacterial infections and higher mortality.[76,77] Further detailed analysis has revealed that certain post-transcriptional structural changes of albumin are associated with clinical complications of cirrhosis.[78] Structural changes of albumin impair its binding and transport function as well as its antioxidant function. Structurally altered albumin has also been hypothesised to induce the formation of anti-albumin antibodies because of the presence of neoepitopes, which may further aggravate immune dysfunction. However, the clinical relevance of this hypothesis is still unclear.[52] These alterations could be a predisposing factor for AD, but prospective studies are needed to confirm this hypothesis.

Genetic predisposition

Potential predisposing genetic factors for decompensation of cirrhosis have been identified. Until now, genetic studies in cirrhosis have mainly been based on studying single or small groups of gene polymorphisms with a defined hypothesis. Genome wide association studies to assess the genetic predisposition to decompensation have not yet been reported. Polymorphisms of pattern recognition receptors, such as nucleotide-binding oligomerisation domain containing 2 (NOD2), Toll-like receptor (TLR) 2 and 4, or nuclear dot protein 52 kDa have been associated with an increased risk of bacterial infections in some studies, but this has not been confirmed by other studies.[79–82] Sodium dismutase polymorphisms, another critical enzyme in immune defence and cell damage, were associated with decompensation and risk of bacterial infections.[83] In another study, the *PNPLA3* G/G genotype was associated with a 2-fold increase in the risk of decompensation.[84] Although genetic predisposition may play a role in shaping an individual's risk of decompensation, the clinical relevance, and the consequences regarding the need for genetic testing are not yet clear.

Epigenetic predisposition

The dynamic nature of chromatin structure and nuclear organisation regulates gene expression through epigenetic modifications: DNA methylation, histone modification, chromatin organisation and remodelling. These epigenetic mechanisms have been implicated in a wide variety of diseases and influence disease expression. One study has suggested that CD14+ monocytes observed in alcoholic hepatitis display altered

transcriptional and epigenetic profiles characterised by downregulation of key innate immune and metabolic pathways alongside upregulation of important immunomodulatory factors responsible for immune exhaustion.[85] Exploring the role of epigenetic alterations in the progression and decompensation of cirrhosis is a new area of research.

Precipitating events

Many precipitating factors have been described and can cause specific types of AD. Hypnotic drugs, constipation, dehydration, and dyselectrolytemia are recognised as precipitating factors of hepatic encephalopathy. Excessive dietary sodium intake, drug-induced renal sodium retention, portal vein thrombosis, invasion of the portal vein by hepatocellular carcinoma, and hypoalbuminemia can cause ascites. Jaundice is mainly precipitated by direct liver injury such as alcoholic hepatitis, drug-induced liver injury (DILI), autoimmune hepatitis flare or superimposed HAV or HEV. Recently, 2 large European prospective (CANONIC and PREDICT) studies characterised AD of cirrhosis and its associated factors (summarised in Table 2).[1,86] Bacterial infections and alcohol-related liver injury are the most frequent precipitating events in Europe.

Bacterial infections

Bacterial infection is frequent and often severe in patients with cirrhosis and is a main driver of AD. Infection is present at admission or occurs during hospitalisation in 25% to 35% of patients with cirrhosis.[87] The susceptibility of patients with cirrhosis to bacterial infections is explained by several predisposing factors: bacterial translocation, dysbiosis, and CAID-related immunodeficiency, as previously described. Overall, bacterial infection is considered to be the most frequent precipitant of AD (causing 22% to 29% of cases of AD and 33%–50% of cases of ACLF), suggesting that infection is a trigger of severe forms of AD.[1,86] The PREDICT study supports this hypothesis by demonstrating a close temporal relationship between the infectious episode and the occurrence of ACLF.[4] In another study including patients with severe alcoholic hepatitis, the occurrence of prior infection was the only independent variable predicting the onset of ACLF. In a large prospective study of 1,672 patients with compensated (Child-Pugh A) biopsy-proven HCV- or HBV-related cirrhosis without previous history of decompensation, the 5-year cumulative incidence of bacterial infections was 13% and these infections preceded and precipitated episodes of decompensation.[28] In this cohort of patients with compensated cirrhosis, the most frequent sites of infection were the urinary tract and lung followed by the abdomen and skin. Bacterial infection precipitates and/or aggravates AD by increasing the intensity of systemic inflammation and portal hypertension, potentially leading to organ dysfunction/failure and variceal haemorrhage.[88,89]

Active alcohol consumption

Alcohol use disorders remain the most common cause of end-stage liver disease and liver-related mortality in Europe and North America. Alcohol causes cirrhosis after prolonged periods of excess consumption but, in addition, it causes an acute presentation characterised by jaundice and liver failure, frequently accompanied by features of decompensation, known as alcoholic hepatitis. The incidence of alcoholic hepatitis is increasing in Europe and North America, although precise

Key point

Precipitating events for ACLF vary between Western countries (bacterial infection, alcohol intake) and Eastern countries (flare of HBV, superimposed HAV or HEV).

Table 2. Precipitating events of AD and ACLF in Europe (adapted from[1,86]).

Precipitating events	AD without ACLF	ACLF
Bacterial infection	22%-29%	33%-50%
Active alcoholism in the past 3 months (suspected alcoholic hepatitis)	15%-26%	24.5%-43.5%
Gastrointestinal bleeding	16%-17%	13%-20%
Neurotoxic drugs	8%	8%
Paracentesis without albumin	10%	10%
TIPS	5%	4%
DILI	1.5%	2%
Viral hepatitis or other viral infections	1%	1.5%
Drug-induced kidney injury	0.3%	0.5%
Surgery	0.3%	0%
Decompensated cardiopulmonary disease	0.4%	1.5%
Dehydration	0.3%	0.5%
Large hematomas	0.3%	0%
Acute pancreatitis	0.1%	0.5%
Portomesenteric vein thrombosis	0.2%	0.5%
Extrahepatic autoimmune disease	0.2%	0%
Cerebrovascular accident	0%	0.5%
Bowel occlusion	0.1%	0%
Indeterminate precipitating event #	59%-62%	29%-44%
More than one precipitating event	5%-6%	13.5%-25%

ACLF, acute-on-chronic liver failure; AD, acute decompensation; DILI, drug-induced liver injury; TIPS, transjugular intrahepatic portosystemic shunt.
#Indeterminate precipitating event denoted the absence of all previously described precipitating event.

estimates are rarely available due to diagnostic or coding inaccuracy.[90,91] Amongst patients with alcoholic hepatitis 80%–90% already have cirrhosis and all have advanced fibrosis. Nevertheless, it is clear that AD can also occur in patients with alcoholic hepatitis in the absence of advanced cirrhosis.[92,93] Episodes of alcoholic hepatitis appear to occur in a context of more intense alcohol consumption.

Evidence from animal models as well as human studies demonstrate that alcohol bingeing increases permeability of the gut epithelial barrier resulting in excess quantities of bacterial products reaching the portal circulation.[94] Bacterial cell wall components and hypomethylated CpG DNA signal through TLRs in hepatic Kupffer cells and macrophages to induce inflammation.[95] Around 25% of patients with alcoholic hepatitis have an infection at the time of presentation and, thus, more circulating bacterial products available to incite an inflammatory response. Inflammation within the hepatic sinusoids triggers activation of stellate cells which transform into myofibrotic cells. Myofibroblast activation exacerbates portal venous hypertension through deposition of collagen and contraction leading to increased sinusoidal resistance.

Key point

ACLF is characterised by intense systemic inflammation leading to organ failures.

Novel insight into the pathogenesis of alcoholic hepatitis was provided by Argemi's study of epigenetics and gene expression in hepatocytes of patients with alcoholic hepatitis.[96] Epigenetic modification of the hepatocyte nuclear factor 4 alpha (*HNF4A*) locus in alcoholic hepatitis leads to expression of a foetal isoform of HNF4a (HNF4a-P2) in response to transforming growth factor-β, rather than the normal adult isoform (HNF4a-P1). The consequence of this switch is suppression of numerous hepatocyte functions, including bile salt transportation, albumin synthesis, gluconeogenesis, coagulation factor production, and cytochrome-P450 enzyme expression. These findings partially explain the substantial loss of liver function observed despite the adequate number of hepatocytes.

Variceal haemorrhage

Variceal haemorrhage is considered to be a precipitating factor of AD or ACLF in around 15% of cases.[1,86] As discussed earlier, portal hypertension predisposes to ACLF directly through haemodynamic derangements exacerbated by escalating inflammation and indirectly through its complications. Paradoxically, variceal haemorrhage was not observed more frequently in patients with ACLF than in patients with AD.[1] A likely explanation is the successful implementation of Baveno recommendations in daily clinical practice for primary and secondary prophylaxis of variceal haemorrhage.[97–99] Thus, optimised management, including both prevention and intervention, has improved outcomes for these patients and, therefore, reduced variceal bleeding's contribution as a trigger of AD and/or ACLF development. Support for this premise is provided by the recent data from the International Variceal Bleeding Observational Study Group and Baveno Cooperation who, in a large multicentre international real-life study, identified ACLF at admission as an independent risk factor for rebleeding and mortality in patients with acute variceal haemorrhage.[100] Moreover, preemptive transjugular intrahepatic portosystemic shunt (TIPS) was associated with improved survival in patients with ACLF and variceal bleeding, highlighting the fact that portal hypertension is indeed a pivotal and necessary predisposing factor in the pathophysiology of ACLF and that TIPS is not a frequent worsening or predisposing factor for ACLF.[100]

Drug-induced liver injury

DILI can result from the administration of a variety of potentially hepatotoxic compounds, including prescription drugs, over-the-counter medications, and herbal and dietary supplements.[101] Whether patients with pre-existing chronic liver diseases are at increased risk of DILI is still a matter of debate.[102] However, frequent need for polypharmacy, drug-drug interactions, and potential impairment of drug metabolism are likely to increase the incidence of DILI in patients with cirrhosis. Furthermore, higher DILI-related mortality has been demonstrated in patients with pre-existing liver disease compared to those without (16% *vs.* 5.2%, respectively).[103] DILI can precipitate decompensation of a previously compensated cirrhosis, and ACLF can occur in the most severe cases as well, entailing a high mortality risk.[101,104,105]

Flare of liver disease

Autoimmune hepatitis (AIH) is an inflammatory process of the liver often characterised by a chronic, fluctuating, asymptomatic, although progressive, course. The clinical picture varies widely, from indolent disease with modest abnormalities of liver enzymes up to acute hepatic failure requiring urgent liver transplantation in patients without chronic histological alterations.[106,107] Cirrhosis is present in up to 40% of adults upon initial clinical presentation and AIH manifests as decompensated cirrhosis in 10% of patients, with a minority of these cases having features of ACLF.[107–114] Acute flares of AIH occurring in patients with established liver damage can result in jaundice, complications of end-stage liver disease and, finally, liver failure. Therefore, early diagnosis and prompt initiation of adequate immunosuppressive therapy in patients with active disease are essential to avoid further disease progression and decompensation. Regression of fibrosis after successful treatment has been reported.[107,111–113] However, immunosuppressive therapy may be

contraindicated in patients with AIH and decompensated cirrhosis, as the risks of therapy may overcome those of the disease. In these patients, treatment should be carefully tailored to the individual patient's characteristics.[106,107]

Hepatitis B flares are a well-known factor for progression towards cirrhosis and repeated, severe flares can boost the transition to decompensation.[115] In untreated (naïve) patients, HBV flares may occur either spontaneously or be favoured by immune restoration (*e.g.* start of active antiretroviral therapy in HIV-HBV coinfected patients or of anti-tuberculosis therapy) or they can be induced by immunosuppression, cancer chemotherapy or DAA therapy for HCV.[115,116] Acute exacerbations of the disease can also occur in chronic hepatitis B patients during the course (emergence of drug resistance) or after discontinuation of nucleos(t)ide analogue therapy.[115] HBV flares occurring in patients with cirrhosis entail a high risk (about 20%) of progression to decompensation, liver failure and even death, and always require immediate management with effective antiviral therapy.[115,117] Accordingly, current guidelines discourage discontinuation of antiviral treatment in patients with cirrhosis. When immunosuppression or chemotherapy are needed, screening for HBsAg, anti-HBs and anti-HBc status is mandatory and prophylactic or preemptive antiviral therapy should be started, according to the phase of HBV infection and the risk of HBV reactivation.[116]

In Wilson's disease the severity of hepatic involvement at diagnosis can vary widely, from asymptomatic biochemical abnormalities to chronic liver disease to, in about half of patients, established cirrhosis with or without overt decompensation.[118,119] Acute liver failure can also occur, either at first clinical presentation or during follow-up, particularly in case of non-adherence to chelation treatment, leading to a rapid and severe clinical deterioration, usually on the background of an already, often unknown, established cirrhosis.[118,120,121] Life-long treatment with copper chelating agents can achieve clinical and laboratory improvement, preventing further disease progression and decompensation.[118] Therefore, transition to decompensation in Wilson's disease can be the result of the natural progression of an unrecognised and/or untreated liver disease, and, in some cases, associated with ACLF. ACLF in Wilson's disease is a life-threatening event, mainly affecting children or young adults and entailing extremely high mortality rates (70%–100%), with death often occurring in the first 2–4 weeks from presentation.[122] Therefore, urgent referral of these patients to a specialised intensive care unit and liver transplant centre is mandatory.[118,123]

Superimposed viral hepatitis

Acute superinfection with hepatotropic viruses, such as hepatitis A and E, is well recognised as a precipitating event for decompensation of cirrhosis. Hepatitis A superinfection has been recognised for the past 25 years as a factor that aggravates the disease course,[124] leading to the recommendation by several guidelines to test and, in cases lacking serological evidence of previous infection, to vaccinate all patients with chronic liver diseases against hepatitis A. Hepatitis A testing is also advisable in patients with AD of cirrhosis who present with elevated transaminases and high bilirubin.[125] Hepatitis E is especially relevant in highly endemic areas with a high prevalence of genotype 4, such as the Indian subcontinent, where HEV was reported to trigger decompensation in 8%–66% of patients in several cohort studies.[39] In Europe and America, genotype 3 is responsible for autochthonous infections. Only limited data are available on the impact of hepatitis E on decompensation of cirrhosis in these areas,[126] but hepatitis E testing in cases of decompensation seems to be advisable irrespective of travel history. A vaccine is not generally available and the safety and efficacy in cirrhosis needs to be explored.

Other viral infections, such as cytomegalovirus or Epstein Barr virus infections, that may affect the liver, seem to be rare events but should also be considered when the initial search for precipitating events of decompensation in cirrhosis does not reveal a clear cause.[127,128] SARS-CoV-2 infection, which can affect the liver by binding to angiotensin-converting enzyme 2 receptors, confers a high risk of AD, development of ACLF, and mortality in cirrhosis.[129,130]

Unknown factors

No precipitating factor is identified in 60% of AD and 29%–44% of ACLF, depending on the study.[1,2,86] Several explanations exist. First, there could be an undiagnosed precipitating event such as some specific bacterial infection, undeclared drug intake, or hidden alcohol intake. Sometimes the causal link between the precipitating factor and the decompensation episode is difficult to establish based on the interval between the 2 events, which can be extremely variable. That said, decompensation could also result from the progressive accumulation of predisposing factors (dysbiosis, translocation, inflammation, portal hypertension) leading to an acute destabilisation of the compensatory state of cirrhosis without an evident precipitating event.

Key point

In more than half of cases of acute decompensation and in almost half of cases of ACLF, the classical diagnostic work-up is not able to identify the precipitating event.

Conclusions

The transition from compensated to decompensated cirrhosis is driven by a complex interplay between liver injuries, local inflammation, gut dysbiosis, increasing gut permeability, and subsequent bacterial translocation with progressive portal hypertension being a pivotal and essential axiom. Several events that precipitate decompensation have been described, but in almost half of

the cases no factor is discovered. Further progression of this highly interacting chain of events forms the prelude to progressive systemic inflammation culminating in ACLF. The challenge of future investigations is to integrate multi-omic data into well-characterised prospective cohorts of patients to decipher the complex mechanisms underlying the transition from compensated to decompensated cirrhosis. This strategy is required to prevent decompensation and significantly improve the outcomes of patients with cirrhosis.

Abbreviations

ACLF, acute-on-chronic liver failure; AD, acute decompensation; CAID, cirrhosis-associated immune dysfunction; CSPH, clinically significant portal hypertension; DAA, direct-acting antiviral; DILI, drug-induced liver injury; HNF4A, hepatocyte nuclear factor 4 alpha; HVPG, hepatic venous pressure gradient; TIPS, Transjugular intrahepatic portosystemic shunt; TLR, Toll-like receptor.

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Conflict of interest

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Authors' contributions

All authors designed the manuscript. All authors wrote part of the manuscript. TG prepared the final version. All authors approved the final version of the manuscript to be published.

Supplementary data

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